Hiroyuki Nakamura · Kazutetsu Aoshiba
*Editors*

# Idiopathic Pulmonary Fibrosis

## Advances in Diagnostic Tools and Disease Management

Springer

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# Preface

Owing to the remarkable advances in the fields of molecular biology and genomics/genetics in recent years, medicine has progressed rapidly in various fields, including respiratory medicine. Many advances that have been made in this field include the advent of novel molecular-targeted therapies for lung cancer, the widespread use of inhaled corticosteroids, anti-cholinergic agents and long-acting beta-adrenergic agonists in the treatment of bronchial asthma/chronic obstructive pulmonary disease (COPD), and the development of novel antimicrobial agents for the treatment of respiratory tract infections. In regard to idiopathic pulmonary fibrosis, however, there have been no important additions to the armamentarium for managing this intractable disease over the last these 3 decades, since I graduated from medical school, with definitive therapeutics still lacking.

Lung tissue can be roughly divided into parenchyma and interstitium. In the narrower sense, the term "interstitium" refers to the alveolar septum which separates the alveoli from one another. Idiopathic interstitial pneumonias (IIPs) are characterized by hypertrophy of the alveolar septa due to inflammation. With progression of the disease, lung tissue remodeling through fibrosis takes place. According to the ATS/ERS International Multidisciplinary Consensus Classification (2013), IIPs can be classified into the following six major types: (1) idiopathic pulmonary fibrosis (IPF), (2) idiopathic nonspecific interstitial pneumonia, (3) respiratory bronchiolitis–interstitial lung disease, (4) desquamative interstitial pneumonia, (5) cryptogenic organizing pneumonia, and (6) acute interstitial pneumonia [1]. This classification is still not complete and is expected to be modified with advances in this research field.

IPF is the most frequent type of IIPs. Recent cohort studies and computed tomography (CT)-based epidemiological studies in Japan have indicated a high prevalence of IPF [2]. IPF is a disease characterized by intense lung fibrosis that follows a chronic and progressive course. In comparison to other types of IIPs, IPF responds poorly to steroid and immunosuppressant drug treatment and in general carries a poor prognosis. Approximately half of the patients with IPF die within 3–5 years of the diagnosis. Acute exacerbations increase the mortality of IPF to as

high as approximately 80 %. Thus, currently, IPF is among the most challenging of respiratory diseases to manage. Pulmonary fibrosis is also encountered in other conditions including viral infection, smoking, pneumoconiosis, medication, radiotherapy, and others. However, as indicated by its epithet "idiopathic," the causes and reasons for the lung fibrosis in IPF remain elusive. According to the current view, the essential feature of IPF is not inflammation caused by immunocompetent cells, but proliferation of fibroblasts (due to apoptosis of alveolar epithelial cells) and their differentiation into myofibroblasts. This view can explain why IPF responds poorly to treatment with steroids (glucocorticoids) (which have long been used clinically as representative anti-inflammatory agents). Furthermore, this view suggests the importance of anti-fibrotic therapy as an essential means of treatment for this condition.

Japanese researchers have made remarkable contributions to the study of this disease, some examples of which include the proposal of the concept of "acute exacerbation" [3], development of serum markers that are relatively highly specific for this disease (KL-6, SP-A, and SP-D) [4, 5], establishment of high-resolution computed tomography (HRCT) for diagnostic imaging, as compared to inflated and fixed lung specimens obtained by open lung biopsy and autopsy [6, 7], and reporting of the treatment outcomes of pirfenidone [8], an antifibrotic agent that was first approved in Japan. Thus, Japanese researchers have made remarkable contributions in the field of research on IIPs and published the results in international journals. Despite these diagnostic and therapeutic improvements, no treatments have been established yet that can boast of being a complete cure for IPF.

In addition, interstitial pneumonia with emphysema (combined pulmonary fibrosis and emphysema: CPFE) has been proposed recently as a new entity [9]. CPFE is a condition characterized by emphysematous lesions in the upper lung regions, accompanied by fibrosis in the lower lung regions. This disease is most often seen in male heavy smokers and is clinically characterized by the development of intense hypoxemia with effort, marked reduction in the lung dilatation, elevation of the serum KL-6 level, frequent complication by pulmonary hypertension and lung cancer, and so on. However, because of insufficient knowledge about the pathophysiology of this condition and the absence of a clear-cut definition, physicians in practice are still confused about this entity.

IPF is frequently complicated by lung cancer. It is therefore speculated that some common molecular mechanisms might be involved in the onset of IPF and lung cancer. The results of basic studies suggest that injury of the alveolar epithelial cells seen in cases of IPF not only stimulates pulmonary fibrosis, but also induces multiple gene abnormalities that can lead to the onset of lung cancer. It has also been suggested that apart from promoting lung carcinogenesis, pulmonary fibrosis may also be involved in the growth/spread of the cancer. Thus, basic research is under way in Japan to try to decode these associations. One of the important clinical problems associated with IPF is the development of acute exacerbations of the condition following surgery in lung cancer patients, but some very remarkable

results of treatment are being obtained in large-scale epidemiologic studies in Japan [10].

To date, there have only been a small number of books containing detailed descriptions of IPF, all of which are uniformly organized in the traditional style. This current project presents readers with clinical questions about issues that are not yet fully resolved as the subtitles for the chapters, to authors who have long been engaged in research on IIPs long and are leading experts in this field in Japan. The authors will provide up-to-date information in response to each question. They will describe their thoughts and the future perspectives in response to the clinical questions, based on up-to-date information. Therefore, besides obtaining up-to-date information, the readers can also understand the authors' real intentions and future perspectives, so that their intellectual curiosity will be satisfied.

Considering the nature of this project, useful information will be provided not only for beginning learners studying about IIPs, but also for physicians in clinical practice, instructors, and the many researchers engaged in basic research on this subject.

The Editors hope that this book, written by Japanese authors, will provide valuable input that will help all practicing physicians and medical researchers in the world to better understand the pathogenesis of IPF and to attempt to develop innovative treatments for this intractable disease. The Editors will be greatly pleased if this book can thus bring about therapeutic breakthroughs for patients worldwide suffering from IPF.

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## References

1. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
2. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190(7):773–9.
3. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. Chest. 1993;103(6):1808–12.
4. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, Yamakido M, Akiyama M. New serum indicator of interstitial pneumonitis activity: Sialylated carbohydrate antigen KL-6. Chest. 1989;96(1):68–73.
5. Honda Y, Kuroki Y, Matuura E, Nagae H, Takahashi H, Akino T, et al. Pulmonary surfactant protein D in sera and bronchoalveolar lavage fluids. Am J Respir Crit Care Med. 1995;152 (6 pt1):1860–6.
6. Nishimura K, Kitaichi M, Izumi T, Nagai S, Kanaoka M, Itoh H. Usual interstitial pneumonia: histologic correlation with high-resolution CT. Radiology. 1992;182(2):337–42.

7. Johkoh T, Sakai F, Noma S, Akira M, Fujimoto K, Watadani T, et al. Honeycombing on CT; its definition, pathologic correlation, and future direction of its diagnosis. Eur J Radiol. 2014;83(1):27–31.
8. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171(9):1040–7.
9. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblonde I, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26 (4):586–93.
10. Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, et al. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014;147(5):1604–11.

# Contents

# Part I
# Definition, Epidemiology, and Pathogenesis

# Chapter 1
# Definition of IPF

## Is the Latest Classification of IIPs [ATS/ERS] Satisfactory?

**Shinji Abe and Akihiko Gemma**

**Abstract** Idiopathic pulmonary fibrosis (IPF), the most common form of idiopathic interstitial pneumonias (IIPs), is a fatal disease with a mean survival time of 2–4 years from the time of diagnosis. Therefore, the early and accurate diagnosis of IPF is important and essential for management and induction of optimal therapies. In 2002, the American Thoracic Society and European Respiratory Society (ATS/ERS) published an international statement on the diagnosis and management of IPF. The 2002 ATS/ERS statement defined IPF as a distinct clinical entity associated with the histology of usual interstitial pneumonia (UIP). The revised evidence-based guidelines for diagnosis and management of IPF were published by collaboration between the ATS, ERS, Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) in 2011. In the revised 2011 criteria, high-resolution CT (HRCT) has a central role for the diagnosis of IPF. The presence of UIP patterns on HRCT is essential and definitive in the diagnosis of IPF without the need for surgical lung biopsy (SLB). The revised 2011 criteria have emphasized the importance of multidisciplinary discussion between clinicians, radiologists, and pathologists experienced in the diagnosis of IPF.

**Keywords** Idiopathic pulmonary fibrosis (IPF) • High-resolution CT (HRCT) • ATS/ERS statement • ATS/ERS/JRS/ALAT statement

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## 1.1 Introduction

The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases of unknown etiology with varying degrees of inflammation and fibrosis [1]. In 1975, Liebow first described five pathologic subgroups of chronic idiopathic interstitial pneumonia: usual interstitial pneumonia (UIP), diffuse lesions similar to UIP with superimposed bronchiolitis obliterans (termed bronchiolitis interstitial pneumonia), desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), and giant cell pneumonia [2].

In 1998, Kazenstein and Myers revised the classification including five histopathologically distinct subgroups: UIP, DIP, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), and nonspecific interstitial pneumonia (NSIP). AIP and NSIP were introduced as IIPs [3].

In 2002, the American Thoracic Society (ATS)/European Respiratory Society (ERS) international multidisciplinary panel proposed a new classification of IIPs that are comprised of seven clinical-pathological entities such as IPF, NSIP, cryptogenic organizing pneumonia (COP), AIP, RB-ILD, DIP, and LIP [1]. The 2002 ATS/ERS statement emphasized the importance of interaction among clinicians, radiologists, and pathologists for the final diagnosis of IIPs. IPF was defined to a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause limited to the lungs and associated with a surgical lung biopsy showing a histopathologic pattern of UIP. The definitive diagnosis of IPF required histopathologic patterns of UIP on surgical lung biopsy (SLB). In the absence of SLB, a presumptive diagnosis can be made by clinical, radiologic, and physiologic criteria (four major and three minor criteria). IPF is the most common and severe form of IIPs. The prognosis of IPF has been reported to be very poor with a mean survival of 2–4 years after the initial diagnosis. Therefore, an early and accurate diagnosis of IPF is critical, especially for the management and induction of treatment to prevent disease progression [4].

In 2011, the ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) has published revised evidenced-based guidelines for diagnosis and management of IPF [5]. This chapter focuses on the definition of IPF in the revised 2011 criteria and discusses clinical application and key problems.

## 1.2 The ATS/ERS/JRS/ALAT 2011 Revised Diagnostic Criteria [5]

In the 2011 revised criteria, IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP.

The diagnosis of IPF requires:

(a) Exclusion of other causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue diseases, and drug toxicity)
(b) The presence of UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy
(c) Specific combination of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

*The major and minor criteria proposed in the 2002 ATS/ERS consensus statement have been eliminated.*

The accuracy of the diagnosis of IPF increases with multidisciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILDs.

IPF is a fatal lung disease; the natural history is variable and unpredictable. Most patients with IPF demonstrate a gradual worsening of lung function over years; a minority of patients remain stable or decline rapidly. Some patients may experience episodes of acute respiratory worsening despite previous stability.

Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death.

Patients with IPF may have subclinical or overt comorbid conditions including pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnea, obesity, and emphysema. The impact of these conditions on the outcome of patients with IPF is unclear.

The diagnostic algorithm for adult patients with suspected IPF is shown in Fig. 1.1. HRCT has an essential role in the diagnostic pathway in IPF (Fig. 1.1 and Table 1.1). UIP is characterized on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis. Honeycombing is common and critical for making a definite diagnosis of IPF. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters in the order rof 3–10 mm but occasionally as large as 25 mm. It is usually subpleural and is characterized by well-defined walls. Ground-glass opacities are common, but usually less extensive than the reticulation. The distribution of UIP on HRCT is characteristically basal and peripheral, though often patchy. The presence of coexistent pleural abnormalities (e.g., pleural plaques, calcifications, significant pleural effusion) suggests an alternative etiology for UIP pattern. Micronodules, air trapping, non-honeycomb cysts, extensive ground-glass opacities, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis. Mild mediastinal lymph node enlargement (usually $<1.5$ cm in short axis) can be seen. Possible UIP and inconsistent with UIP patterns on

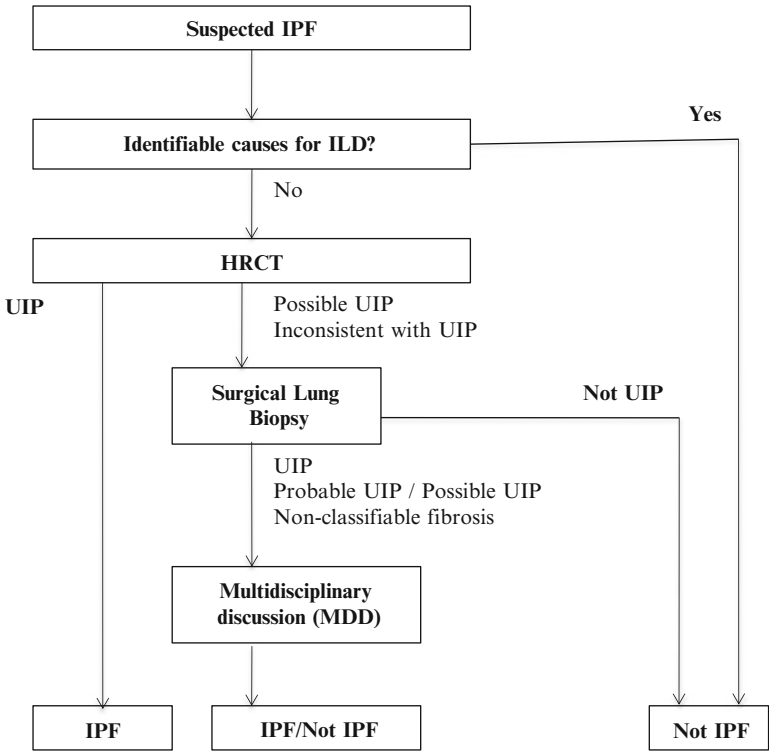


**Fig. 1.1** Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). Patients with suspected IPF should be carefully evaluated for identifiable causes of interstitial lung disease (ILD). In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathologic pattern. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion among ILD experts [5]

HRCT are presented in Table 1.1. The UIP pattern does not need to be confirmed by histopathology. In patients demonstrating radiological features that meet the criteria for "possible UIP" or "inconsistent with UIP" patterns on HRCT, SLB should be considered. Patients with a possible UIP pattern on HRCT and UIP or probable histological UIP pattern allow for the diagnosis of IPF (Table 1.2). Combinations of HRCT and SLB for the diagnosis are presented in the revised 2011 criteria (Table 1.2). The major and minor criteria for the clinical diagnosis of IPF in the 2002 ATS/ERS consensus statement have been eliminated. It is most important to make an accurate diagnosis of IPF through multidisciplinary discussion between clinicians, radiologists, and pathologists.

**Table 1.1** High-resolution computed tomography criteria for UIP pattern (2011)

| UIP pattern (all four features) | Possible UIP pattern (all three features) | Inconsistent with UIP pattern (any of the seven features) |
|---|---|---|
| Subpleural, basal predominance | Subpleural, basal predominance | Upper or mid-lung predominance |
| Reticular abnormality | Reticular abnormality | Peribronchovascular predominance |
| Honeycombing with or without traction bronchiectasis | Absence of features listed as inconsistent with UIP pattern (*see* third column) | Extensive ground-glass abnormality (extent > reticular abnormality) |
| Absence of features listed as inconsistent with UIP pattern (*see* third column) | | Profuse micronodules (bilateral, predominantly upper lobes) |
| | | Discrete cysts (multiple, bilateral, away from areas of honeycombing) |
| | | Diffuse mosaic attenuation/air trapping (bilateral, in three or more lobes) |
| | | Consolidation in bronchopulmonary segment (s)/lobe(s) |

**Table 1.2** Combination of high-resolution computed tomography and surgical lung biopsy for the diagnosis of IPF (requires multidisciplinary discussion)

| HRCT Pattern | Surgical Lung Biopsy Pattern (When Performed) | Diagnosis of IPF? |
|---|---|---|
| **UIP**<br>**Possible UIP**<br>Inconsistent with UIP | **UIP**<br>**Probable UIP**<br>**Possible UIP**<br>**Nonclassifiable fibrosis** | **YES** |
| | Not UIP | No |
| | **UIP**<br>**Probable UIP** | **YES** |
| | Possible UIP<br>Nonclassfiable fibrosis | Probable |
| | Not UIP | No |
| | UIP | Possible |
| | Probable UIP<br>Possible UIP<br>Nonclassifiable fibrosis<br>Not UIP | No |

## 1.3 Clinical Application and Key Problems

To exclude other known causes of lung fibrosis represents a key factor in the diagnostic process of IPF. Careful medical history and physical examinations focusing on comorbidities, drug use, environmental exposures, and family histories are needed. It is very important to evaluate possibilities of chronic hypersensitivity pneumonitis (CHP), because such patients might mimic IPF. Patients who met the criteria for collagen vascular disease do not have the diagnosis of IPF. Even without clinical or serologic features at presentation, clinical features of collagen vascular disease may reveal thereafter. Even though surgical lung biopsy demonstrates histopathological features of UIP, a definitive diagnosis required the exclusion of other causes of ILDs, including chronic hypersensitivity pneumonitis, collagen vascular disease, drug toxicity, asbestosis, and familial interstitial pneumonia.

The identification of honeycombing is central in the diagnosis of IPF. Several studies have documented that the positive predictive value with HRCT diagnosis of UIP is more than 90 % [5]. The accuracy of trained observers in distinguishing IPF from other ILDs is approximately 80–90 % [6]. There is substantial variation in the distinction between typical and atypical HRCT findings of IPF among less experienced observers [6]. Interobserver variation is a significant problem in the diagnostic process of IPF. If honeycombing is absent, however, other HRCT features meet the criteria for IPF, the imaging features are regarded as possible UIP, and SLB is necessary to make an accurate diagnosis. Even in patients without honeycombing on HRCT, combinations of interstitial scoring and older age (over 65) have reported to be highly predictive of the diagnosis of IPF [7]. It is necessary to establish the standardization of prognostic pathway and quality assurance for the accurate diagnosis of IPF.

## 1.4 Conclusion

The 2011 ATS/ERS/JRS/ALAT evidenced-based guidelines for IPF are major improvement from the previous 2002 ATS/ERS statements. The guidelines emphasize the importance of HRCT for the diagnosis of definite IPF. In the absence of UIP patterns on HRCT, combined radiological and pathological findings are needed. It is most important to make a final diagnosis of IPF through multidisciplinary discussion between clinicians, radiologists, and pathologists. There is a need for clinician training in integrating data from clinical, radiological, and histological examinations to achieve the accurate diagnosis of IPF.

## References

1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2002;165:277–304.
2. Liebow AA. Definition and classification of interstitial pneumonia in human pathology. Prog Respir Res. 1975;8:1–31.
3. Kazenstein AA, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157:1301–15.
4. Kim DS, Collard HR, Talmadge E, et al. Classification and natural history of the idiopathic interstitial pneumonia. Proc Am Thorac Soc. 2006;3:285–92.
5. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
6. Wells AU. Managing diagnostic procedures in idiopathic pulmonary fibrosis. Eur Respir Rev. 2013;22:158–62.
7. Fell CD, Martinez FJ, Liu LX, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2010;181:832–7.

# Chapter 2
# Epidemiology and Risk Factors of IPF

## Can We Dare to Ask, "What Are the Possible Causes?"

**Kazuyoshi Kuwano, Jun Araya, and Hiromichi Hara**

**Abstract** Idiopathic pulmonary fibrosis (IPF) is the most common disease among idiopathic interstitial pneumonias (IIPs). The prognosis of idiopathic pulmonary fibrosis (IPF) is worse than any form of other IIPs, because there are few effective treatments clinically approved. Although many risk factors are recognized, the etiologies of fibrotic lung diseases are not clear. Genetic background and environmental factors are thought to be involved in the etiological factors. There are a number of candidate genes associated with the IPF; however, precise functional significances have not been verified yet. Alveolar epithelial cells are thought to be the initial lesion of lung injury caused by environmental factors, such as smoking, inhalational agents, drugs, oxygen radicals, toxins, and viruses. There is now growing evidence that repeated injury to alveolar epithelial cells leads to apoptosis, necrosis, or senescence. Surfactant gene mutations induce endoplasmic reticulum (ER) stress response in epithelial cells, and telomere shortening induces epithelial cell apoptosis and senescence. The failure of tissue repair due to impaired homeostasis and deregulated immunological mechanisms leads to disordered epithelial-mesenchymal interactions and finally results in pulmonary fibrosis. These results may explain the increase of IPF associated with aging and also suggest the involvement of cellular senescence in the pathogenesis of IPF. Although the etiological agents or factors are various and not completely understood, the mechanisms how these etiological agents trigger fibrosis and the understanding of the mechanisms of deregulated homeostasis after initial injury may lead to the development of effective treatment strategy against IPF.

**Keywords** Idiopathic pulmonary fibrosis (IPF) • Epidemiology • Risk factors • Genetic factors

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## 2.1 Introduction

Fibrosis is closely associated with the prognosis of various lung diseases. Although many risk factors are recognized, the etiologies of fibrotic lung diseases are not clear. Idiopathic pulmonary fibrosis (IPF) is the most common disease among idiopathic interstitial pneumonias (IIPs). The prognosis of idiopathic pulmonary fibrosis (IPF) is worse than any form of other IIPs, because there are few effective treatments clinically approved. Genetic background and environmental factors are thought to be involved in the etiological factors. The presence of familial IPF suggests the genetic predisposition. Telomerase mutations induce telomere shortening. Familial IPF has been found to have telomerase mutations more frequently than sporadic IPF. However, a similar degree of telomere shortening has been found in sporadic IPF as well as familial IPF. These results may explain the increase of IPF associated with aging and also suggest the involvement of cellular senescence in the pathogenesis of IPF. Alveolar epithelial cells are thought to be the initial lesion of lung injury caused by environmental factors, such as smoking, inhalational agents, drugs, oxygen radicals, toxins, and viruses. There is now growing evidence that repeated epithelial injury is the primary site of disease. Repeated injury to alveolar epithelial cell leads to apoptosis, necrosis, or senescence. The failure of tissue repair due to impaired homeostasis and deregulated immunological mechanisms leads to disordered epithelial-mesenchymal interactions and finally results in pulmonary fibrosis. In this chapter, the etiological factors which are thought to be associated with epithelial cell injury and the pathogenesis of IPF will be described.

## 2.2 Incidence and Prevalence

Although recent studies show that the incidence and prevalence of IPF are increasing, those results vary depending on the studies, because there had been no uniform definition or diagnostic criteria for IPF and there were differences in the methods of case identification and study designs in old studies. Recent studies usually use ATS/ERS criteria, which consist of the narrow and broad case definition [1]. The narrow case definition is compatible to all major and minor ATS/ERS criteria with definite UIP pattern on HRCT scans. The broad case definition includes the patients having possible UIP pattern on CT scans in addition to those compatible with the narrow definition.

### 2.2.1 In the USA

For the incidence, Raghu et al. reported that the annual incidence of IPF was 6.8 and 16.3 per 100,000 populations with a narrow and a broad IPF definition, respectively [2]. A population-based study in New Mexico from 1997 to 2005 showed an incidence of 11 and 7/100,000 in men and women, respectively [3]. In a population-based study in Minnesota from 1997 to 2005, age- and sex-adjusted incidence among residents older than 50 years was 8.8 and 17.4 per 100,000 populations with a narrow and broad case definition, respectively [4]. This study also showed median survival for narrow criteria and broad criteria being 3.5 and 4.4 years, respectively. In summary, the incidence of IPF increased with age, and the sixth and seventh decades were the most, whereas patients less than 50 years were rare. Most of the patients were ex- or current smokers.

For the prevalence, in a population-based study in Minnesota from 1997 to 2005, age- and sex-adjusted prevalence on 2005 was 27.9 per 100,000 and 63 per 100,000 persons by narrow and broad criteria, respectively [4]. IPF prevalence in the USA differed among studies, which varied from 14 to 27.9 cases and from 42.7 to 63 cases per 100,000 using narrow and broad case definitions, respectively [5]. Concerning the IPF prevalence by age and sex, males had higher prevalence than females, and older males had higher prevalence than younger ones.

### 2.2.2 In Europe

The annual IPF incidence in European countries were 0.22 per 100,000 population in Belgium, 0.93 in 2004 in Greece, 0.94 during 1981–1990 in the Czech Republic, 2.17 in Denmark, 3.0 per 100,000 in Spain, 4.3 in Norway, and 7.94 in the UK. The IPF incidence was higher among males than females in the UK, but not in Norway [5, 6]. The IPF prevalence in European countries was 1.25 cases in Belgium per 100,000 population, 3.38 in Greece, from 6.5 to 12.1 in the Czech Republic, from 16 to 18 in Finland, and 23.4 in Norway [5, 6]. Concerning the IPF prevalence by age and sex, IPF prevalence increased with age, and there was no clear sex trend in Europe. The highest prevalence was observed in patients older than 75 years. The prevalence appeared to be lower in Europe compared to those reported in the USA [5].

### 2.2.3 In Japan

Ohno et al. reported the prevalence of IIPs was 3.44 cases per 100,000 populations in Japan. In this study, 86 % of patients with IIPs were classified as IPF. However, their survey was unable to determine the total number of IPF patients, because

milder cases were excluded [7]. Recently, Natsuizaka et al. demonstrated that the cumulative incidence and prevalence of IPF in Hokkaido prefecture of Japan were 2.23 and 10.0 per 100,000 populations, respectively. IPF incidence and prevalence were higher in males than females. The highest incidence was observed at 70–79 and 60–69 years old groups in males (14.05 per 100000 population) and females (3.41), respectively. The highest prevalence was found at 60–69 years old both in males (44.44) and females (13.65) [8]. The results of Natsuizaka et al.'s study probably reflect the incidence and prevalence of IPF in all Japanese populations.

## 2.3 Potential Risk Factors

The etiology of IPF remains poorly understood. However, it is likely that inhalational agents are the prominent risk factor. The interaction between genetic predisposition and abnormal epithelial cell reaction against environmental triggers induces epithelial cell damage and fibrosis. Epithelial cell damage is accelerated by repeated and persistent injury. Potential risk factors of developing IPF are addressed below.

### *2.3.1 Smoking*

Alveolar epithelial cells are the primary target of initial injury in the pathogenesis of IPF. Inhaled agents are candidates for the initiating agents for epithelial cell damage. Meta-analysis from five case-control studies showed that ever smoking is the consistent risk factor in IPF ($OR = 1.58$), as well as other risk factors such as agriculture/farming (odds ratio, $OR = 1.65$), livestock ($OR = 2.17$), wood dust ($OR = 1.94$), metal dust ($OR = 2.44$), and stone/sand ($OR = 1.97$) [9]. Smoking is not only one of the risk factors for IPF but also affects IPF patient's survival. Interestingly, King Jr et al. demonstrated that current smokers have a longer survival than former smokers [10]. Concerning this issue, Antoniou et al. reported that survival and severity-adjusted survival are higher in nonsmokers than in former smokers or current smokers. They suggested that a better outcome in current smokers compared with former smokers in King's study may represent a healthy smoker effect [11].

Although the mechanism how smoking contributes to the pathogenesis of IPF is largely unknown, increased oxidative stress by smoking may induce the development of IPF. Cigarette smoke contains particles containing numerous toxic chemicals and reactive oxygen species. Because the incidence and prevalence of IPF are increased with aging, the development of IPF induced by smoking may be dependent on age [12]. Aging and oxidant/antioxidant imbalance may be associated with each other. We recently reported that cellular senescence was predominantly found in metaplastic epithelial cells and overlaying epithelial cells on fibroblastic

foci in lung tissues from patients with IPF [13]. We demonstrated that cigarette smoking extract or TGF-β induced cellular senescence in bronchial epithelial cells in vitro. We also showed that supernatant of senescent epithelial cells induced differentiation from lung fibroblast to myofibroblast in vitro [14]. We hypothesized that several factors such as smoking, reactive oxygen species, TNF-α, Fas ligand, and TGF-β induced epithelial cell apoptosis or necrosis. When some of epithelial cells are resistant to cell death, those cells are induced to senescence. Smoking contains so much kind of stimuli to lung cells, and downstream signaling pathways and responses to smoking are diverse and different on various types of cells in IPF. The effects of smoking on lung cell fate should be intensively addressed.

### *2.3.2 Inhalational Exposures*

As well as smoking, several other environmental exposures have been reported to be associated with increased risk for IPF. A meta-analysis indicated that exposure to burning stoves, birch dust, hardwood dust, livestock, sand, stone, silica, and vegetable dust/animal dust is associated with IPF [9]. Kitamura et al. show that the number of inorganic particles, such as Si and Al, was increased in the hilar lymph nodes in autopsy samples from patients with IPF. They suggested that inorganic particles may play a role in the pathogenesis of IPF [15].

### *2.3.3 Viral Infection*

Viral infection has been investigated as one of the candidates for the etiology and the pathophysiology of IPF. Epstein-Barr virus (EBV), herpes simplex virus, cytomegalovirus (CMV), human herpesviruses (HHVs) 7 and 8, hepatitis C virus, and parvovirus B19 were implicated as causative agents [16]. However, it is difficult to conclude that the viral infections are the etiological agents of IPF, because the sensitivity and specificity of identification methods are variable among studies. Furthermore, it is not clear whether the presence of viruses really reflects the true etiological agents or merely reflects an increased susceptibility to infection in IPF.

### *2.3.4 Herpesviruses*

The herpesviruses, in particular EBV, have been intensively investigated. The DNA of EBV, CMV, HHV-7, or HHV-8 was found to be present in 97 % of lung tissues from patients with IPF while in 36 % of control lung tissues [17], although there were negative studies showing that there is no herpesvirus DNA in any of the lung

tissues from patients with IPF and control lung tissues [18, 19]. Tang et al. reported that EBV DNA was detected by real-time PCR in 5 of 8 familial IPF cases (62.5 %) and in 16 of 25 sporadic cases of IPF (64 %) [20]. In other studies, EBV protein and DNA were detected in lung tissue, usually in the alveolar epithelial cells, by immunohistochemistry and PCR in 40–60 % of IPF, whereas in 0–4 % of control patients [21, 22]. EBV genome rearrangement associated with productive EBV replication was found in 11 of 18 EBV-positive IPF biopsies [23]. Furthermore, lytic replication of EBV, as indicated by the presence of the lytic cycle antigens pg340/220 and viral capsid antigen, has been found to localize to alveolar epithelial cells in lung specimens from patients with IPF more frequently than controls [22, 23]. Latent membrane protein 1 (LMP1) which is expressed by EBV-infected cells and a marker of latent and lytic phases was detected in 9 of 29 patients, but none of 14 controls. LMP1 expression was associated with the respiratory failure due to the progression of IPF, although the number of patients was small [24].

Recently, Kropski et al. investigated viral load in BAL fluid from normal controls, at-risk subjects, and IPF patients. They found that at-risk subjects and IPF patients had elevated herpesvirus load in BAL fluid, although inflammatory cell populations were similar among groups. They also showed that EBV and CMV antigens were frequently detectable by immunohistochemistry in type II alveolar epithelial cells obtained by transbronchial biopsy from at-risk subjects, but uncommon in lung tissues from normal subjects [25].

Endoplasmic reticulum stress (ER stress) has been demonstrated to be involved in the pathophysiology of IPF through inducing epithelial cell apoptosis and/or senescence [26, 27]. Lawson et al. reported that ER stress markers were commonly found in alveolar epithelial cells and were associated with the presence of herpesvirus antigens [28]. Kropski et al. suggested that increased copy numbers of EBV and CMV DNA in BAL fluid from at-risk subjects may reflect viral replication and that enhanced herpesvirus replication in epithelial cells may be an important source of ER stress in early stage of IPF [25].

### *2.3.5 Hepatitis C Virus*

Variable results have been reported in hepatitis C. Ueda et al. demonstrated that serum antibodies to hepatitis C virus were detected in 19 of 66 patients (28.8 %) with IPF by an enzyme-linked immunosorbent assay, which was significantly higher than those in 9,464 control subjects (3.66 %) [29]. In contrast, Irving et al. showed that HCV infection was no more prevalent in patients with IPF than in the general population in the UK [30]. Meliconi et al. showed an increased prevalence (approximately 13 %) of HCV infection and viral replication in patients with IPF, but the prevalence of anti-HCV antibodies does not differ between IPF patients and patients with other lung diseases in Italy [31]. More recently, Arase et al. showed that 15 patients among more than 6,000 patients with HCV infection developed IPF during an 8-year follow up, whereas none of more than 2,000

patients with HBV infection developed IPF during a 6-year follow-up [32]. They also reported that the IPF development rate in patients with HCV infection was significantly higher in patients older than 55 years, in patients who had smoking index more than 20 pack-years, and in patients with liver cirrhosis.

### 2.3.6 Gastroesophageal Reflux

Gastroesophageal reflux (GER)-associated erosive esophagitis has been reported to link with a number of respiratory diseases including IPF. El-Serag et al. demonstrated that erosive esophagitis and esophageal stricture were associated with chronic bronchitis ($OR = 1.28$), asthma (1.51), COPD (1.22), pulmonary fibrosis (1.36), bronchiectasis (1.26), and pneumonia (1.15) in 101,366 subjects [33]. Repeated and chronic micro aspiration has been considered to contribute to the repeated injury of the lung, which leads to the development of IPF. Tobin et al. showed that patients with IPF have a high prevalence of increased esophageal acid exposure without typical GER symptoms [34]. Systemic sclerosis patients with ILD have more severe and more proximal reflux episodes compared to those without ILD [35]. Raghu et al. also showed that the prevalence of abnormal acid GER in IPF patients was 87 % and significantly more common than that in patients with asthma. They also showed that abnormal GER is often clinically occult in patients with IPF [36]. D'Ovidio et al. reported that GER is highly prevalent in patients with end-stage lung disease who are candidates for lung transplantation [37]. In animal models, instilled gastric acid can spread to lung periphery and induce lung injury, which results in pulmonary fibrosis. Occult aspiration of gastric contents has been proposed as one of the possible mechanisms leading to acute exacerbations of IPF. Lee et al. demonstrated that pepsin levels in BAL fluid appeared higher in patients with acute exacerbations compared with stable controls [38]. They suggested that occult aspiration may play a role in some cases of acute exacerbation of IPF. Interestingly, Tcherakian et al. have shown that the rate of GER was significantly higher in patients with asymmetrical IPF (62.5 %) than symmetrical IPF (31.3 %) and that acute exacerbations occurred more frequently in asymmetrical IPF (46.9 %) than in symmetrical IPF (17.2 %). They concluded that GER may be responsible for both disease expansion and the occurrence of acute exacerbations [39].

### 2.3.7 Diabetes Mellitus

Enomoto et al. firstly reported the association between type II diabetes and IPF. They showed that the adjusted OR of diabetes for IPF was 4.06, although the presence of DM did not affect the clinical characteristics of IPF [40]. García-Sancho Figueroa et al. showed that type II diabetes mellitus was an independent

risk factor for IPF (11.3 % in IPF patients vs. 2.9 % in controls; $OR = 4.3$) [41]. Gribbin et al. also reported that the use of insulin increased the risk for IPF ($OR = 2.36$) [42].

We previously found that insufficient autophagy was a potent underlying pathology of both accelerated cellular senescence in epithelial cells and myofibroblast differentiation in a cell-type-specific manner and is a promising clue for understanding the molecular mechanisms of IPF [43]. We also demonstrated that excessive IGF-1 signaling may be involved in the CSE-induced epithelial cell senescence. We speculate that type II diabetes mellitus with hyperinsulinemia may be associated with increased IGF-1/insulin signaling and reduced autophagy, resulting in acceleration of cellular senescence [44].

## 2.4 Genetic Factors

### *2.4.1 Familial Interstitial Pneumonia (FIP)*

A significant number of patients with IPF have a familial form of interstitial pneumonia. In fact, it has been reported that family history of pulmonary fibrosis was strongly associated with increased risk of IPF ($OR = 6.1$) compared to gastroesophageal reflux ($OR = 2.9$), former cigarette smoking ($OR = 2.5$), and past or current occupational exposure to dusts or smokes ($OR = 2.8$) [45]. It is difficult to distinguish between familial and sporadic IPF by the clinical, radiologic, and pathologic characteristics, although familial IPF tends to occur at younger than sporadic IPF (61.9 vs. 65.3 years old) [46]. An official ATS/ERS/JRS/ALAT statement described that many studies of apparent "familial IPF" actually included familial pulmonary fibrosis, because at least half of them include NSIP, COP, and unclassified ILD [47]. Therefore, we describe them as familial interstitial pneumonia (FIP) instead of familial IPF according to an official ATS/ERS statement in 2013 [48]. Different histological forms of interstitial pneumonia (FIP) are present within the same family. Familial predisposition to interstitial pneumonia and individual susceptibilities may determine the type of interstitial pneumonia. FIP is present at approximately 20 % of patients with idiopathic interstitial pneumonias (IIPs) [45, 49].

Recently, Kropski et al. examined the phenotype of individuals at risk for FIP compared to FIP and IPF to investigate the pathogenesis of early stages of FIP. In the results, 11 of 75 at-risk subjects (14 %) had interstitial changes on HRCT, while 35.2 % of at-risk subjects had abnormalities on transbronchial biopsies [25]. They also found that herpesvirus DNA in BAL fluid was increased in at-risk subjects and that herpesvirus antigen was detected in alveolar epithelial cells, which was correlated with the protein expression specific for ER stress. They also reported that telomere length of peripheral blood mononuclear cells and alveolar epithelial cells was shorter in at-risk subjects than in healthy controls. Levels of several plasma

biomarkers, such as MMP-7, SP-D, TIMP2, and EF-1, in at-risk subjects were correlated with abnormal HRCT scans. These results suggest that the susceptibility to telomere shortening, viral infection, and abnormal responses of epithelial cells including deregulated ER stress was present in asymptomatic individuals at risk for FIP, which leads to epithelial dysfunction and lung parenchymal remodeling.

### 2.4.2 *ELMOD2*

Recent GWAS analysis demonstrated that *ELMOD2*, a gene located on chromosome 4q31, may be a candidate gene for IPF. ELMOD2 is essential for phagocytosis of apoptotic cells, cell migration, and interferon-related antiviral responses [50]. ELMOD2 is expressed by lung epithelial cells and alveolar macrophages. Epithelial cells and alveolar macrophages are the predominant targets of infection by respiratory viruses. ELMOD2 mRNA expression is significantly decreased in lung tissues from patients with IPF compared with those from control lungs [51]. Interaction of host and viruses may trigger the epithelial cell damage and fibrogenesis, in which ELMOD2 deficiency may play some roles.

### 2.4.3 *Surfactant Protein*

Recently, current genetic analysis of IIPs has revealed at least a part of the pathogenesis of FIP and sporadic IPF. Mutations in surfactant proteins C (*SFTPC*) [52] and A2 (*SFTPA2*) [53] have been identified in 10–15 % of FIP. Mutations in the surfactant protein C gene were found to be associated with FIP, but not with sporadic IPF [54]. Phenotype of SP-C mutations also includes nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), and pulmonary alveolar proteinosis in adults [55]. SP-C mutations are frequently found in children with severe idiopathic pneumonias [56]. Mutations in SP-C resulted in the accumulation of premature pro-SP-C protein in type II alveolar epithelial cells. Immunohistochemistry results showed aberrant subcellular localization of pro-SP-C protein in type II cells. Electron microscopic findings showed alveolar type II cell atypia with numerous abnormal lamellar bodies [55]. Although these mutations have not been found in sporadic IPF, specific protein expressions induced by ER stress were detected in epithelial cells from patients with sporadic IPF [57]. Therefore, epithelial cell damage, including ER stress, and epithelial cell apoptosis are common mechanisms of pulmonary fibrosis. SP-A and SP-C gene mutations in the alveolar epithelium as well as *hTERT* and *hTERC* mutations affect ER stress, cellular senescence, and apoptosis, which lead to abnormal homeostasis of the alveolar epithelium.

### 2.4.4 Telomerase

Telomeres protect chromosome ends from erosion and shorten with each cell division, and once a critical length is reached, cells were induced to cellular senescence and ultimately apoptosis. Telomerase restores telomere length, which consists of two essential components, telomerase reverse transcriptase (TERT) and telomerase RNA (TERC). Loss-of-function mutations in TERT have been found in 15 % of FIP and in 3 % of sporadic IPF [58, 59]. These patients showed significantly shorter telomeres length in peripheral blood lymphocytes and granulocytes. In sporadic IPF, these mutations are less common; however, telomere shortening is similar to those of FIP in peripheral blood leukocytes and alveolar epithelial cells compared with those of healthy controls.

Recently, nine nucleotide polymorphisms including *TERT* gene were identified to be associated with IPF susceptibility in Japanese patients [60]. Telomere attrition is induced by oxidative stress, smoking, as well as aging. These are risk factors which have been implicated to have a role in the pathogenesis of IPF. TGF-β plays central roles in fibrogenesis and is highly expressed in lung tissues of IPF. TGF-β suppresses telomerase expression and may affect telomere shortening. Weisberg et al. demonstrated that the decrease of telomerase expression correlated with type II alveolar epithelial cell apoptosis in IPF lungs [61]. They suggested that low ratio of telomerase/apoptosis may reduce regenerative capacity in injured lungs, which subsequently results in fibrosis.

### 2.4.5 MUC5B

Seibold et al. demonstrated that a common polymorphism in the promoter of MUC5B has been found to be associated with the development of FIP and IPF [62]. They also showed that MUC5B expression in the lung was much higher in lung tissues from patients with IPF compared to normal lung tissues. Therefore, they suggested that deregulated MUC5B expression may be involved in the pathogenesis of pulmonary fibrosis, although it is not clear how MUC5B hyperexpression associates with IPF pathogenesis. Interestingly, Kropski et al. [25] also demonstrated that MUC5B promoter polymorphism was increased in asymptomatic relatives of patients with FIP (at-risk subjects) compared to controls and that MUC5B protein levels of BAL fluids were higher in at-risk patients than controls. Recently, Molyneaux et al. showed that the bacterial burden in BAL fluid from patients with IPF was increased compared with controls and associated with the polymorphisms of MUC5B gene [63]. MUC5B expression is seen in bronchial epithelial cells; therefore, how the airway abnormality leads to lung fibrosis is an attractive issue to investigate.

## 2.5 Conclusions

Besides genetic factors described above, there are a number of candidate genes associated with the IPF. Polymorphisms of genes such as cytokines, enzymes, profibrotic genes, and coagulation pathway genes and HLA class I and II allele haplotypes have been reported to be associated with IPF [47]. However, the significance of these results has not been verified in subsequent studies. Epidemiologically, males had higher prevalence than females, and older males had higher prevalence than younger males in IPF. Inhalational agents are the prominent risk factor for IPF. Although many inhalational agents were thought to induce epithelial injury, the repeated and prolonged injury is responsible for the initiation of fibrotic processes. The association between genetic predisposition and abnormal epithelial cell responses against environmental triggers may induce pulmonary fibrosis. Smoking contains numerous toxic contents, and the significance of downstream signaling pathways and responses is dependent on various stimuli and on various types of cells in IPF. The role of viral infection has been investigated as one of the candidates for the etiology of pulmonary fibrosis, the trigger of acute exacerbation, or the cause of disease progression. GER has been reported to link with a number of respiratory diseases including IPF. The failure of tissue repair due to impaired

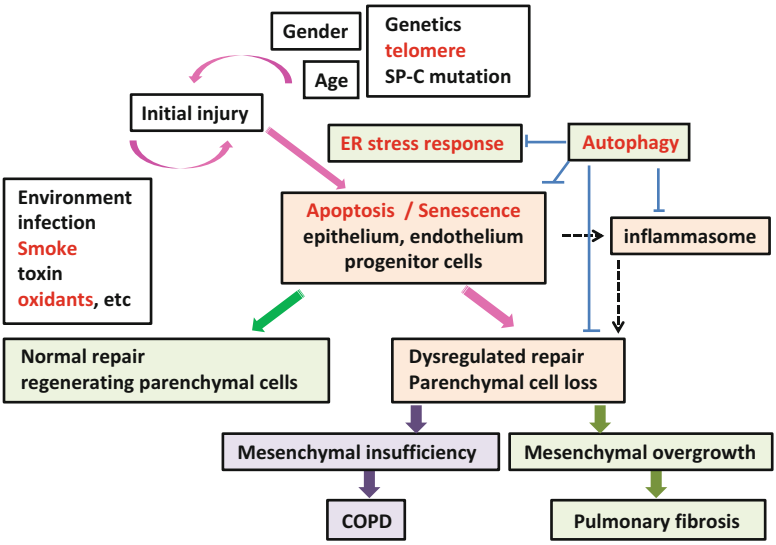


**Fig. 2.1** Alveolar epithelial cells are thought to be the initial lesion of lung injury caused by environmental factors, such as smoking, inhalational agents, drugs, oxygen radicals, toxins, and viruses, and intrinsic factors such as genetics and aging. Repeated epithelial injury leads to apoptosis, necrosis, and/or senescence. Surfactant gene mutations induce ER stress response in epithelial cells, and telomere shortening induces epithelial cell apoptosis and senescence. The failure of tissue repair due to impaired homeostasis and deregulated immunological mechanisms leads to disordered epithelial-mesenchymal interactions and finally results in pulmonary fibrosis

homeostasis and deregulated immunological mechanisms leads to disordered epithelial-mesenchymal interactions and finally results in pulmonary fibrosis. Although the etiological agents or factors are various and not completely understood, the understanding of the mechanisms of deregulated homeostasis may lead to the development of effective treatment strategy against IPF (Fig. 2.1).

## References


1. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
2. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174:810–16.
3. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994;150:967–72.
4. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010;137:129–37. doi:10.1378/chest.09-1002.
5. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012;21:355–61. doi:10.1183/09059180.00002512.
6. Borchers AT, Chang C, Keen CL, Gershwin ME. Idiopathic pulmonary fibrosis-an epidemiological and pathological review. Clin Rev Allergy Immunol. 2011;40(2):117–34. doi:10.1007/s12016-010-8211-5.
7. Ohno S, Nakaya T, Bando M, Sugiyama Y. Nationwide epidemiological survey of patients with idiopathic interstitial pneumonias using clinical personal records. Nihon Kokyuki Gakkai Zasshi. 2007;45:759–65.
8. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190:773–9. doi:10.1164/rccm.201403-0566OC.
9. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc. 2006;3(4):293–8.
10. King Jr TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164:1171–81.
11. Antoniou KM, Hansell DM, Rubens MB, Marten K, Desai SR, Siafakas NM, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. Am J Respir Crit Care Med. 2008;177:190–4.
12. Selman M, Rojas M, Mora AL, Pardo A. Aging and interstitial lung diseases: unraveling an old forgotten player in the pathogenesis of lung fibrosis. Semin Respir Crit Care Med. 2010;31:607–17. doi:10.1055/s-0030-1265901.
13. Minagawa S, Araya J, Numata T, Nojiri S, Hara H, Yumino Y, et al. Accelerated epithelial cell senescence in IPF and the inhibitory role of SIRT6 in TGF-β-induced senescence of human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2011;300:L391–401. doi:10.1152/ajplung.00097.2010.
14. Hara H, Araya J, Takasaka N, Fujii S, Kojima J, Yumino Y, et al. Involvement of creatine kinase B in cigarette smoke-induced bronchial epithelial cell senescence. Am J Respir Cell Mol Biol. 2012;46:306–12. doi:10.1165/rcmb.2011-0214OC.

15. Kitamura H, Ichinose S, Hosoya T, Ando T, Ikushima S, Oritsu M, et al. Inhalation of inorganic particles as a risk factor for idiopathic pulmonary fibrosis–elemental microanalysis of pulmonary lymph nodes obtained at autopsy cases. Pathol Res Pract. 2007;203:575–85.
16. Wuyts WA, Agostini C, Antoniou KM, Bouros D, Chambers RC, Cottin V, et al. The pathogenesis of pulmonary fibrosis: a moving target. Eur Respir J. 2013;41:1207–18. doi:10.1183/09031936.00073012.
17. Borchers AT, Chang C, Keen CL, Gershwin ME. Idiopathic pulmonary fibrosis-an epidemiological and pathological review. Clin Rev Allergy Immunol. 2011;40:117–34. doi:10.1007/s12016-010-8211-5.
18. Wangoo A, Shaw RJ, Diss TC, Farrell PJ, du Bois RM, Nicholson AG. Cryptogenic fibrosing alveolitis: lack of association with Epstein-Barr virus infection. Thorax. 1997;52:888–91.
19. Zamò A, Poletti V, Reghellin D, Montagna L, Pedron S, Piccoli P, et al. HHV-8 and EBV are not commonly found in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22:123–8.
20. Tang YW, Johnson JE, Browning PJ, Cruz-Gervis RA, Davis A, Graham BS, et al. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol. 2003;41:2633–40.
21. Egan JJ, Stewart JP, Hasleton PS, Arrand JR, Carroll KB, Woodcock AA. Epstein-Barr virus replication within pulmonary epithelial cells in cryptogenic fibrosing alveolitis. Thorax. 1995;50:1234–9.
22. Stewart JP, Egan JJ, Ross AJ, Kelly BG, Lok SS, Hasleton PS, et al. The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1999;159(4 Pt 1):1336–41.
23. Kelly BG, Lok SS, Hasleton PS, Egan JJ, Stewart JP. A rearranged form of Epstein-Barr virus DNA is associated with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2002;166:510–13.
24. Tsukamoto K, Hayakawa H, Sato A, Chida K, Nakamura H, Miura K. Involvement of Epstein-Barr virus latent membrane protein 1 in disease progression in patients with idiopathic pulmonary fibrosis. Thorax. 2000;55:958–61.
25. Kropski JA, Pritchett JM, Zoz DF, Crossno PF, Markin C, Garnett ET, et al. Extensive phenotyping of individuals at-risk for familial interstitial pneumonia reveals clues to the pathogenesis of interstitial lung disease. Am J Respir Crit Care Med. 2015;191(4):417–26. doi:10.1164/rccm.201406-1162OC.
26. Korfei M, Ruppert C, Mahavadi P, Henneke I, Markart P, Koch M, et al. Epithelial endoplasmic reticulum stress and apoptosis in sporadic idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178:838–46. doi:10.1164/rccm.200802-313OC.
27. Araya J, Kojima J, Takasaka N, Ito S, Fujii S, Hara H, et al. Insufficient autophagy in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2013;304:L56–69. doi:10.1152/ajplung.00213.2012.
28. Lawson WE, Crossno PF, Polosukhin VV, Roldan J, Cheng DS, Lane KB, et al. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol. 2008;294:L1119–26. doi:10.1152/ajplung.00382.2007.
29. Ueda T, Ohta K, Suzuki N, Yamaguchi M, Hirai K, Horiuchi T, et al. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. Am Rev Respir Dis. 1992;146:266–8.
30. Irving WL, Day S, Johnston ID. Idiopathic pulmonary fibrosis and hepatitis C virus infection. Am Rev Respir Dis. 1993;148:1683–4.
31. Meliconi R, Andreone P, Fasano L, Galli S, Pacilli A, Miniero R, et al. Incidence of hepatitis C virus infection in Italian patients with idiopathic pulmonary fibrosis. Thorax. 1996;51:315–17.
32. Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. Hepatitis C virus enhances incidence of idiopathic pulmonary fibrosis. World J Gastroenterol. 2008;14:5880–6.

33. El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology. 1997;113:755–60.
34. Tobin RW, Pope 2nd CE, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased pre valence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158:1804–8.
35. Savarino E, Bazzica M, Zentilin P, Pohl D, Parodi A, Cittadini G, et al. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. Am J Respir Crit Care Med. 2009;179:408–13. doi:10.1164/rccm.200808-1359OC.
36. Raghu G, Freudenberger TD, Yang S, Curtis JR, Spada C, Hayes J, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27(1):136–42.
37. Pashinsky YY, Jaffin BW, Litle VR. Gastroesophageal reflux disease and idiopathic pulmonary fibrosis. Mt Sinai J Med. 2009;76:24–9. doi:10.1002/msj.20088.
38. Lee JS, Song JW, Wolters PJ, Elicker BM, King Jr TE, Kim DS, et al. Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. Eur Respir J. 2012;39:352–8. doi:10.1183/09031936.00050911.
39. Tcherakian C, Cottin V, Brillet PY, Freynet O, Naggara N, Carton Z, et al. Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. Thorax. 2011;66:226–31. doi:10.1136/thx.2010.137190.
40. Enomoto T, Usuki J, Azuma A, Nakagawa T, Kudoh S. Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis. Chest. 2003;123:2007–11.
41. García-Sancho Figueroa MC, Carrillo G, Pérez-Padilla R, Fernández-Plata MR, Buendía-Roldán I, Vargas MH, et al. Risk factors for idiopathic pulmonary fibrosis in a Mexican population. A case–control study. Respir Med. 2010;104:305–9. doi:10.1016/j.rmed.2009.08.013.
42. Gribbin J, Hubbard R, Smith C. Role of diabetes mellitus and gastro-oesophageal reflux in the aetiology of idiopathic pulmonary fibrosis. Respir Med. 2009;103:927–31. doi:10.1016/j.rmed.2008.11.001.
43. Araya J, Kojima J, Takasaka N, Ito S, Fujii S, Hara H, et al. Insufficient autophagy in idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol. 2013;304:L56–69. doi:10.1152/ajplung.00213.2012.
44. Takasaka N, Araya J, Hara H, Ito S, Kobayashi K, Kurita Y, et al. Autophagy induction by SIRT6 through attenuation of insulin-like growth factor signaling is involved in the regulation of human bronchial epithelial cell senescence. J Immunol. 2014;192:958–68. doi:10.4049/jimmunol.1302341.
45. García-Sancho C, Buendía-Roldán I, Fernández-Plata MR, Navarro C, Pérez-Padilla R, Vargas MH, et al. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. Respir Med. 2011;105:1902–7. doi:10.1016/j.rmed.2011.08.022.
46. Marshall RP, Puddicombe A, Cookson WO, Laurent GJ. Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. Thorax. 2000;55:143–6.
47. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824. doi:10.1164/rccm.2009-040GL.
48. Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48. doi:10.1164/rccm.201308-1483ST.
49. Loyd JE. Pulmonary fibrosis in families. Am J Respir Cell Mol Biol. 2003;29:S47–50.
50. Hodgson U, Pulkkinen V, Dixon M, Peyrard-Janvid M, Rehn M, Lahermo P, et al. ELMOD2 is a candidate gene for familial idiopathic pulmonary fibrosis. Am J Hum Genet. 2006;79:149–54.

51. Pulkkinen V, Bruce S, Rintahaka J, Hodgson U, Laitinen T, Alenius H, et al. ELMOD2, a candidate gene for idiopathic pulmonary fibrosis, regulates antiviral responses. FASEB J. 2010;24:1167–77. doi:10.1096/fj.09-138545.
52. Nogee LM, Dunbar 3rd AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344:573–9.
53. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009;84:52–9. doi:10.1016/j.ajhg.2008.11.010.
54. Nogee LM, Dunbar 3rd AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344(8):573–9.
55. Thomas AQ, Lane K, Phillips 3rd J, Prince M, Markin C, Speer M, et al. Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med. 2002;165:1322–8.
56. Selman M, Lin HM, Montaño M, Jenkins AL, Estrada A, Lin Z, et al. Surfactant protein A and B genetic variants predispose to idiopathic pulmonary fibrosis. Hum Genet. 2003;113:542–50.
57. Lawson WE, Cheng DS, Degryse AL, Tanjore H, Polosukhin VV, Xu XC, et al. Endoplasmic reticulum stress enhances fibrotic remodeling in the lungs. Proc Natl Acad Sci U S A. 2011;108:10562–7. doi:10.1073/pnas.1107559108.
58. Cronkhite JT, Xing C, Raghu G, Chin KM, Torres F, Rosenblatt RL, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178:729–37. doi:10.1164/rccm.200804-550OC.
59. Alder JK, Chen JJ, Lancaster L, Danoff S, Su SC, Cogan JD, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A. 2008;105:13051–6. doi:10.1073/pnas.0804280105.
60. Mushiroda T, Wattanapokayakit S, Takahashi A, Nukiwa T, Kudoh S, Ogura T, et al. A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. J Med Genet. 2008;45:654–6. doi:10.1136/jmg.2008.057356.
61. Waisberg DR, Barbas-Filho JV, Parra ER, Fernezlian S, de Carvalho CR, Kairalla RA, et al. Abnormal expression of telomerase/apoptosis limits type II alveolar epithelial cell replication in the early remodeling of usual interstitial pneumonia/idiopathic pulmonary fibrosis. Hum Pathol. 2010;41:385–91. doi:10.1016/j.humpath.2009.08.019.
62. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364:1503–12. doi:10.1056/NEJMoa1013660.
63. Molyneaux PL, Cox MJ, Willis-Owen SA, Mallia P, Russell KE, Russell AM, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190:906–13. doi:10.1164/rccm.201403-0541OC.

# Chapter 3
# Acute Exacerbation of IPF

## The Concept Was Proposed in Japan, But Why Was It Not Recognized in Western Countries?

**Yoshiki Ishii**

**Abstract** Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrosing disease. Acute exacerbation of IPF (AE-IPF) is an abrupt and rapid deterioration by unidentifiable causes which occurs during chronic clinical course of IPF. The estimated incidence is 5–15 % per year in IPF patients. Moreover, AE-IPF is not only associated with a very high mortality rate (over 70 %), but it is also an important determinant of overall prognosis in patients with IPF. Pathologically, AE-IPF is characterized by acute diffuse alveolar damage (DAD) lesion that develops close to the chronic progressive usual interstitial pneumonia (UIP) lesion. Because DAD is also a common pathological feature observed in acute respiratory distress syndrome (ARDS), acute interstitial pneumonia (AIP), and AE-IPF, it is possible to regard AE-IPF as ARDS developed due to IPF. Although the trigger factors for AE-IPF are often unclear, sometimes the triggers such as surgery, corticosteroid dose reduction, or viral infection are evident. Evidence-based and effective therapies are lacking for AE-IPF, with the current management guidelines recommending only supportive care and corticosteroid use. Novel treatments for AE-IPF that have been investigated in small-scale studies, including the use of polymyxin B-immobilized fiber column (PMX) hemoperfusion, may be promising. When AE with DAD pathology develops once, treatment is extremely difficult; therefore, development of effective prevention methods is required. To this date, there is emerging evidence from clinical trials of investigational treatments for chronic phase of IPF which may reduce the incidence of AE-IPF.

**Keywords** Idiopathic pulmonary fibrosis • Acute exacerbation • Diffuse alveolar damage • Trigger factor • Pulse therapy

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## 3.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrosing disease. It has a poor prognosis, with a median survival period of approximately 3 years from the time of diagnosis [1, 2]. The typical natural history of IPF is the slow progression of the disease that eventually leads to respiratory failure and death. In some cases of IPF, abrupt and rapid deteriorations that have no identifiable cause occur during the chronic clinical course (Fig. 3.1). In Japan, clinical case reports of an acute exacerbation of IPF (AE-IPF) appeared from the 1970s, and the concept of AEX-IPF has since become widely recognized by pulmonologists. In1984, Yoshimura et al. [3] reported a clinical study of 35 cases, while Kondo et al. [4] published the first literature on AE of IPF in English in 1989, followed by Kondoh et al. [5] in 1993. In contrast, this concept was not accepted in Europe and America for a long time. This may have been for the following reasons: (1) The acute worsening was interpreted as a part of the natural progress of IPF, and (2) it was not easy to distinguish it from other conditions with similar presentations such as pneumonia, pulmonary emboli, or cardiac failure. Nevertheless, the concept of AE-IPF was first described in the American Thoracic Society/European Respiratory Society (ATS/ERS) International Multidisciplinary Consensus Classification in 2001 [6], and it has since been recognized worldwide [7–10]. When AE-IPF develops, not only it is associated with a very high mortality rate, but it is also an important determinant of overall prognosis in patients with IPF [11].

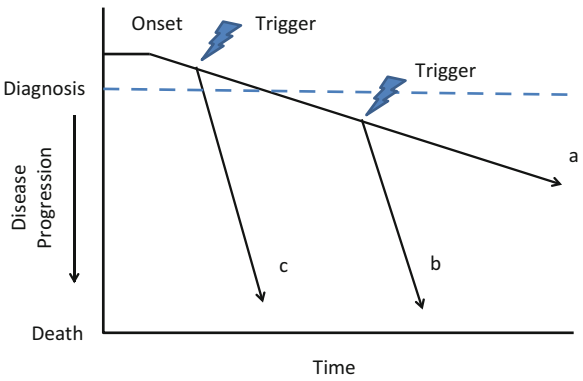


**Fig. 3.1** Clinical disease courses in patients with IPF. The typical natural history of IPF is the slow progression of the disease with a median survival period of approximately 3 years from the time of diagnosis (*a*). In some cases of IPF, abrupt and rapid deteriorations, triggered by unidentifiable causes or obvious causes, occur during the chronic clinical course (*b*). The deterioration is termed an acute exacerbation of IPF (AE-IPF). AE-IPF can occur even before diagnosis of IPF (*c*)

## 3.2 Definition

Diagnostic criteria were first established in 1995 and later revised in 2004 by The Study Group on Diffuse Pulmonary Disorders, Scientific Research/Refractory Disease-Overcoming Research Business, Japan Ministry of Health, Labor and Welfare. According to these criteria, diagnosis requires the following: (1) progressive dyspnea over 1 month or less, (2) new pulmonary infiltrates seen on a high-resolution computed tomography (HRCT) scan with evidence of underlying usual interstitial pneumonia (UIP), (3) worsening hypoxemia (i.e., a fall in $PaO_2$ of $>10$ mmHg), and (4) the absence of an underlying cause such as pulmonary infection, pneumothorax, malignancy, pulmonary embolism, and cardiac failure. A study group in the United States reported a similar definition in 2007 [10] (Table 3.1), which includes an item to exclude pulmonary infection by endotracheal aspirate or bronchoalveolar lavage (BAL) to this criterion. Although the presence of overt infection is considered to be an exclusion criterion, occult infection could be a trigger factor for AE-IPF. In fact, bacterial and viral pneumonias are often seen in patients with AE-IPF and may be the trigger factor. Therefore, although it is important to exclude simple pulmonary infection from AE-IPF, the existence of infection should not preclude the diagnosis of an AE [12].

**Table 3.1** Diagnosis of acute exacerbation

| Diagnostic criteria |
|---|
| Previous or concurrent diagnosis of idiopathic pulmonary fibrosis[a] |
| Unexplained worsening or development of dyspnea within 30 days |
| High-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern[b] |
| No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage[c] |
| Exclusion of alternative causes, including the following: |
| Left heart failure |
| Pulmonary embolism |
| Identifiable cause of acute lung injury[d] |

Patients with idiopathic clinical worsening who fail to meet all five criteria due to missing data should be termed "suspected acute exacerbations"

[a]If the diagnosis of idiopathic pulmonary fibrosis is not previously established according to the American Thoracic Society/European Respiratory Society consensus criteria, this criterion can be met by the presence of radiologic and/or histopathologic changes consistent with usual interstitial pneumonia pattern on the current evaluation

[b]If no previous high-resolution computed tomography is available, the qualifier "new" can be dropped

[c]Evaluation of samples should include studies for routine bacterial organisms, opportunistic pathogens, and common viral pathogens

[d]Causes of acute lung injury include sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation (Adapted from Ref. [10])

In AE-IPF without a prior diagnosis of IPF, differentiation from acute interstitial pneumonia (AIP) represents an important diagnostic challenge. However, if the typical honeycomb findings of IPF are observed in the lungs by HRCT, an AE-IPF is diagnosable.

## 3.3 Pathophysiology

AE-IPF is considered to be a sudden acceleration of the disease or acute lung injury by an unknown cause that is superimposed on the diseased lung. Pathologically, AE-IPF is characterized by an acute-onset diffuse alveolar damage (DAD) that develops close to chronic UIP lesion. Given that DAD is also a common pathological feature of acute respiratory distress syndrome (ARDS) and AIP, it is possible to regard AE-IPF as ARDS due to IPF. In IPF, the lung tissue without fibrosis is primed by inflammatory cytokines produced by chronic inflammation, and it seems to be susceptible to develop DAD through some unknown trigger. Therefore, it is easy to understand AE-IPF as complication of ARDS-like DAD in IPF rather than as deterioration of IPF itself. This is supported by the fact that AE occurs not only in IPF (UIP) but also in other chronic interstitial pneumonias such as nonspecific interstitial pneumonia [13, 14].

## 3.4 Trigger Factors

Although the triggers for AE-IPF are often unclear, surgical operation, corticosteroid dose reduction, and viral infection can present as obvious triggers [11]. Diagnostic procedures such as BAL and video-assisted thoracoscopic surgery (VATS) are also potential triggers [15]. Gastroesophageal reflux disease (GERD) is another potential cause of AE-IPF [10].

According to the diagnostic criteria, pulmonary infection should be excluded; however, in practice, viral and bacterial infections are often obvious triggers [16, 17]. Simon-Blancal et al. [18] demonstrated that AE-IPF was more frequent in winter and spring than during summer and fall, suggesting that unidentified infections might be an important trigger. Despite this, a study using standard PCR analysis of BAL fluid demonstrated that common respiratory viruses were detected in only four of the 43 patients with AE-IPF, with no evidence of viral infection in most cases [19]. However, limitations with this finding mean that viruses cannot be definitively excluded as the cause of AE-IPF [20].

Some medications have been reported to be triggers for AE-IPF. Implicated drugs include biologic (anakinra, etanercept, and infliximab), nonbiologic (ambrisentan), immunomodulatory (interferon alpha/beta, everolimus, and leflunomide), and anticancer agents [21–23]. In fact, patients with lung fibrosis are prone to drug-induced lung injury. However, because drug-induced DAD-type

lung injury can develop in patients without lung fibrosis, it is debatable whether such cases should be regarded as drug-induced AE-IPF or simply as comorbid drug-induced lung injury.

Pulmonary resection in patients with lung cancer and interstitial lung disease can provoke AE-IPF at higher rates and with higher mortality. A systematic review showed that the incidence of postoperative AE-IPF ranged from 0 to 20.8 %, with mortality ranging from 37.5 to 100 % [24]. A large-scale multi-institutional cohort study reported that AE-IPF occurred in 164 of 1763 (9.3 %) patients with non-small cell lung cancer who underwent pulmonary resection and that it was the leading cause of 30-day mortality (71.7 %), with an overall mortality rate of 43.9 % when it developed [25]. Surgical procedures show the strongest association with AE-IPF; for example, using wedge resection as a reference, lobectomy or segmentectomy has an odds ratio of 3.83, and bi-lobectomy or pneumonectomy has an odds ratio of 5.70 ($P < 0.001$). In high-risk patients, surgical procedures associated with a higher risk of AE-IPF should be chosen cautiously. No benefit was found for perioperative steroids and sivelestat prophylaxis in that study.

Suzuki H et al. [26] analyzed the HRCT findings of patients with IPF to identify radiological characteristics of IPF susceptible to acute exacerbation after surgery for lung cancer. They demonstrated that the degree of fibrosis on preoperative HRCT was significantly higher in the exacerbation group ($P < 0.003$).

## 3.5 Epidemiology

The incidence of AE-IPF varies greatly between studies (8.5–60 %), and the precise determination is made difficult by the use of retrospective analyses of selected cases. The incidence also changes depending on whether pulmonary infection is completely excluded. AE-IPF is also increasingly common because of the spreading recognition that it is a common clinical feature of IPF. Recent data from randomized controlled trials have provided incidences that are more conservative, with rates of 14 % over 9 months and 4.8, 5.4, and 9.6 % over 1 year in the control groups [27–29]. Using retrospective data from a large observational cohort of 461 patients, 1- and 3-year incidences are suggested to be 14 % and 21 %, respectively [11]. A population-based analysis demonstrated the rate of AE was 0.13 cases per person year [30].

There are no significant differences in disease duration, pulmonary function, age, gender, or smoking history between patients with and without AE [9, 31]. By multivariate analysis, Song et al. [11] demonstrated that low forced vital capacity (FVC) levels and the absence of a history of smoking were risk factors for AE-IPF; however, the role of smoking in AE-IPF is controversial [32, 33]. Pulmonary hypertension may also be a risk factor for AE-IPF [34].

The mortality rates reported in small case series have been very poor, and they are as high as 85 % [7, 35–39]. In a summary of 16 studies, Collard et al. [10] reported an overall mortality rate of 70 %, while a systematic review reported 1-

and 3-month mortality rates of 60 % and 67 %, respectively [40]. Kishaba et al. [41] reported that extensive disease on chest HRCT, including traction bronchiectasis, honeycombing, ground-glass opacity, and consolidation, was associated with particularly poor mortality in AE-IPF. Indeed, the 3-month mortality was 80.6 % among patients with extensive HRCT-related disease findings, which compared negatively with the mortality of 54.5 % in patients with limited disease ($P = 0.007$).

## 3.6 Histopathology

The histopathology of AE is characterized by an underlying fibrotic interstitial pneumonia with superimposed DAD [9, 10]. The latter usually appears in a relatively normal area without prior honeycombing, and it is histologically the same as DAD that occurs without a background of UIP such as that observed in AIP and ARDS. Kang et al. [42] investigated the pathological differences depending on the underlying risk, determining the degree of α-smooth muscle actin-positive or collagen type I-positive alveolar interstitial myofibroblasts in the proliferative phase of DAD by immunohistochemical staining. Only two of seven patients with septic ARDS showed interstitial myofibroblast proliferation as opposed to 15 of 16 patients with drug-induced ARDS. Only three patients had AIP, but all patients showed myofibroblast proliferation. These findings indicated that DAD can be divided into two subphenotypes: less fibrogenic and more fibrogenic. The former is seen in patients with septic ARDS and a high incidence of multi-organ dysfunction syndrome (MODS), while the latter is seen in those with drug-induced ARDS, AIP, and AE-IPF with a low incidence of MODS.

## 3.7 Radiological Assessment

The most common radiological finding in patients with AE-IPF is the presence of new bilateral ground-glass opacities or of consolidation superimposed on the underlying UIP (i.e., subpleural reticular and honeycombing densities) [43]. Acute exacerbations of either IPF or other chronic interstitial lung diseases can closely resemble ARDS in both clinical presentation and chest radiographic abnormalities. Similar to ARDS, pathological findings are dominated by DAD, although the prognosis is substantially worse. The diagnosis of AE-IPF is suggested by a careful review of previous chest radiographic images, by the discovery of subpleural reticular changes intermixed with alveolar opacities on a chest CT scan obtained shortly after the onset of ARDS, or by surgical lung biopsy.

Akira et al. [44] classified the new onset parenchymal abnormalities into three patterns: peripheral, multifocal, and diffuse (Fig. 3.2). By multivariate analysis, the strongest correlations were observed between CT patterns (combined diffuse and multifocal versus peripheral) and survival (odds ratio, 4.629; $P = 0.001$). Diffuse

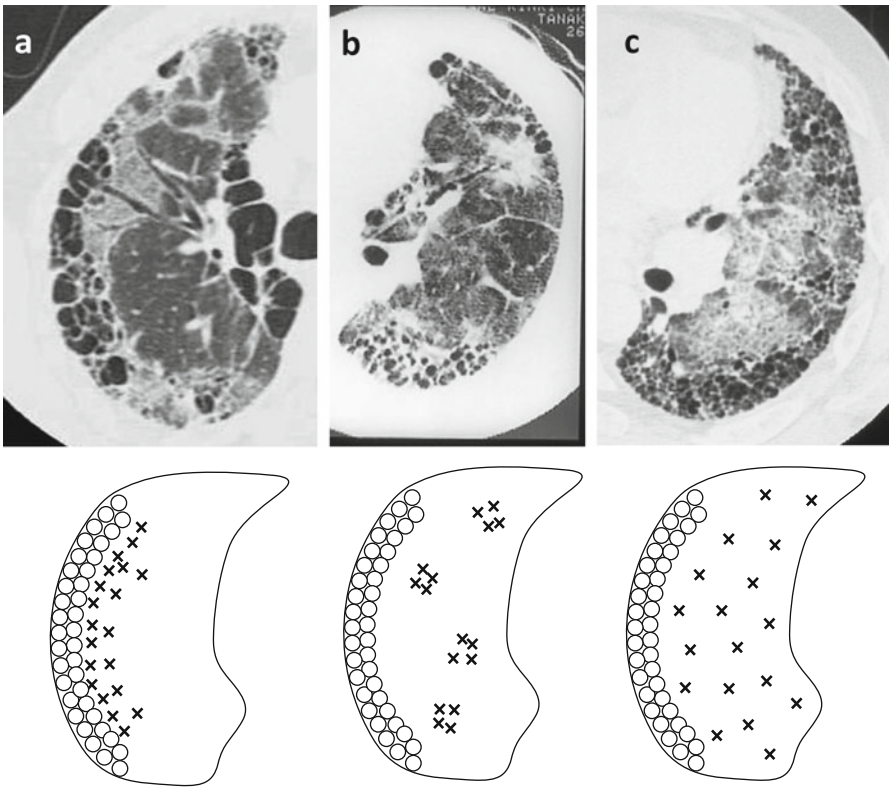


**Fig. 3.2** High-resolution computed tomography (*HRCT*) patterns of acute exacerbation of IPF: (**a**) peripheral pattern, (**b**) multifocal pattern, (**c**) diffuse pattern (Adapted from Ref. [44])

and multifocal ground-glass patterns appear to predict a worse survival in patients with AE-IPF compared with those with peripheral patterns. In contrast to these findings, Silva et al. [45] were unable to show any relationship between radiographic pattern and survival. Data that are more recent suggest that the extent of lesion on HRCT is a more important determinant of the outcome than the distribution of lesion [46]. Using the HRCT score, which was calculated based on normal attenuation areas and extent of abnormalities (i.e., areas of ground-glass attenuation and/or consolidation with or without traction bronchiectasis or bronchiolectasis and areas of honeycombing), survival among patients was worse with an HRCT score of $\geq$245 than those with a lower score (log-rank test, $P < 0.0001$).

## 3.8 Laboratory Tests and Biomarkers

When the acute exacerbation occurs, cough and dyspnea become acutely worse within one month. Blood test typically shows increases in the white cell count and both C-reactive protein and lactate dehydrogenase levels. In addition, markers of fibrosis are increased, including surfactant protein-A (SP-A), surfactant protein-D (SP-D), and sialylated carbohydrate antigen (KL-6). Measurement of serum KL-6 level is very useful when assessing disease activity and prognosis in IPF, and it is a useful predictive marker for AE-IPF. Ohshimo et al. [47] reported that baseline serum KL-6 levels were significantly higher in patients who later developed AE-IPF than in those with stable IPF ($P < 0.0001$). At a KL-6 cutoff level of 1300 U/mL, the sensitivity, specificity, accuracy, and likelihood ratio for predicting AE-IPF were 92 %, 61 %, 66 %, and 2.36, respectively. In a Kaplan-Meier analysis, they reported that patients with baseline serum KL-6 levels of $\geq$1300 U/mL experienced earlier onset of AE-IPF ($P = 0.002$). Thus, it is suggested that baseline serum KL-6 (both continuous and at a cutoff level of $\geq$1300 U/mL) is a sensitive independent predictive factor for the onset of AE-IPF. However, it is essential that care be taken while prescribing steroids or immunosuppressive therapy in IPF because of the risk of opportunistic infections by pneumocystis pneumonia or cytomegalovirus. In patients with pneumocystis pneumonia, although serum KL-6 rises in a similar manner to AE-IPF, blood β-D-glucan levels rise concurrently.

Pneumonia represents the most problematic differential in the diagnosis of AE-IPF. According to the current diagnostic criteria, pulmonary infection must be ruled out by endotracheal aspiration or BAL. However, performing bronchoscopy in patients with AE-IPF is associated with a high risk of worsening the respiratory condition, with BAL itself recognized to be a trigger factor for AE-IPF. In practice, it is often difficult to differentiate between AE-IPF and bacterial pneumonia, and a surrogate marker has, therefore, been sought to exclude infectious pathology. To this end, serum procalcitonin (PCT) is useful while attempting to differentiate between typical bacterial and nonbacterial causes of inflammation. Nagata et al. [48] reported that serum PCT levels in AE-IPF were significantly lower than those in bacterial pneumonia with IP ($0.62 \pm 1.30$ vs. $8.31 \pm 14.83$ ng/mL; $P < 0.05$). Thus, serum PCT is a useful surrogate marker for discriminating between AE-IPF and concurrent bacterial pneumonia with IPF.

In addition, circulating fibrocytes have been reported to be a good biomarker of fibrosis. Fibrocytes are circulating bone marrow-derived spindle-shaped cells, produce extracellular matrix components, and may play an important role in wound repair and tissue fibrosis. Fibrocytes were defined as cells positive for CD45 and collagen-1 by flow cytometry. Circulating fibrocytes defined as CD45-positive and collagen-1-positive cells by flow cytometry are increased threefold in patients with stable IPF compared with healthy controls [49]. During AE-IPF, fibrocyte counts have been shown to further increase to an average of 15 % of peripheral blood leukocytes. The increased fibrocyte counts then tend to decrease to

pre-exacerbation levels in patients who recover. Circulating fibrocyte counts can also indicate prognosis; patients with IPF and fibrocytes of >5 % had a poor prognosis when compared with those with fibrocytes of <5 % (mean survival time, 7.5 months vs. 27 months; $P = 0.0001$).

## 3.9 Pharmacological Treatments

To date, no evidence-based effective therapy has been established for AE-IPF. Indeed, international consensus guidelines produced by the ATS, ERS, Japanese Respiratory Society, and Latin American Thoracic Association only recommend management supportive care and corticosteroid use [50].

Empirical treatment with high-dose corticosteroid therapy is generally used in AE-IPF without any clear evidence that they are effective. No randomized controlled trials have been conducted using corticosteroids in AE-IPF. Methylprednisolone pulse therapy [1 g intravenously (IV)] is usually given on days 1–3 with a maintenance prednisolone dose equivalent to approximately 40 mg daily [5]. The 3-day pulse therapy is repeated weekly on 1–4 occasions until the patient's condition stabilizes.

Steroid pulse therapy came to be used for respiratory diseases based on its biological plausibility and experience, with a similar method used for renal and collagen diseases [51]. In Japan, this therapy has been used for IPF and AE-IPF since 1978. It is also usually used in the treatment of other lung diseases presenting with DAD, such as ARDS and AIP. Although the rapidly progressive clinical condition is often temporarily stabilized by the pulse therapy, thereby improving oxygenation, there is no evidence that it improves mortality. Indeed, the mortality rate remains high, despite therapy. In recent years, a low-dose steroid therapy has been employed (methylprednisolone, 1 mg/kg/day) in reference to trials in the treatment of ARDS [52], but the benefits remain unclear. Given that the pathological evidence of DAD is an extremely poor prognostic factor, it seems that the effect of steroids may be insufficient. Nevertheless, surgical lung biopsies reveal that some cases of AE-IPF have organizing pneumonia rather than DAD [53], in which case glucocorticoid therapy might be effective.

Immunosuppressants, such as cyclosporine A (CsA), cyclophosphamide, or tacrolimus, are used together when the reaction of steroid alone is poor. These drugs can also be used in combination with a steroid from the beginning. Several investigators reported better survival in patients treated with this type of combination therapy [54–56]. Although these studies have mostly been retrospective, have included small samples, and have used various definitions of AE-IPF, they suggest that the use of immunosuppressants in combination with corticosteroids is more effective than corticosteroid monotherapy. Sakamoto et al. [54] reported that the mean survival period after the first onset of AE-IPF was 285 days in a CsA-treated group and 60 days in a non-CsA-treated group. Thus, prognosis was significantly better in the CsA-treated group. In this study, a low dosage of CsA (100–150 mg/

day) was started at the same time as the pulse therapy. Morawiec et al. [55] reported their experience with cyclophosphamide pulse therapy for AE-IPF in a small case series. Patients with AE-IPF were treated with a methylprednisolone pulse (1,000 mg) on days 1–3, before the escalating regimen of cyclophosphamide was started on day 4 with an initial intravenous dose of 500 mg. The dose of cyclophosphamide was then increased by 200 mg every 2 weeks up to the maximum dose of 1,500 mg.

The majority of patients with AE-IPF receive empiric broad-spectrum antibiotics against respiratory pathogens, even if there is no obvious infection. This is based on the following clinical rationale: (1) an underlying infection can be easily missed on microbiological testing, (2) the mortality rate is very high, (3) many patients present with fever and flu-like symptoms and have elevated blood neutrophil counts and CRP levels, and (4) antimicrobial therapy has a low risk of complications.

Because a coagulation disorder subsequent to vascular injury could be important for the pathogenesis of AE-IPF, anticoagulant therapy may be effective. A small prospective clinical trial of anticoagulation with warfarin and low molecular weight heparin in patients with IPF reportedly improved survival in the group receiving anticoagulation mostly by reducing the mortality associated with AE-IPF [57]. In that study, the mortality associated with AE-IPF was significantly reduced in the anticoagulant group when compared with the non-anticoagulant group (18 % vs. 71 %, respectively; $P = 0.008$). Conversely, a randomized, double-blind, placebo-controlled study of warfarin as a treatment for IPF had to be terminated early because of higher mortality in the warfarin arm and a low likelihood of benefit [58]. Therefore, at present, anticoagulant therapy in patients with IPF is discouraged.

Combination therapy with sivelestat, a neutrophil elastase inhibitor, and corticosteroids was examined in a multicenter, double-blind prospective phase II study in Japan [59]. In total, 78 cases were divided into placebo, low-dose, and high-dose groups. High doses of sivelestat treatment for 14 days improved oxygenation and global clinical status but not mortality. A subsequent phase III trial has since confirmed the clinical utility for AE-IPF [60]. Currently sivelestat is clinically available for lung injury with systemic inflammatory response syndrome (SIRS) and it is often used for AE-IPF [61].

Pharmacological treatments such as thrombomodulin [62] have also been studied. However, their efficacy in the treatment of AE-IPF is based on a few small, retrospective studies that do not provide conclusive evidence of benefit.

## 3.10 Therapy with Polymyxin B-Immobilized Fiber Column

One possible treatment for AE-IPF currently under study is a direct hemoperfusion with a polymyxin B (PMX)-immobilized fiber column (PMX-DHP). In this technique, PMX-DHP columns not only absorb endotoxins and reactive oxygen species, and other substances, but also selectively remove activated neutrophils that cause endothelial injury [63–65]. Several case studies indicated that PMX-DHP treatment may improve oxygenation and survival in patients with AE-IPF. Abe et al. [66] reported a multicenter retrospective analysis (18 institutions in Japan) of 160 patients with interstitial pneumonia (including 73 with IPF) who had acute disease exacerbations treated by PMX. In patients with AE-IPF, the ratio of $PaO_2/FiO_2$ was significantly improved after treatment with PMX compared with that before treatment ($173.9 \pm 105.4$ to $195.2 \pm 106.8$ Torr; $P = 0.003$). Recently, Enomoto et al. [67] reported 31 patients with AE-IPF; they found a significantly greater improvement in $PaO_2/FiO_2$ ratio in those treated with PMX-DHP ($n = 14$) after 2 days of treatment than in those who did not receive PMX-DHP treatment (mean ± SEM, $58.2 \pm 22.5$ vs. $0.7 \pm 13.3$; $P = 0.034$). The 12-month survival rate was also significantly higher in patients treated with PMX-DHP (48.2 % vs. 5.9 %; $P = 0.041$). These studies suggest that PMX-DHP therapy is promising and that large randomized controlled trials are needed.

## 3.11 Prevention

Prevention of AE-IPF may be the most effective approach to management. Clinical trials of several investigational treatments for IPF have evaluated whether daily treatment of chronic phase of IPF reduces the incidence of AE-IPF.

Pirfenidone, an antifibrotic molecule, has shown inconsistent effects on AE-IPF. A phase II study in Japanese patients with IPF was terminated after 9 months of a planned 1-year follow-up because of a higher frequency of AE-IPF in the placebo group than in the pirfenidone group [27]. However, in a phase III trial in Japanese patients, no significant differences were observed in the incidence of AE-IPF over 52 weeks between patients treated with pirfenidone and those treated with placebo [28]. Subsequent larger clinical trials of pirfenidone in patients with IPF (CAPACITY-1 and CAPACITY-2) also failed to confirm any reduction in the incidence of AE-IPF [68]. Therefore, at present, pirfenidone cannot be considered to be effective in preventing the onset of AE-IPF.

Nintedanib is a tyrosine kinase inhibitor of platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and fibroblast growth factor receptor (FGFR) that has been developed for the treatment of IPF. In a phase II trial (the TOMORROW trial, lasting for 12 months), a lower incidence of AE-IPF was observed in patients treated with nintedanib than those treated with

placebo [69]. Two subsequent replicate 52-week, randomized, double-blind, phase III trials (INPULSIS-1 and INPULSIS-2) were performed [29]. However, in INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first AE (hazard ratio in the nintedanib group, 1.15; $P = 0.67$), with similar proportions of patients with AE-IPF in the treatment and placebo groups (6.1 % and 5.4 %, respectively). In contrast, INPULSIS-2 reported a significant increase in the time to the first AE in the nintedanib group when compared with the placebo group (hazard ratio, 0.38; $P = 0.005$), and the proportion of patients with AE was also lower in the nintedanib group than in the placebo group (3.6 % vs. 9.6 %). In the prespecified pooled analysis, there was no significant difference between the nintedanib and placebo groups in the time to first AE (hazard ratio, 0.64; $P = 0.08$) and also in the proportion of patients with AE (4.9 % in the nintedanib group and 7.6 % in the placebo group). Because nintedanib did not show a consistent effect on the incidence of AE in these trials, its effectiveness remains unclear.

Antacid drugs have been considered to be useful for preventing AE-IPF because gastroesophageal reflux disease (GERD) is a risk factor for both IPF and AE-IPF. A retrospective analysis using data from controls in three randomized controlled trials showed that patients taking antacid treatments (proton pump inhibitors or histamine receptor-2 blockers) at baseline had fewer AE-IPF than those who were not (zero vs. nine events after a mean follow-up of 30 weeks; $P < 0.01$) [70]. The decrease in FVC at 30 weeks was also smaller in the patients who were treated with antacid drugs than those who were not treated ($-0.06$ vs. $-0.12$L; $P = 0.05$). These findings suggest that antacid treatment could be beneficial in patients with IPF. Controlled clinical trials are needed to confirm those observational findings.

Postoperative AE-IPF is also common and associated with a high mortality rate. Therefore, appropriate measures should be employed to prevent the onset of AE. Various preventive measures have been considered to date, but none has been established. In general, high-pressure ventilation, high oxygen concentrations, long operation times, and overhydration during operation should be avoided.

## 3.12 Conclusions

AE-IPF and AE of other fibrotic lung diseases are life-threatening events that decrease overall survival and are associated with high mortality rates. They have been recognized in Japan since the 1970s but have only recently been recognized in Europe and America. One reason for this is that there was the difference of recognition whether AE was regarded as a part of the natural progression of the underlying disease or as a newly developed distinct condition. The other possibilities for the reason are a racial factor and an environmental factor. However, this is not likely because recent reports demonstrated that there are no great differences in the incidence of AE-IPF between Japan and other countries.

A critical problem in the management of AE-IPF is the differentiation from comorbidities, such as pneumonia, pulmonary thromboembolism, pneumothorax, or cardiac failure, which may present similarly with abrupt, acute deterioration of respiratory failure in the context of chronic disease progression. In that setting, the emergence of new bilateral lung shadows not caused by apparent infection should be considered to be the decisive factor in favor of AE. Indeed, because they are pathologically characterized by DAD, AE-IPF is easy to understand when one considers them as ARDS due to IPF. Although the diagnosis of AE-IPF requires that infection be excluded, concomitant infection may play a role such as that when ARDS is caused by infection. Triggers for AE-IPF also appear to be variable and unclear.

Despite trials of various therapies, no concrete therapy has been established to date. Given the high incidence of AE-IPF following lung resection surgery, a high-priming state probably makes the patient susceptible to a second attack. Unfortunately, when an AE with DAD has occurred once, subsequent treatment becomes extremely difficult. Therefore, efforts need to focus on the development of effective prevention methods. Although emerging evidence from clinical trials suggests that some treatments may reduce the incidence of AE-IPF in the context of chronic IPF, robust evidence is needed to confirm their efficacy before they can be put into routine practice.

## References

1. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;157:199–203.
2. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med. 2000;161:1172–8.
3. Yoshimura K, Nakatani T, Nakamori Y, et al. Acute exacerbation in idiopathic interstitial pneumonia. Nihon Kyobu Shikkan Gakkai Zasshi. 1984;22:1012–20. Japanese.
4. Kondo A, Saiki S. Acute exacerbation in idiopathic interstitial pneumonia. In: Interstitial pneumonia of unknown etiology. Tokyo: University of Tokyo Press; 1989. p. 34–42.
5. Kondoh Y, Taniguchi H, Kawabata Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest. 1993;103:1808–12.
6. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
7. Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. Eur Respir J. 2003;22:821–6.
8. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med. 2005;142:963–7.
9. Kim DS, Park JH, Park BK, et al. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27:143–50.
10. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176:636–43.
11. Song JW, Hong SB, Lim CM, et al. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:56–63.

12. Huie TJ, Olson AL, Cosgrove GP, et al. A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes. Respirology. 2010;15:909–17.
13. Suda T, Kaida Y, Nakamura Y, et al. Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. Respir Med. 2009;103:846–53.
14. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest. 2007;132:214–20.
15. Hiwatari N, Shimura S, Takishima T, et al. Bronchoalveolar lavage as a possible cause of acute exacerbation in idiopathic pulmonary fibrosis patients. Tohoku J Exp Med. 1994;174:379–86.
16. Molyneaux PL, Cox MJ, Willis-Owen SA, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190:906–13.
17. Umeda Y, Morikawa M, Anzai M, et al. Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination. Intern Med. 2010;49:2333–6.
18. Simon-Blancal V, Freynet O, Nunes H, et al. Acute exacerbation of idiopathic pulmonary fibrosis: outcome and prognostic factors. Respiration. 2012;83:28–35.
19. Wootton SC, Kim DS, Kondoh Y, et al. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:1698–702.
20. Kolb MR, Richeldi L. Viruses and acute exacerbations of idiopathic pulmonary fibrosis: rest in peace? Am J Respir Crit Care Med. 2011;183:1583–4.
21. Ling VY, Mortimore M, Serisier DJ. Suspected acute exacerbation of idiopathic pulmonary fibrosis associated with interferon alpha therapy for hepatitis C: case report. Springerplus. 2013;2:101.
22. Malouf MA, Hopkins P, Snell G, et al. An investigator-driven study of everolimus in surgical lung biopsy confirmed idiopathic pulmonary fibrosis. Respirology. 2011;16:776–83.
23. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41:256–64.
24. Watanabe A, Kawaharada N, Higami T. Postoperative acute exacerbation of IPF after lung resection for primary lung cancer. Pulm Med. 2011;2011:960316.
25. Sato T, Teramukai S, Kondo H, et al. Japanese Association for Chest Surgery. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014;147:1604–11.
26. Suzuki H, Sekine Y, Yoshida S, et al. Risk of acute exacerbation of interstitial pneumonia after pulmonary resection for lung cancer in patients with idiopathic pulmonary fibrosis based on preoperative high-resolution computed tomography. Surg Today. 2011;41:914–21.
27. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–7.
28. Taniguchi H, Ebina M, Kondoh Y, Pirfenidone Clinical Study Group in Japan, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:821–9.
29. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
30. Fernandez Perez ER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010;137:129–37.
31. Stern JB, Mal H, Groussard O, et al. Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. Chest. 2001;120:213–19.
32. Tachikawa R, Tomii K, Ueda H, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases related versus idiopathic. Respiration. 2012;83:20–7.
33. Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J. 2010;35:105–11.
34. Judge EP, Fabre A, Adamali HI, et al. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Eur Respir J. 2012;40:93–100.

35. Panos RJ, Mortenson RL, Niccoli SA, et al. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med. 1990;88:396–404.
36. Akira M, Hamada H, Sakatani M, et al. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 1997;168:79–83.
37. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest. 2005;128:3310–15.
38. Nava S, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax. 1999;54:390–5.
39. Fumeaux T, Rothmeier C, Jolliet P. Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis. Intensive Care Med. 2001;27:1868–74.
40. Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. Eur J Int Med. 2008;19:227–35.
41. Kishaba T, Tamaki H, Shimaoka Y, et al. Staging of acute exacerbation in patients with idiopathic pulmonary fibrosis. Lung. 2014;192:141–9.
42. Kang D, Nakayama T, Togashi M, et al. Two forms of diffuse alveolar damage in the lungs of patients with acute respiratory distress syndrome. Hum Pathol. 2009;40:1618–27.
43. Hyzy R, Huang S, Myers J, et al. Acute exacerbation of idiopathic pulmonary fibrosis. Chest. 2007;132:1652–8.
44. Akira M, Kozuka T, Yamamoto S, et al. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;15(178):372–8.
45. Silva CI, Muller NL, Fujimoto K, et al. Acute exacerbation of chronic interstitial pneumonia: high-resolution computed tomography and pathologic findings. J Thorac Imaging. 2007;22:221–9.
46. Fujimoto K, Taniguchi H, Johkoh T, et al. Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. Eur Radiol. 2012;22:83–92.
47. Ohshimo S, Ishikawa N, Horimasu Y, et al. Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. Respir Med. 2014;108:1031–9.
48. Nagata K, Tomii K, Otsuka K, et al. Serum procalcitonin is a valuable diagnostic marker in acute exacerbation of interstitial pneumonia. Respirology. 2013;18:439–46.
49. Moeller A, Gilpin SE, Ask K, et al. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179:588–94.
50. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
51. Keogh BA, Bernardo J, Hunninghake GW, et al. Effect of intermittent high dose parenteral corticosteroids on the alveolitis of idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1983;127(1):18–22.
52. Meduri GU, Golden E, Freire AX, et al. Effect of intermittent high dose parenteral corticosteroids on the alveolitis of idiopathic pulmonary fibrosis. Am Rev Respir Dis. 1983;127:18–22.
53. Churg A, Muller NL, Silva CI, et al. Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. Am J Surg Pathol. 2007;31:277–84.
54. Sakamoto S, Homma S, Miyamoto A, et al. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2010;49:109–15.
55. Morawiec E, Tillie-Leblond I, Pansini V, et al. Exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids and cyclophosphamide pulses. Eur Respir J. 2011;38:1487–9.
56. Horita N, Akahane M, Okada Y, et al. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2011;50:189–95.
57. Kubo H, Nakayama K, Yanai M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest. 2005;128:1475–82.
58. Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186:88–95.

59. Ishii Y, Kitamura S, Kira S, et al. A phase II clinical study of a neutrophil elastase inhibitor; ONO-5046・Na on acute exacerbation in IIP patients. J Clin Therap Med. 1998;14:397–420 (in Japanese).
60. Ishii Y, Kitamura S, Ando M. A phase III clinical study of a neutrophil elastase inhibitor; ONO-5046・Na on acute exacerbation in IIP patients. J Clin Therap Med. 1998;14:421–46 (in Japanese).
61. Nakamura M, Ogura T, Miyazawa N, et al. Outcome of patients with acute exacerbation of idiopathic interstitial fibrosis (IPF) treated with sivelestat and the prognostic value of serum KL-6 and surfactant protein D. Nihon Kokyuki Gakkai Zasshi. 2007;45:455–9 (in Japanese).
62. Tsushima K, Yamaguchi K, Kono Y, et al. Thrombomodulin for acute exacerbations of idiopathic pulmonary fibrosis: a proof of concept study. Pulm Pharmacol Ther. 2014;29:233–40.
63. Kase Y, Obata T, Okamoto Y, et al. Removal of 2-arachidonylglycerol by direct hemoperfusion therapy with polymyxin B immobilized fibers benefits patients with septic shock. Ther Apher Dial. 2008;12:374–80.
64. Kohro S, Imaizumi H, Yamakage M, et al. Anandamide absorption by direct hemoperfusion with polymixin B-immobilized fiber improves the prognosis and organ failure assessment score in patients with sepsis. J Anesth. 2006;20:11–6.
65. Cruz DN, Antonelli M, Fumagalli R, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA. 2009;301:2445–52.
66. Abe S, Azuma A, Mukae H, et al. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. Intern Med. 2012;51:1487–91.
67. Enomoto N, Mikamo M, Oyama Y, et al. Treatment of acute exacerbation of idiopathic pulmonary fibrosis with direct hemoperfusion using a polymyxin B-immobilized fiber column improves survival. BMC Pulm Med. 2015;15:15.
68. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–9.
69. Woodcock HV, Molyneaux PL, Maher TM. Reducing lung function decline in patients with idiopathic pulmonary fibrosis: potential of nintedanib. Drug Des Devel Ther. 2013;7:503–10.
70. Lee JS, Collard HR, Anstrom KJ, et al. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomized controlled trials. Lancet Respir Med. 2013;1:369–76.

# Chapter 4
# Pathogenesis of IPF

## Is Abnormal Repair of Epithelial Damage Involved in the Basic Pathogenesis of This Disease?

**Yasuhiko Nishioka**

**Abstract** The molecular pathogenesis in IPF is not fully understood. However, epithelial injury and subsequent aberrant wound healing, rather than chronic inflammation, are thought to play central roles in the recent hypothesis. Alveolar epithelial cells predisposed with genetic mutations may involve in the abnormal responses subsequent to injury. Growth factors, such as transforming growth factor-β and platelet-derived growth factors, are critical mediators that control the growth and differentiation of lung fibroblasts. The novel topics in pulmonary fibrosis include the origin of lung fibroblasts, alveolar epithelial integrity, and resolution of extracellular matrixes. The further studies are required to clarify the mechanisms involved in the fibrogenesis in the lungs of IPF.

**Keywords** Epithelial injury • Fibroblasts • Growth factors • Epithelial integrity

### 4.1 Hypothesis of the Molecular Pathogenesis of IPF: From Inflammation to Epithelial Injury

IPF is believed to be caused by chronic inflammation in the lungs. In 2001, a novel pathogenesis was advocated, in which epithelial injury and subsequent aberrant wound healing, rather than chronic inflammation, play central roles [1, 2]. As a result of injury, alveolar epithelial type II cells (AECII) secrete several mediators capable of triggering profibrotic responses. Among these factors, growth factors, such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), possess the ability to stimulate the migration, proliferation, and collagen production of lung fibroblasts, indicating that the interaction between AECII and fibroblasts is fundamental to the onset of

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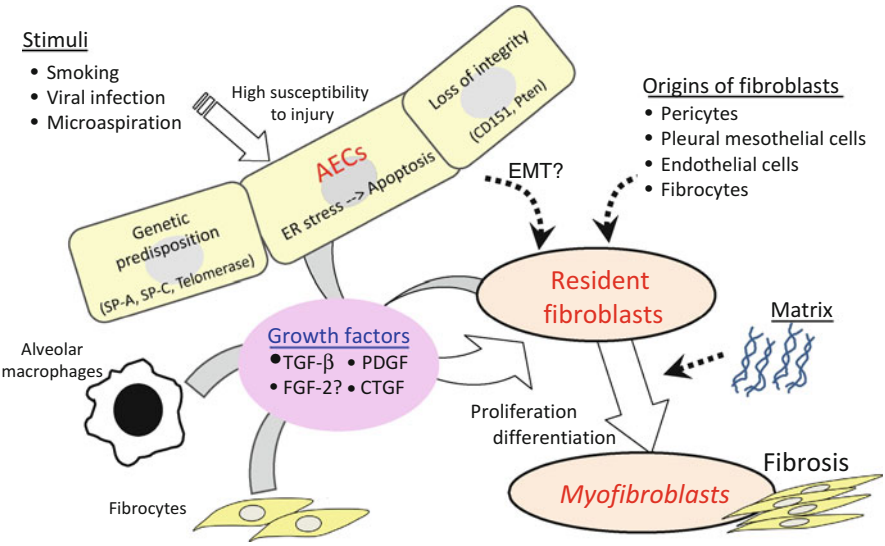


**Fig. 4.1** Schematic drawing of the proposed molecular pathogenesis of IPF. AEC, alveolar epithelial cell; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix

fibrogenesis in the lungs [3, 4]. In addition, growth factors are produced by alveolar macrophages and fibrocytes [3, 4]. Once the profibrotic pathway is stimulated, activated fibroblasts differentiate into myofibroblasts and cause excessive extracellular matrix (ECM) deposition, leading to remodeling of the lungs, with a so-called "honeycomb" appearance [1–4]. The updated hypothesis for the pathogenesis of IPF is summarized in Fig. 4.1.

## 4.2 Epithelial Injury and Genetic Background

Studies of the genetic backgrounds of patients with familial pulmonary fibrosis have revealed the existence of germline mutations in several genes. Surfactant proteins SP-A, SP-B, SP-C, and SP-D are produced from AECII and play roles in preserving lung homeostasis [5]. SP-B and SP-C are extremely hydrophobic and essential for reducing surface tension, whereas SP-A and SP-D belong to the collectin family of proteins and are involved in the host defenses. Among these genes, the SP-C gene mutation was first reported in children with familial pulmonary fibrosis [6, 7]. A mutation in the SP-A2 gene was subsequently identified in cases of familial disease [8, 9]; these mutations in the SP genes cause the accumulation of misfolded proteins in AECII. Other mutations have since been reported in telomerase genes [10, 11]. These mutations are believed to be associated with a reduced enzyme activity of telomerase and inversely correlate with the length of the telomere. An analysis of *terc*$^{-/-}$ mice also showed a reduced number of AECII in

the distal lung epithelium [12]. Furthermore, the ATP-binding cassette protein A3 (ABCA3) is highly expressed in AECII and thought to be involved in the transport of surfactant proteins. The mutation in the ABCA3 gene was originally reported to cause the fatal interstitial lung disorder, whereas a later report showed an association with pediatric interstitial lung disease [13, 14]. More recently, a common MUC5B promoter polymorphism was identified to be associated with familial interstitial pneumonia, although the role of MUC5B in the pathogenesis of IPF remains unclear [15].

The above gene mutations are thought to render AEC susceptible to various stimuli, such as genetic predispositions. However, the frequency of these gene mutations appears to be rare in sporadic cases of IPF [16].

## 4.3 Biological Alteration in Injured AEC in IPF

Gene mutations in SP-C or SP-A2 cause the production of misfolded proteins that are not secreted or accumulated in the endoplasmic reticulum (ER) of AECs [17, 18]. Subsequently, the response to ER stress is induced, thereby upregulating the expressions of XBP-1, GRP78/BiP, and HDJ-2/HSP40, followed by the activation of caspase3 and apoptosis. Increased ER stress is seen in epithelial cells in the lungs of patients with IPF [19, 20], and apoptosis is reported to be increased in AECs in IPF lungs [21]. ER stress is enhanced by numerous factors. For example, viral infections, such as that with the influenza virus and cytomegalovirus, stimulate ER stress in AECs [20, 22]. In addition, environmental exposure to toxins, including cigarette smoke, upregulates ER stress in AECs [23], and aging is related to enhanced susceptibility to ER stress induced by murine herpesvirus [24]. These findings suggest that ER stress and apoptosis in AECs may be critical in both sporadic and familial cases of IPF and that similar mechanisms leading to ER stress, such as SP genes, may function in sporadic cases.

How do AECs under ER stress or apoptosis promote pulmonary fibrosis? The answer is not fully understood. However, it was recently demonstrated that the expression of TGF-β is mediated by ER stress associated with the SP-A2 gene mutation and influenza infection in AECs [20, 25]. ER stress may also generate EMT of AECs [26]. Since AECs have various biological functions, further research is required to clarify the link with epithelial injury and pulmonary fibrosis.

## 4.4 Critical Roles of Growth Factors in the Progression of Pulmonary Fibrosis

As mentioned above, injury to AECs is believed to be the first event triggering the onset of pulmonary fibrosis. However, growth factors are produced by various cells in addition to AECs in the IPF lungs [27]. Alveolar macrophages are known to produce numerous soluble factors under conditions of fibrogenesis in the lungs. Furthermore, emerging cells called fibrocytes also have the ability to produce profibrotic growth factors.

Among profibrotic mediators, transforming growth factor (TGF)-β and PDGF are thought to play a critical role in the onset of fibrogenesis of the lungs due to the activation of lung fibroblasts. Despite the limited evidence, other growth factors, including fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF)-1, etc., are also believed to contribute to the pathogenesis of pulmonary fibrosis.

Representative growth factors with a profibrotic activity are summarized in Table 4.1.

### *4.4.1 PDGF and PDGF Receptors*

PDGF is a homo- or heterodimeric molecule with a molecular weight of 30 kDa [28]. PDGF genes consist of four different genes, including PDGF-A, PDGF-B, PDGF-C, and PDGF-D, which are located on chromosomes 7, 22, 4, and 11, respectively [29, 30]. There are two types of PDGF receptors (PDGFRs), α and β, which have a molecular weight of 170–180 kDa and are composed of homo- or heterodimers. Possible PDGF-PDGFR interactions are multiple and complex according to an in vitro study [7]. However, an in vivo study showed a limited pattern of binding of PDGF-AA or –CC to PDGFR-α and PDGF-BB to PDGFR-β [30].

PDGFs are expressed in many types of cells, including fibroblasts, vascular endothelial cells, macrophages, and platelets/megakaryocytes [30]. It is also known that the expression of PDGFs is upregulated by various inflammatory cytokines and growth factors, including both TGF-β and PDGF. Moreover, PDGFRs are expressed in various cells, although the classical targets of PDGF are fibroblasts and smooth muscle cells, and the expression of PDGFRs is induced by various stimuli. In contrast to PDGFs, the expression of PDGFR in some cells is limited to PDGFR-α or PDGFR-β, not both.

PDGF is known to be a major mitogen for mesenchymal cells. In fact, PDGF is the strongest stimulus of the proliferation of fibroblasts [28, 30], and the depletion of the PDGF-A gene in mice has been shown to be homozygous and lethal, with two different restriction points, one located prenatally and one located postnatally [31]. Postnatally surviving PDGF-A-deficient mice develop lung emphysema

**Table 4.1** Major growth factors related to IPF and their biological effects

| Growth factor | Producing cells | | | | | Biological activities | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Endothelial cells | Epithelial cells | Fibroblasts | Fibrocyte | Myofibroblasts | Proliferation | Migration | Collagen production | Fibrosis |
| TGF-β | + | + | + | + | + | → | ↑ | ↑↑ | ↑ |
| PDGF | + | + | + | + | + | ↑↑ | ↑↑ | ↑ | ↑ |
| FGF2 | - | - | + | + | + | ↑ | ↑ | ↑ | ↑? |

secondary due to the loss of alveolar myofibroblasts containing PDGFR-α. On the other hand, PDGFR-a null mice show cranial malformations and deficiency of myotome formation [32]. Mice deficient for PDGF-B or PDGFR-β exhibit renal, cardiovascular, and hematological, but not pulmonary, abnormalities [33, 34]. In summary, PDGF-A/PDGFR-α pathway plays a role in the secondary septation process, since PDGFR-α-expressing cells located in the alveolar entry ring have characteristics of myofibroblasts [35].

PDGF is known to be a growth factor that plays a role in the pathogenesis of pulmonary fibrosis [28, 30]. In animal models, the induction of pulmonary fibrosis with bleomycin (BLM) has been used to assess the molecular pathogenesis. For example, Maeda et al. reported that the expression of the PDGF-A gene is increased in mice showing BLM-induced pulmonary fibrosis using semiquantitative reverse transcriptase polymerase chain reaction (RT-PCR) [36]. Walsh et al. also examined the bronchoalveolar lavage fluid of rats treated with BLM and found 38- to 40-kDa and 29-kDa peptides detected with anti-PDGF-BB and anti-PDGF-AA antibodies, respectively, demonstrating the growth-promoting activity of lung fibroblasts [37]. In that study, the growth-promoting activity was neutralized 64 % by the anti-PDGF-BB antibody and 15 % by the anti-PDGF-AA antibody. In contrast, Zhuo et al. showed that the PDGF-C, but not the PDGF-A, PDGF-B, or PDGF-D, gene is induced in the lungs of mice treated with BLM according to a Northern blot analysis [38]. Moreover, Shimizu et al. reported that PDGF-A and PDGF-B are induced and elevated in the BLM-treated lungs of mice at both the mRNA and protein levels [39]. Additionally, the adoptive transfer of an adenovirus expressing the PDGF-B gene into the lungs induces severe fibrosis in mice [40]. Based on these reports, the expression of PDGF isoforms is enhanced in the setting of fibrogenesis of the lungs, although the details require a further analysis.

On the other hand, an enhanced expression of PDGF in epithelial cells and alveolar macrophages in the lungs of patients with IPF has been reported [41, 42]. However, the mechanisms involved in the enhanced expression and actions of PDGF in the fibrotic lung are poorly understood. Recently, Gochuico et al. examined growth factors in the alveolar lining fluid of patients with rheumatoid arthritis complicated with pulmonary fibrosis and reported that PDGF-AB and PDGF-BB, but not TGF-β or PDGF-AA, are associated with the progressive stage of pulmonary fibrosis [43], indicating the importance of PDGF-B in the onset of fibrogenesis of the lungs.

The evidence described above suggests that targeting the PDGF/PDGFR signaling pathway may have therapeutic effects against pulmonary fibrosis. This hypothesis has been investigated using animal models of pulmonary fibrosis with specific inhibitors of PDGFR [44]. Rice et al. first reported that AG1296, a tyrosine kinase inhibitor (TKI) for PDGFR, prevents the development of pulmonary fibrosis induced by vanadium pentoxide ($V_2O_5$) in rats [45]. In addition, imatinib mesylate (Gleevec in the United States, Glivec in Europe) has been applied, as imatinib inhibits PDGFR in addition to bcr-abl and c-kit [46]. The antifibrotic effects of imatinib in various pulmonary fibrosis models have been extensively examined, and it has been reported that imatinib strongly inhibits fibrogenesis in the lungs

[47–49]. In addition, Yoshida et al. reported that the in vivo gene transfer of an extracellular domain of PDGFR-β reduces the onset of BLM-induced pulmonary fibrosis [50]. Recently, nilotinib, another compound with a similar profile to that of imatinib, was also reported to show a higher antifibrotic activity than imatinib [51]. These observations suggest that the PDGF/PDGFR axis is a potential therapeutic target for pulmonary fibrosis.

### *4.4.2 FGF and FGF Receptors*

FGF and FGF receptor (FGFR) are thought to be involved in the onset of fibrogenesis in the lungs. The FGF/FGFR family is composed of 18 FGF ligands and four FGFRs [52, 53]. Alternative splicing of the domain III of FGFR1–3 yields two different isoforms, IIIb in epithelial tissue and IIIc in mesenchymal tissues. Heparan sulfate glycosaminoglycan (HSGAG) binds to both FGF and FGFR in order to stabilize the binding of FGF to FGFR by facilitating dimerization. The specificity of different FGFs for different receptor isoforms has also been reported [54].

The physiological functions of FGF are diverse and complex, and studies have evaluated the roles of FGF proteins in vitro and in genetically modified mice in vivo [52–54]. Since FGFs originally possess mitogenic, chemotactic, and angiogenic activities, the biology of FGF has been examined in cancer research. In addition, knockout mice have been used to demonstrate the role of FGFs in the embryonic development of various organs. However, the physiological roles of most FGFs/FGFRs remain unclear. Both $Fgf1^{-/-}$ and $Fgf2^{-/-}$ mice are viable and fertile, with the exception of some abnormalities in the vascular system, although exogenous FGF-2 induces the proliferation of endothelial cells, smooth muscle cells, and fibroblasts.

The profibrogenic activities of FGFs have been observed in FGF-2 (basic FGF). For example, Hetzel et al. reported the proliferative activity of FGF-2 for lung fibroblasts [55], and fibroblasts derived from IPF show a reduced response to FGF-2, IGF-1, and EGF, but not PDGFs, as compared with normal fibroblasts. Meanwhile, Kanazawa et al. reported the activity of these compounds in promoting the migration of skin fibroblasts [56]. However, FGF-2 does not stimulate the production of fibronectin by lung fibroblasts. In IPF patients, there are scant data regarding the localization of FGF-2 in the lungs. However, the expression of FGF-2 mRNA has been reported to be upregulated in BLM-treated lungs in mice [57]. Although immunohistochemical staining has been reported to show the expression of FGF-2 in inflammatory cells, the role of the FGF-2/FGFR axis in mouse models of lung fibrosis remains unclear. Ju et al. reported that the administration of soluble FGFR2c ectodomain significantly reduces the extent of lung fibrosis in TGF-β-induced lung fibrosis mice [58]. However, Guzy et al. recently reported that $Fgf2^{-/-}$ mice show increased mortality due to epithelial injury induced by BLM without any effects on lung fibrosis [57]. At present, it is not

possible to draw firm conclusions regarding the role of FGF-2 in the pathogenesis of pulmonary fibrosis in mice or in humans.

In contrast to FGF-2, FGF-1 has been reported to be an antifibrotic factor. FGF-1 reverts the profibrogenic effects of TGF-β such as α-SMA induction [59]. In addition, FGF-1 reduces the expression of collagen-I and induces the apoptosis of lung fibroblasts [60, 61].

It is currently difficult to determine the overall roles of FGF/FGFR in the pathogenesis of IPF. Further studies with an inhibitor specific for FGFR in pulmonary fibrosis models may help to clarify the roles of FGF/FGFR, although each isoform of FGF/FGFR cannot be analyzed minutely.

### *4.4.3 VEGF and VEGF Receptors*

VEGF and VEGF receptors play a central role in both physiological and pathological angiogenesis [62]. The VEGF family is composed of seven members, VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PIGF, and svVEGF, while VEGF receptors include three members, VEGFR1, VEGFR2, and VEGFR3. Within the VEGF family, VEGF-A apparently serves as a key player in angiogenesis. Ebina et al. reported that the number of CD34-positive vessels is increased in the early phase of IPF of the lungs [63]. The role of angiogenesis in the development of lung fibrogenesis has not yet been determined, although Antoniou showed elevated VEGF levels in the BAL in patients with IPF [64]. There is limited evidence concerning the relationship between VEGF and lung fibrosis. Farkas et al. reported the direct effects of VEGF-A on lung fibroblasts and found that VEGF-A enhances the collagen-I expression induced by TGF-β [65]. In addition, Hamada et al. demonstrated that gene therapy with the soluble flt-1 gene reduces pulmonary fibrosis in a BLM-induced model in mice [66]. On the other hand, Ou et al. reported that the VEGFR-2 antagonist SU5416 attenuates BLM-induced lung fibrosis in mice [67]. These reports suggest the possibility of the profibrotic effects of VEGF, although the effects are unknown with respect to the role of each isoform of VEGF/VEGFR.

### *4.4.4 TGF-β and TGF-β Receptors*

The signaling pathway via the TGF-β/TGF-β receptor complex is complicated [68, 69]. Human TGF-β ligand has three isoforms TGF-β1, TGF-β2, and TGF-β3, among which TGF-β1 has been reported to be a predominant isoform in cases of pulmonary fibrosis [70]. The TGF-β ligand binds heterodimeric serine/threonine kinase receptors of the TGF-β receptor I (TβRI) (ALK5) and TβRII. The binding of TGF-β to these receptors is regulated by several molecules, including latent TGF-β binding protein (LTBP) and integrins αVβ6. The signaling pathway in the

cytoplasm is also complex. The classical Smad pathway and non-Smad pathway differentially regulate the profibrotic effects of TGF-β. The biological activities of TGF-β are extremely pleiotropic and dependent on the type of cell and pathological condition. Representative activities are known to inhibit cell proliferation, regulate the extracellular matrix, suppress the immune response, and induce the epithelial-mesenchymal transition (EMT) [69]. Therefore, TGF-β is believed to play a central role in the pathogenesis of lung fibrosis.

The expression of TGF-β has been reported to be upregulated in the IPF lungs, particularly in AECs [71]. TGF-β stimulates the migration and production of collagen in lung fibroblasts [68, 69]. In addition, TGF-β inhibits the apoptosis of myofibroblasts. The involvement of TGF-β in lung fibrosis was recently demonstrated using BLM models of pulmonary fibrosis [72–74]. However, Andorianifahanana et al. showed that profibrotic TGF-β responses require the cooperative actions of PDGF and ErbB receptor tyrosine kinases [75]. Of course, the TGF-β function is partly mediated by the productions of CTGF and FGF-2 [76, 77]. Based on these reports, the profibrotic effects of TGF-β are mediated by several other growth factors, including PDGF, EGF, CTGF, and FGF-2, indicating that the role of TGF-β in lung fibrogenesis may have been overestimated. The other concern in targeting therapy for TGF-β is the paradoxical induction of persistent inflammation by blocking TGF-β signals [78, 79]. Therefore, further evidence is required to completely understand and control TGF-β signals.

### *4.4.5 Origin of Lung Fibroblasts and Their Contribution to Pulmonary Fibrosis*

Lung fibroblasts are thought to be differentiated from the mesoderm during embryonic development and exist in the interstitium of the lungs as resident fibroblasts [80]. However, recent findings have demonstrated other origins of lung fibroblasts [81]. In 2004, Hashimoto et al. clearly showed the existence of bone marrow-derived fibroblasts in the lungs treated with BLM in mice [82]. The typical phenotype of these cells was both CD45 and collagen positive, suggesting that the characteristics of these cells are compatible with those of so-called fibrocytes [83]. The presence of fibrocytes in the BLM model was also reported by Phillips et al., who confirmed that the trafficking of fibrocytes is dependent on the CXCL12/CXCR4 axis [84]. In the setting of IPF, patients with progressive fibrosis or acute exacerbation show increased numbers of fibrocytes in the peripheral blood [85]. However, the role of fibrocytes is currently moving to a supportive role for resident fibroblasts via the production of growth factors as a result of the direct contribution of collagen production in mice [86–89]. The significance of fibrocytes in IPF should be further examined.

The other source of these cells is believed to be EMT-derived fibroblasts. In 2005, Willis et al. reported the existence of the EMT in AECs in vitro as well as in

IPF lungs [90]. According to their data, AECs expressing both pro-SP-B and α-SMA are present in cases of IPF. Kim et al. also reported the existence of EMT-derived fibroblasts expressing both pro-SP-C and α-SMA in a BLM model [91], and Tanjore found EMT-derived cells ($S100A4^{+}$SP-C+) in a BLM model in mice, although the myofibroblasts expressing α-SMA were not derived from an EMT origin [92]. Subsequently, Rock et al. demonstrated no contribution of the EMT in α-SMA cells or $S100A4^{+}$ cells using a confocal microscopic analysis [93]. Although these results suggest the negligible contribution of the EMT in the pathogenesis of pulmonary fibrosis, we cannot rule out the possibility that the EMT is partially generated or that the incomplete differentiation of AECs still contributes by producing several mediators, albeit not ECM.

Pleural mesothelial cells (PMCs) are reported to transform into fibroblasts in response to TGF-β in vitro [94]. In recombinant mice for GFP driven by the Wilms tumor-1 promotor, PMCs trafficking into the lungs are found to express α-SMA [95]. Although PMC-derived myofibroblasts are detected in the subpleural area of the IPF lungs, the number of these cells is reduced, indicating that PMCs are not a major source of myofibroblasts in IPF [95]. Meanwhile, endothelial cells are a major cellular component of the lungs. Hashimoto et al. reported that endothelial cells differentiate into myofibroblasts in vitro as well as in mice [96]. Although further research is required in humans, the endothelial-mesenchymal transition (EndoMT) may contribute to the onset of fibrogenesis in the case of IPF. More recently, pericytes have become a center of attention as a novel origin of lung myofibroblasts. Pericytes are known to be specialized mesenchymal cells that share a common basement membrane with endothelial cells. Using Foxd1-mapping system in genetically modified mice, Hung et al. demonstrated that 45–68 % of myofibroblasts are derived from pericytes in the lungs of BLM-treated mice [97]. Further analyses of pericytes in the IPF lungs are expected in future studies.

### *4.4.6 Loss of Alveolar Epithelial Integrity and Pulmonary Fibrosis*

The concept of epithelial cell integrity may have an effect on the pathogenesis of IPF. Tsujino et al. found that $CD151^{-/-}$ mice spontaneously develop age-related pulmonary fibrosis and display increased susceptibility to BLM-induced lung fibrosis [98]. CD151 is a tetraspanin protein expressed on the basolateral surface of AECs that exhibits binding with integrin α3β1 and maintains epithelial integrity to support the adhesion of AECs to the basement membrane. In the setting of IPF, the expression of CD151 is significantly downregulated in AECs. A similar phenomenon is observed in mice deficient for phosphatase and tensin homolog deleted from chromosome 10 (Pten). Pten is a multifunctional phosphatase that negatively regulates the PI3K/Akt pathway. Miyoshi et al. showed that the knockdown of *Pten* in AECs induces the dysfunction of tight junctions and exacerbates lung fibrosis

induced by BLM [99]. Furthermore, the phosphorylation of Akt is enhanced in the lungs of *Pten*-deleted mice, and the blockade of Akt by the inhibitor reduces pulmonary fibrosis. Moreover, a decreased expression of Pten and enhanced phosphorylation of Akt are observed in the lungs of IPF animals, and the AECs in *Pten*-deficient mice show reduced expressions of surfactant proteins [100]. However, it remains undetermined whether the loss of epithelial cell integrity is a causative factor in IPF. In contrast to that observed in CD151-deficient mice, lung fibrosis in *Pten*-deficient mice is not dependent on TGF-β signals. Therefore, disorders in epithelial integrity may be crucial and fundamental for the progression of lung fibrosis in the case of IPF.

### *4.4.7 Resolution of ECM and Fibrosis*

The resolution of pulmonary fibrosis is dependent on the degradation of ECMs. The irreversible fibrosis noted in cases of IPF may be related with the abnormalities in the resolution phase. It is known that the balance between matrix metalloproteases and its inhibitors is theoretically crucial for ECM metabolism. The gene expression profile determined using a microarray analysis has demonstrated that several MMPs are associated with pulmonary fibrosis in mice and IPF patients [101–103]. However, mice deficient for MMP-3 or MMP-7 are protected from the onset of BLM-induced lung fibrosis. On the other hand, MMP-19$^{-/-}$ mice show marked enhancement of pulmonary fibrosis, indicating that the role of MMPs is complicated due to the interaction of both direct and indirect effects. Recently, LeBleu et al. identified a novel proteinase inhibitor, a human epididymis protein (HE)-4, of the novel serine proteases Prss35 and Prss23 in a renal fibrosis model [104]. Furthermore, the neutralizing antibody for HE-4 significantly improves renal fibrosis in mice. Therefore, specific molecules related to ECM metabolism in the lungs may be important for regulating pulmonary fibrosis.

Another interesting point in terms of the matrix is the degree of stiffness of the IPF lungs. Booth et al. reported the significance of the matrix, but not cells (fibroblasts), in regulating the profibrotic phenotype [105].

### *4.4.8 Conclusions*

Recent understanding with respect to the molecular pathogenesis of IPF was summarized in this chapter. However, the etiology of IPF is not fully understood. In addition, IPF is undoubtedly heterogeneous in clinical phenotype as well as pathogenesis. It is therefore difficult to fully explore the characteristics of fibrogenesis in the case of IPF. However, updated technology in the fields of genetics, proteomics, and mechanics (i.e., microscopy) may help to clarify the

remaining problems, particularly issues pertaining to the fundamental topics "what is IPF?," in the future.

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## References

1. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med. 2001;345:517–25.
2. Selman M, King Jr TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med. 2001;134:136–51.
3. White ES, Lazar MH, Thannickal VJ. Pathogenetic mechanisms in usual interstitial pneumonia/idiopathic pulmonary fibrosis. J Pathol. 2003;201:343–54.
4. King Jr TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378:1949–61.
5. Wright JR. Immunoregulatory functions of surfactant proteins. Nat Rev Immunol. 2005;5:58–68.
6. Nogee LM, Dunbar 3rd AE, Wert SE, et al. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344:573–9.
7. Brasch F, Griese M, Tredano M, et al. Interstitial lung disease in a baby with a de novo mutation in the SFTPC gene. Eur Respir J. 2004;24:30–9.
8. Wang Y, Kuan PJ, Xing C, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009;84:52–9.
9. Maitra M, Cano CA, Garcia CK. Mutant surfactant A2 proteins associated with familial pulmonary fibrosis and lung cancer induce TGF-β1 secretion. Proc Natl Acad Sci U S A. 2012;109:21064–9.
10. Armanios MY, Chen JJ-L, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356:1317–26.
11. Tsakiri KD, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A. 2007;104:7552–7.
12. Lee J, Reddy R, Barsky L, et al. Lung alveolar integrity is compromised by telomere shortening in telomerase-null mice. Am J Physiol Lung Cell Mol Physiol. 2009;296:L57–70.
13. Shulenin S, Nogee LM, Annilo T, et al. ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med. 2004;350:1296–303.
14. Bullard JE, Wert SE, Whitsett JA, et al. ABCA3 mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med. 2005;172:1026–31.
15. Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364:1503–12.
16. Garcia CK. Idiopathic pulmonary fibrosis: update on genetic discoveries. Proc Am Thor Soc. 2011;8:158–62.
17. Mulugeta S, Nguyen V, Russo SJ, et al. A surfactant protein C precursor protein BRICHOS domain mutation causes endoplasmic reticulum stress, proteasome dysfunction, and caspase 3 activation. Am J Respir Cell Mol Biol. 2005;32:521–30.
18. Maitra M, Wang Y, Gerard RD, et al. Surfactant protein A2 mutations associated with pulmonary fibrosis lead to protein instability and endoplasmic reticulum stress. J Biol Chem. 2010;285:22103–13.

19. Korfei M, Ruppert C, Mahavadi P, et al. Epithelial endoplasmic reticulum stress and apoptosis in sporadic idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178:838–46.
20. Lawson WE, Crossno PF, Polosukhin VV, et al. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol. 2008;294:L1119–26.
21. Kuwano K, Kunitake R, Kawasaki M, et al. P21Waf1/Cip1/Sdi1 and p53 expression in association with DNA strand breaks in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1996;154:477–83.
22. Roberson EC, Tully JE, Guala AS, et al. Influenza induces endoplasmic reticulum stress, caspase-12-dependent apoptosis, and c-Jun N-terminal kinase-mediated transforming growth factor-β release in lung epithelial cells. Am J Respir Cell Mol Biol. 2011;46:573–81.
23. Jorgensen E, Stinson A, Shan L, et al. Cigarette smoke induces endoplasmic reticulum stress and the unfolded protein response in normal and malignant human lung cells. BMC Cancer. 2008;8:229.
24. Torres-Gonzalez E, Bueno M, Tanaka A, et al. Role of endoplasmic reticulum stress in age-related susceptibility to lung fibrosis. Am J Respir Cell Mol Biol. 2012;46:748–56.
25. Marita M, Cano CA, Garcia CK. Mutant surfactant A2 proteins associated with familial pulmonary fibrosis and lung cancer induce TGF-β1 secretion. Proc Natl Acad Sci U S A. 2012;109:21064–9.
26. Tanjore H, Cheng DS, Degryse AL, et al. Alveolar epithelial cells undergo epithelial-to-mesenchymal transition in response to endoplasmic reticulum stress. J Biol Chem. 2011;286:30972–80.
27. Gharaee-Kermani M, Gyetko MR, Hu B, et al. New insights into the pathogenesis and treatment of idiopathic pulmonary fibrosis: a potential role for stem cells in the lung parenchyma and implications for therapy. Pharm Res. 2007;24(5):819–41.
28. Herdin CH, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. Physiol Rev. 1999;79:1283–316.
29. Li X, Eriksson U. Novel PDGF family members. PDGF-C and PDGF-D. Cytokine Growth Factor Rev. 2003;14:91–8.
30. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;22:1276–312.
31. Boström H, Willetts K, Pekny M, et al. PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell. 1996;14:863–73.
32. Soriano P. The PDGFα receptor is required for neural crest cell development and for normal patterning of the somites. Development. 1997;124:2691–700.
33. Levéen P, Pekny M, Gebre-Medhin S, et al. Mice deficient for PDGF B show renal, cardiovascular, and hematological abnormalities. Genes Dev. 1994;8:1875–87.
34. Soriano P. Abnormal kidney development and hematological disorders in PDGF beta-receptor mutant mice. Genes Dev. 1996;8:1888–96.
35. McGowan SE, Grossmann RE, Kimani PW, et al. Platelet-derived growth factor receptor-alpha-expressing cells localize to the alveolar entry ring and have characteristics of myofibroblasts during pulmonary alveolar septal formation. Anat Rec (Hoboken). 2008;291:1649–61.
36. Maeda A, Hiyama K, Yamakido H, et al. Increased expression of platelet-derived growth factor A and insulin-like growth factor-I in BAL cells during the development of bleomycin-induced pulmonary fibrosis in mice. Chest. 1996;109:780–6.
37. Walsh J, Absher M, Kelley J. Variable expression of platelet-derived growth factor family proteins in acute lung injury. Am J Respir Cell Mol Biol. 1993;9:637–44.
38. Zhou Y, Zheng J, Laboy M, et al. Modulation of PDGF-C and PDGF-D expression during bleomycin-induced lung fibrosis. Am J Physiol Lung Cell Mol Physiol. 2004;286:L182–8.
39. Shimizu S, Gabazza EC, Taguchi O, et al. Activated protein C inhibits the expression of platelet-derived growth factor in the lung. Am J Respir Crit Care Med. 2003;167:1416–26.

40. Yoshida M, Sakuma J, Hayashi S, et al. A histologically distinctive interstitial pneumonia induced by overexpression of the interleukin 6, transforming growth factor beta 1, or platelet-derived growth factor B gene. Proc Natl Acad Sci U S A. 1995;92:9570–4.
41. Antoniades HN, Bravo MA, Avila RE, et al. Platelet-derived growth factor in idiopathic pulmonary fibrosis. J Clin Invest. 1990;86:1055–64.
42. Homma S, Nagaoka I, Abe H, et al. Localization of platelet-derived growth factor and insulin-like growth factor I in the fibrotic lung. Am J Respir Crit Care Med. 1995;152:2084–9.
43. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168:159–66.
44. Nishioka Y, Azuma M, Kishi M, et al. Targeting platelet-derived growth factor as a therapeutic approach in pulmonary fibrosis. J Med Invest. 2013;60(3, 4):175–83.
45. Druker BJ, Tamura S, Buchdunger E, et al. Effects of s selective inhibitor of the abl tyrosine kinase on the growth of bcr-abl positive cells. Nat Med. 1996;2:561–6.
46. Rice AB, Moomaw CR, Morgan DL, et al. Specific inhibitors of platelet-derived growth factor or epidermal growth factor receptor tyrosine kinase reduce pulmonary fibrosis in rats. Am J Pathol. 1999;55:213–21.
47. Aono Y, Nishioka Y, Inayama M, et al. Imatinib as a novel antifibrotic agent in bleomycin-induced pulmonary fibrosis in mice. Am J Respir Crit Care Med. 2005;171:1279–85.
48. Daniels CE, Wilkes MC, Edens M, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-β and prevents bleomycin-mediated lung fibrosis. J Clin Invest. 2004;114:1308–16.
49. Abdollahi A, Li M, Ping G, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. J Exp Med. 2005;201:925–35.
50. Yoshida M, Sakuma-Mochizuki J, Abe K, et al. In vivo gene transfer of an extracellular domain of platelet-derived growth factor beta receptor by the HVJ-liposome method ameliorates bleomycin-induced pulmonary fibrosis. Biochem Biophys Res Commun. 1999;265:503–8.
51. Rhee CK, Lee SH, Yoon HK, et al. Effect of nilotinib on bleomycin-induced acute lung injury and pulmonary fibrosis in mice. Respiration. 2011;82:273–87.
52. Turner N, Grose R. Fibroblast growth factor signaling: from development to cancer. Nat Rev Cancer. 2010;10:116–20.
53. Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy. Nat Rev Drug Discov. 2009;8:235–53.
54. Powers CJ, McLeskey SW, Wellstein A. Fibroblast growth factors, their receptors and signaling. Endocr-Relat Cancer. 2000;7:165–97.
55. Hetzel M, Bachem M, Anders D, et al. Different effects of growth factors on proliferation and matrix production of normal and fibrotic human lung fibroblasts. Lung. 2005;183:225–37.
56. Kanazawa S, Fujiwara T, Matsuzaki S, et al. bFGF regulates PI3-kinase-Rac1-JNK pathway and promotes fibroblast migration in wound healing. PLoS One. 2010;5, e12228.
57. Guzy RD, Stoilov I, Elton TJ, et al. Fibroblast growth factor 2 is required for epithelial recovery, but not for pulmonary fibrosis, in response to bleomycin. Am J Respir Cell Mol Biol. 2015;52:116–28.
58. Ju W, Zhihong Y, Zhiyou Z, et al. Inhibition of α-SMA by the ectodomain of FGFR2c attenuates lung fibrosis. Mol Med. 2012;18:992–1002.
59. Ramos C, Becerril C, Montano M, et al. FGF-1 reverts epithelial-mesenchymal transition induced by TGF-β1 through MAPK/ERK kinase pathway. Am J Physiol Lung Cell Mol Physiol. 2010;299:L222–31.
60. Ramos C, Montano M, Becerril C, et al. Acidic fibroblast growth factor decreases a-smooth muscle actin expression and induces apoptosis in human normal lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2006;291:L871–9.
61. Becerril C, Pardo A, Montano M, et al. Acidic fibroblast growth factor induces an antifibrogenic phenotype in human lung fibroblasts. Am J Respir Cell Mol Biol. 1999;20:1020–7.

62. Shibuya M. Vascular endothelial growth factor receptor-1 (VEGFR-1/Flt-1): a dual regulator for angiogenesis. Angiogenesis. 2006;9:225–30.
63. Ebina M, Shimizukawa M, Shibata N, et al. Heterogeneous increase in CD34-positive alveolar capillaries in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2004;169 (11):1203–8.
64. Antoniou KM, Soufla G, Proklou A, et al. Different activity of the biological axis VEGF-Flt-1 (fms-like tyrosine kinase 1) and CXC chemokines between pulmonary sarcoidosis and idiopathic pulmonary fibrosis: a bronchoalveolar lavage study. Clin Dev Immunol. 2009;2009:537929.
65. Farkas L, Farkas D, Ask K, et al. VEGF ameliorates pulmonary hypertension through inhibition of endothelial apoptosis in experimental lung fibrosis in rats. J Clin Invest. 2009;119:1298–311.
66. Hamada N, Kuwano K, Yamada M, et al. Anti-vascular endothelial growth factor gene therapy attenuates lung injury and fibrosis in mice. J Immunol. 2005;175:1224–31.
67. Ou X-M, Li W-C, Liu D-S, et al. VEGFR-2 antagonist SU5416 attenuates bleomycin-induced pulmonary fibrosis. Int Immunopharmacol. 2009;9:70–9.
68. Varga J, Pasche B. Transforming growth factor b as a therapeutic target in systemic sclerosis. Nat Rev Rheumatol. 2009;5:200–6.
69. Akhurst R, Hata A. Targeting the TGFβ signaling pathway in disease. Nat Rev Drug Discov. 2012;11:790–812.
70. Coker RK, Laurent GJ, Shahzeidi S, et al. Transforming growth factors-β1, −β2, and -β3 stimulate fibroblast procollagen production in vitro but are differentially expressed during bleomycin-induced lung fibrosis. Am J Pathol. 1997;150:981–91.
71. Khalil N, O'Connor RN, Unruh HW, et al. Increased production and immunohistochemical localization of transforming growth factor-beta in idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol. 1991;150:981–91.
72. Sime PJ, Xing Z, Graham FL, et al. Adenovector-mediated gene transfer of active transforming growth factor-beta1 induces prolonged severe fibrosis in rat lung. J Clin Invest. 1997;100:768–76.
73. Wang Q, Wang Y, Hyde DM, et al. Reduction of bleomycin induced lung fibrosis by transforming growth factor beta soluble receptor in hamsters. Thorax. 1999;54:805–12.
74. Zhao J, Shi W, Wang YL, et al. Smad3 deficiency attenuates bleomycin-induced pulmonary fibrosis in mice. Am J Physiol Lung Cell Mol Physiol. 2002;282:L585–93.
75. Andrianifahanana M, Wilkes MC, Gupta SK, et al. Profibrotic TGFb responses require the cooperative action of PDGF and ErbB receptor tyrosine kinases. FASEB J. 2013;27:4444–54.
76. Li C-M, Khosla J, Pagan I, et al. TGF-β1 and fibroblast growth factor-1 modify fibroblast growth factor-2 production in type II cells. Am J Physiol Lung Cell Mol Physiol. 2000;279: L1038–46.
77. Kucich U, Rosenbloom JC, Herrick DJ, et al. Signaling events required for transforming growth factor-beta stimulation of connective tissue growth factor expression by cultured human lung fibroblasts. Arch Biochem Biophys. 2001;395(1):103–12.
78. Horan GS, Wood S, Ona V, et al. Partial inhibition of integrin αvβ6 prevents pulmonary fibrosis without exacerbating inflammation. Am J Respir Crit Care Med. 2008;177:56–65.
79. Puthawala K, Hadjiangelis N, Jacoby SC, et al. Inhibition of integrin αvβ6, an activator of latent transforming growth factor-β, prevents radiation-induced lung fibrosis. Am J Respir Crit Care Med. 2008;177:82–90.
80. Dunsmore SE, Shapiro SD. The bone marrow leases its scar: new concepts in pulmonary fibrosis. J Clin Invest. 2004;113:180–2.
81. Garantziotis S, Steele MP, Schwartz DA. Pulmonary fibrosis: thinking outside of the lung. J Clin Invest. 2004;114:319–21.
82. Hashimoto N, Jin H, Liu T, et al. Bone marrow-derived progenitor cells in pulmonary fibrosis. J Clin Invest. 2004;113:243–52.

83. Bucala R, Spiegel LA, Chesney J, et al. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. Mol Med. 1994;1:71–81.
84. Phillips RJ, Burdick MD, Hong K, et al. Circulating fibrocytes traffic to the lungs in response to CXCL12 and mediates fibrosis. J Clin Invest. 2004;114:438–46.
85. Reilkoff RA, Bucala R, Herzog E. Fibrocytes: emerging effector cells in chronic inflammation. Nat Rev Immunol. 2011;11:427–35.
86. Abe S, Okazaki H, Kishi M, et al. Fibrocytes regulates lung fibroblast activation. Am J Respir Crit Care Med. 2012;185:A4460.
87. Kleaveland KR, Velikoff M, Yang J, et al. Fibrocytes are not an essential source of type I collagen during lung fibrosis. Am J Respir Cell Mol Biol. 2014;193:5229–39.
88. Aono Y, Ledford JG, Mukherjee S, et al. Surfactant protein-D regulates effector cell function and fibrotic lung remodeling in response to bleomycin injury. Am J Respir Crit Care Med. 2012;185(5):525–36.
89. Aono Y, Kishi M, Yokota Y, et al. Role of PDGF/PDGFR axis in the trafficking of circulating fibrocytes in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2014;51(6):793–801.
90. Willis BC, Liebler JM, Luby-Phelps K, et al. Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor-β1. Am J Pathol. 2005;166:1321–32.
91. Kim KK, Kugler MC, Wolters PJ, et al. Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. Proc Natl Acad Sci U S A. 2006;103:13180–5.
92. Tanjore H, Xu XC, Polosukhin VV, et al. Contribution of epithelial-derived fibroblasts to bleomycin-induced lung fibrosis. Am J Respir Crit Care Med. 2009;180:657–65.
93. Rock JR, Barkauskas CE, Cronce MJ, et al. Multiple stromal populations contribute to pulmonary fibrosis without evidence for epithelial to mesenchymal transition. Proc Natl Acad Sci U S A. 2011;108:E1475–83.
94. Nasreen N, Mohammed KA, Mubarak KK, et al. Pleural mesothelial cell transformation into myofibroblasts and haptotactic migration in response to TGF-b1 in vitro. Am J Physiol Lung Cell Mol Physiol. 2009;297:L115–24.
95. Mubarak KK, Montes-Worboys A, Regev D, et al. Parenchymal trafficking of pleural mesothelial cells in idiopathic pulmonary fibrosis. Eur Respir J. 2012;39:133–40.
96. Hashimoto N, Phan SH, Imaizumi K, et al. Endothelial– mesenchymal transition in bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol. 2012;43:161–72.
97. Hung C, Linn G, Chow Y-H, et al. Role of lung pericytes and resident fibroblasts in the pathogenesis of pulmonary fibrosis. Am J Respir Crit Care Med. 2013;188:820–30.
98. Tsujino K, Takeda Y, Arai T, et al. Tetraspanin CD151 protects against pulmonary fibrosis by maintaining epithelial integrity. Am J Respir Crit Care Med. 2012;186(2):170–80.
99. Miyoshi K, Yanagi S, Kawahara K, et al. Epithelial Pten controls acute lung injury and fibrosis by regulating alveolar epithelial cell integrity. Am J Respir Crit Care Med. 2013;187:262–75.
100. Yanagi S, Kishimoto H, Kawahara K, et al. Pten controls lung morphogenesis, bronchioalveolar stem cells, and onset of lung adenocarcinomas in mice. J Clin Invest. 2007;117:2929–40.
101. Zuo F, Kaminski N, Eugui E, et al. Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. Proc Natl Acad Sci U S A. 2002;99:6292–7.
102. Yamashita CM, Dolgonos L, Zemans RL, et al. matrix metalloproteinase 3 is a mediator of pulmonary fibrosis. Am J Pathol. 2011;179:1733–45.
103. Yu G, Kovkarova-Naumovski E, Jara P, et al. matrix metalloproteinase 19 is a key regulator of lung fibrosis in mice and humans. Am J Repir Crit Care Med. 2012;186:752–62.
104. LeBleu VS, Teng Y, O'Connell JT, et al. Identification of human epididymis protein-4 as a fibroblast-derived mediator of fibrosis. Nat Med. 2013;19(2):227–31.
105. Booth AJ, Hadley R, Cornett AM, et al. Acellular normal and fibrotic human lung matrices as a culture system for in vitro investigation. Am J Respir Crit Care Med. 2012;186:866–76.

# Part II
# Diagnosis

# Chapter 5
# Specific Serum Markers of IPF

## What Is the Significance of KL-6, SP-A, and SP-D?

**Hirofumi Chiba and Hiroki Takahashi**

**Abstract** Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It is characterized by the progressive worsening of lung function and has a poor prognosis (median survival is approximately 3 years). However, the clinical course of disease shows considerable individual variability. Therefore, it is important to monitor the clinical course and to predict prognosis for optimal therapy. Serum biomarkers are both less invasive and reproducible diagnostic tools. Useful biomarkers for patients with IPF are strongly coveted; however, to date, there are no biomarkers that are globally known. In Japan, surfactant protein (SP)-A, SP-D, and KL-6 are commonly used as serum markers of interstitial pneumonia, including IPF, in the clinical setting, and empirical data has been accumulated over 10 years. SP-A and SP-D are hydrophilic proteins and members of the collectin family. These collectins have been shown to function as host defense lectins in the lung. KL-6 is a high molecular weight glycoprotein and now classified as a human MUC1 mucin protein. These three proteins are mainly synthesized by alveolar type II cells. The mechanisms of increase for these protein levels in sera of patients with IPF are probably a combination of a loss of epithelial integrity due to injury and an increased mass of type II cells due to hyperplasia. It has been revealed that those proteins are useful for monitoring the clinical course and predicting prognosis as well as for the diagnosis of IPF. In this review article, the molecular structures and biological functions of these biomarkers are outlined, and we discuss the clinical application of these biomarkers for patients with IPF.

**Keywords** Idiopathic pulmonary fibrosis • SP-A • SP-D • Collectins • KL-6 • Biomarker

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## 5.1 Introduction

Idiopathic pulmonary fibrosis (IPF), the most common form of the idiopathic interstitial pneumonias (IIPs), is a progressive, irreversible, life-threatening disease of unknown etiology. IPF occurs primarily in older adults, is limited to the lungs, and is associated with the histopathological and/or radiological patterns of usual interstitial pneumonia (UIP) [1–3]. Many IPF patients have a relatively slow clinical course; however, some patients experience acute respiratory deterioration. Patients with IPF have a poor prognosis (median survival is approximately 3 years) with considerable individual variability in the clinical course of disease [4, 5]. Options for the treatment of IPF are limited, and lung transplantation is the only curative therapy. To prompt consideration for lung transplantation, the importance of identifying patients with increased risk of mortality within 2 years has been mentioned [1, 6].

Currently, several factors in predicting prognosis and evaluating disease severity for patients with IPF have been proposed. Patients that are older and male have been reported as having a worse prognosis in some but not all studies. Longitudinal change in physiology is clearly an important predictor of mortality in IPF. A decline in FVC over 6 or 12 months has been reliably associated with decreased survival [7–10]. A decline in DLco has also been associated with decreased survival [9, 10]. Some studies have suggested that desaturation during the 6-min walk test is a marker for an increased risk of mortality [11, 12].

Biomarkers for IPF are highly desired for several reasons. These include predicting patients at risk for developing IPF (predisposition biomarkers), diagnosing patients with IPF (screening or diagnostic biomarkers), monitoring clinical course and therapeutic effects (monitoring or therapeutic biomarkers), and predicting prognosis and evaluating disease severity (prognostic and staging biomarkers). In addition, serological biomarkers are preferred because they do not require an effort from patients, can be reproducible, and are less invasive. To date, there are no biomarkers used worldwide in the clinical setting. Several candidate biomarkers have been mentioned, namely, surfactant protein (SP)-A, SP-D, KL-6, matrix metalloproteinase (MMP)-1, MMP-7, and CC chemokine ligand-18 (CCL18) [13–18]. In Japan, SP-A, SP-D, and KL-6 are commonly used as serum markers of interstitial pneumonia, including IPF, in clinical settings, with empirical data accumulated for the last 10 years. We extensively discuss this issue in this article based on accumulated experience.

## 5.2 What Molecules Are SP-A and SP-D?

### *5.2.1 Structural Organization of SP-A and SP-D*

SP-A and SP-D are structurally similar to the C1q component of complement- and mannose-binding protein. These molecules are members of the collectin family. The collectins possess four major structural domains: (1) an amino terminus containing a cysteine involved in interchain disulfide bond formation, (2) a collagen-like domain consisting of Gly-X-Y repeats, (3) a neck domain containing a short hydrophobic stretch of amino acids and amphipathic helix, and (4) a lectin domain (a carbohydrate recognition domain, CRD). The collagenous domains promote trimerization, and the trimers undergo disulfide cross-linking to form higher-order oligomers. SP-A forms a bouquet-like octadecamer assembled from six trimers, whereas SP-D forms a cruciform dodecamer assembled from four trimers (Fig. 5.1) [19–22]. The monomeric molecular mass of SP-A and SP-D is 30–36 kD and 43 kD, respectively. The molecular mass of the SP-A octadecamer is reported to be approximately 650 kD by gel filtration analysis and that of the SP-D dodecamer is approximately 540 kD [23].

### *5.2.2 Biochemical and Biological Functions of SP-A and SP-D*

Within the lung, SP-A and SP-D are produced in alveolar type II cells and Clara cells. These pulmonary collectins bind to mannose, maltose, glucose, and fucose with higher affinities [24, 25]. SP-A interacts with surfactant phospholipids including dipalmitoylphosphatidylcholine (DPPC) and glycosphingolipids, such as galactosylceramide, in addition to the carbohydrates [26, 27]. SP-D also binds to phosphatidylinositol (PI) and glucosylceramide [28, 29].

Pulmonary collectins have been shown to function as host defense lectins [30]. The proteins have been shown to bind gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*, gram-positive organisms such as *Streptococcus pneumoniae*, fungi including *Aspergillus* and *Candida*, and other pathogens including *Mycobacterium tuberculosis*, *Pneumocystis carinii*, and influenza virus. SP-A is thought to bind to pathogens via its CRD [31, 32]. The in vivo studies clearly reveal that pulmonary collectins are involved in bacterial clearance. SP-A binds to and enhances the phagocytosis of bacteria including *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, and *Haemophilus influenzae* by alveolar macrophages [33]. SP-D also binds to microorganisms and aids opsonization and phagocytosis by alveolar macrophages [34]. Pulmonary collectins have been shown to function as inflammatory modulators in the lung. Pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) and peptidoglycan, are potent stimulators of

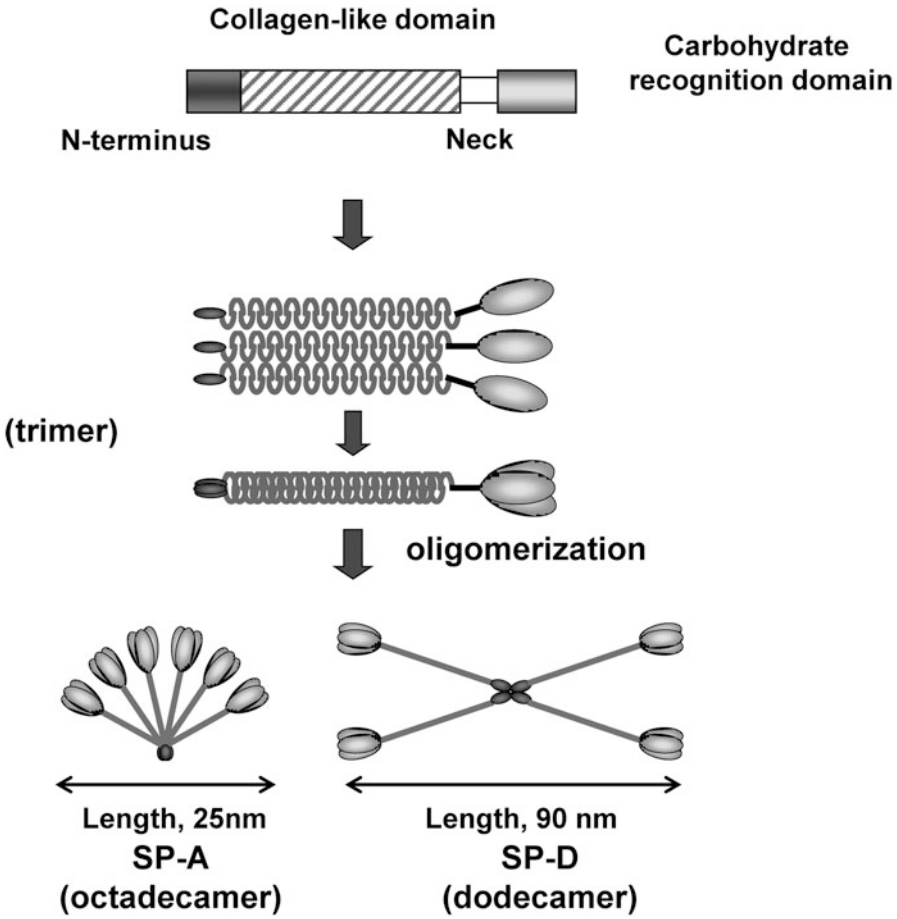


**Fig. 5.1** *Structures of SP-A and SP-D*. Monomeric and oligomeric structures of SP-A and SP-D. Monomeric structures can be conceptually divided into four major structural domains: a short N-terminal segment containing two intermolecular disulfide bonds, a collagen-like sequence of Gly-X-Y repeats, an acidic and hydrophobic neck domain, and a C-terminal carbohydrate recognition domain (CRD). The CRD contains a calcium-dependent, carbohydrate-binding site. The matured molecule of SP-A and SP-D contains six and four trimeric subunits, respectively

inflammatory cytokine secretion. Pattern recognition receptors, including Toll-like receptor (TLR) and CD14, are responsible for the recognition and signaling of PAMPs and cytokine production. A previous study demonstrated the different actions of SP-A for distinct serotypes of LPS. SP-A inhibits the macrophage-derived TNF-α secretion induced by smooth LPS, which is a complete structural form of LPS. On the other hand, SP-A does not attenuate or even augment TNF-α secretion elicited by rough LPS, which does not express O-specific antigen and is an SP-A ligand. These distinct effects of SP-A occur through the direct interaction of SP-A with CD14 [35]. SP-A also inhibits TNF-α secretion by gram-positive bacteria via the interaction with SP-A and TLR2, which recognizes peptidoglycan,

a major cell wall component of gram-positive bacteria [36]. Taken together, lung collectins exhibit both inflammatory and anti-inflammatory functions. These distinct activities depend on the ligand-binding specificities of collectins.

## 5.3 What Molecule Is KL-6?

Anti-KL-6 monoclonal antibody (mAb) was first developed to recognize sialylated sugar chains as a serum tumor biomarker for pulmonary, breast, and pancreatic cancers. Although the precise epitope structure recognized by the anti-KL-6 mAb was unclear, the possible carbohydrate epitopes have been reported to be novel O-linked glycans containing 6′sulfo-Gal/GalNAc of MUC1 [37]. Hirasawa et al. reported that KL-6 was a submolecule of MUC1 based on the results of a carbohydrate composition analysis [38]. KL-6/MUC1 is commonly used to denote the KL-6 molecule.

MUC1 is a large glycoprotein containing three domains: (1) a cytoplasmic tail, (2) a single transmembrane region, and (3) an extracellular domain. The extracellular region of MUC1 contains sites of O- and N-linked glycosylation and variable number tandem repeat (VNTR) domains with 20–100 repeats of a 20-amino-acid sequence. MUC1 has an extended, rigid structure protruding 200–500 nm above the plasma membrane and is found on the apical surface of normal glandular epithelial cells (Fig. 5.2) [39, 40].

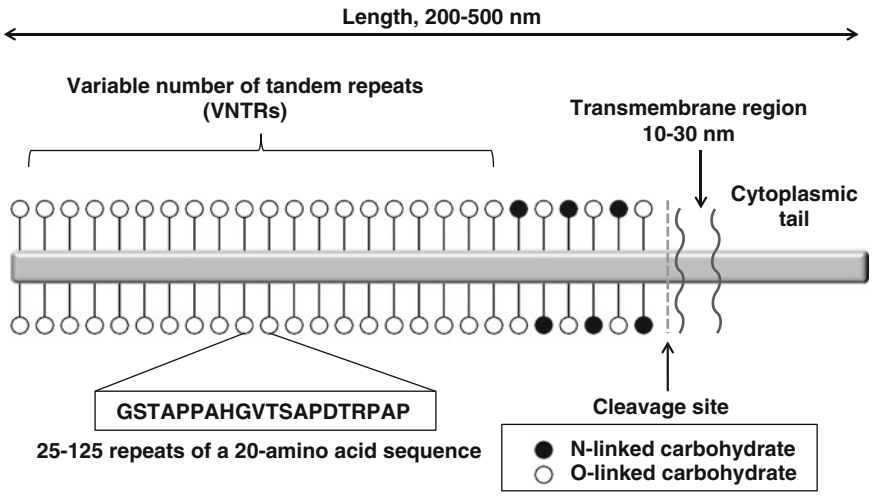


**Fig. 5.2** *Structure of MUC1*. MUC1 is a large glycoprotein that contains three major structures: a cytoplasmic tail, a single transmembrane region, and an extracellular domain. The extracellular region contains sites of O- and N-linked glycosylation and variable number tandem repeat (VNTR) domains of 20–100 repeats of a 20-amino-acid sequence

### 5.3.1 *Biochemical and Biological Functions of KL-6*

KL-6 is normally expressed on the apical surface of glandular epithelial cells in many types of tissue including the breast, lung, and ovary. In the normal lung tissue, it is produced in alveolar type II cells and respiratory bronchiolar epithelial cells and is weakly expressed in basal cells of the terminal bronchial epithelium [41, 42]. KL-6 can be cut and released from the cell surface through the action of TNF-α converting enzyme (TACE; also called a disintegrin and metalloproteinase 17 [ADAM17]) and potentially ADAM9 [40, 43]. In addition, some soluble KL-6 may result from alternative splicing. In a transfection study using breast cancer cells, MUC1 prevented E-cadherin-mediated cell-cell and cell surface adhesion [44]. Another study demonstrated that anti KL-6 mAb mediates capping of MUC1 and restores E-cadherin, leading to inhibition of tumor proliferation [45]. These results suggested that KL-6 may be a target molecule of cancer therapy. In relation to the pathological role of lung fibrosis, previous reports have shown that KL-6 is one of the chemotactic factors for fibroblasts and has both proliferative and antiapoptotic effects for fibroblasts [38, 46]. These results indicate that KL-6 may stimulate fibrotic processes in interstitial lung diseases and support the theory that KL-6 is one of the key molecules involved in the intra-alveolar fibrotic process of pulmonary fibrosis.

## 5.4 How Do SP-A, SP-D, and KL-6 Appear in the Bloodstream?

Although surfactant proteins had been believed to be solely in the lungs, Chida et al. reported that surfactant proteins could be found in the sera of patients with RDS using a competitive ELISA with polyclonal antibody against SP-A or SP-B. A positive result for SP-A was obtained in four infants with RDS at 1 week of age and one surfactant-treated infant. All sera obtained at 2 months of age were negative for SP-A and SP-B. The specificities of antibodies and the presence of surfactant proteins in serum were not demonstrated in this study [47]. The enzyme-linked immunosorbent assay (ELISA) with two mAbs (PC6 and PE10) to human SP-A has been applied to the sera of patients with interstitial lung diseases. The sandwich ELISA is capable of determining an SP-A level ranging from 2 to 250 ng/mL when native SP-A isolated from patients with pulmonary alveolar proteinosis is used as a standard [15, 48]. Since human SP-A has been found to contain group A antigenic determinants, the criticism may be raised that monoclonal antibodies PC6 and PE10 may recognize simply group A antigen but not SP-A in the blood samples. When human serum is applied to an affinity column on mannose-sepharose and the serum proteins binding to the mannose-affinity matrix are analyzed by immunoblotting using anti-SP-A monoclonal antibody or anti-SP-D monoclonal antibody, the fraction with lectin activity contains approximately 35 kDa protein and 43 kDa

protein, which correspond to the molecular sizes of SP-A and SP-D, respectively, purified from bronchoalveolar lavage fluid (BALF) [49]. This demonstrates that SP-A and SP-D exist in the bloodstream. One study has experimentally demonstrated that SP-A leaks from alveolar spaces into vessels. Human recombinant SP-A and/or artificial surfactant was intratracheally injected into immature newborn rabbits, and human SP-A in alveolar washings and sera was monitored by ELISA with PC6 and PE10, which do not cross-react with rabbit SP-A. The group that intratracheally received human SP-A and saline showed that 2.4 % of the human SP-A which was instilled into the lungs was detected in sera by ELISA. Since the group receiving saline alone showed no detectable human SP-A in sera, this study clearly demonstrates that SP-A leaks from alveolar space into the bloodstream [50]. Although the exact mechanism for the increase of SP-A and SP-D in sera of patients with interstitial pneumonia remains unknown, it is probably a combination of a loss of epithelial integrity due to injury and an increased mass of alveolar type II cells due to hyperplasia (Fig. 5.3).

Regenerating alveolar type II cells are the main cellular source of KL-6 in the lungs of patients with interstitial pneumonias, including IPF and KL-6, which are present at high levels in BALF [51]. A correlation between KL-6 levels measured in BALF and in serum was shown in patients with interstitial pneumonia. In patients with chronic beryllium disease, KL-6 serum levels correlated with albumin levels in BALF [52]. These results demonstrated that KL-6, which was produced in the lungs, appeared in the bloodstream as well as lung collectins and that serum KL-6

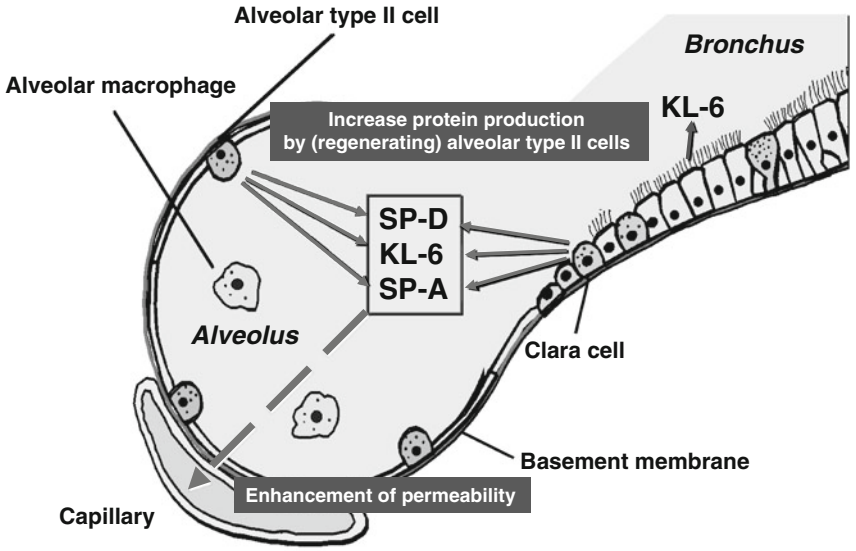


**Fig. 5.3** *Mechanism for the blood uptake of SP-A, SP-D, and KL-6*. The increased serum levels of SP-A, SP-D, and KL-6 may be due to an increase in production of these proteins by (regenerating) alveolar type II cells and enhanced permeability following the destruction of the alveolar-capillary barrier

levels reflected the permeability of the air-blood barrier (Fig. 5.3). Since KL-6 is an extremely high molecular weight glycoprotein, both the destruction of the alveolar-capillary barrier and the enhancement of alveolar-capillary permeability are thought to be necessary for the leakage of KL-6 into the bloodstream.

## 5.5 Utility as Biomarkers for Screening and Monitoring of Patients with IPF

The mean level of SP-A in sera from 323 healthy control subjects was estimated to be $24.6 \pm 9.6$ ng/mL [53], and there was no difference in the levels stratified by gender and age [54]. However, the SP-A levels tend to be slightly higher in cigarette smokers [55]. The mean level of SP-D in sera from 129 healthy control subjects was $49 \pm 24$ ng/mL, and there was also no difference between SP-D levels by gender and age [56]. We reported that the serum SP-A and SP-D levels in patients with IPF were increased: mean levels of $77.6 \pm 47.6$ ng/mL and $303 \pm 220$ ng/mL ($n = 57$), respectively. When the cutoff values (mean $\pm$ 2SD of healthy control subjects) were set at 43.8 ng/mL for serum SP-A and 109.8 ng/mL for serum SP-D, IPF patients showed high sensitivities for SP-A (78 %) and SP-D (87 %). These values were extremely high in comparison with lactate dehydrogenase (LDH) (17 %), which is not specific to the lungs and is released from many organs [13–15, 48, 56].

Kohno et al. reported that the average serum levels of KL-6 for 160 healthy control subjects was $258 \pm 131$ U/mL (mean $\pm$ SD). When the upper limit of normal range was set at 520 U/mL (mean $\pm$ 2SD), the positive late for idiopathic interstitial pneumonia, including IPF, is 74 % (28 of 38) [42].

It should be noted that serum levels of these three markers increase in some diseases and are not specific to IPF. Previous studies have demonstrated that the levels of SP-A, SP-D, and KL-6 are elevated in sera from patients with IPF and other interstitial lung diseases (ILDs) such as collagen vascular disease (CVD)-ILD, radiation-induced pneumonitis, pulmonary alveolar proteinosis, and ARDS [14, 15, 48, 57–60]. Thus, these biomarkers may reflect alveolar epithelium cell dysfunction in a broad sense, which may not be specific to the pathogenesis of IPF. In addition, patients with advanced stages of lung cancer show high concentrations of these biomarkers in sera. Serum KL-6 is also elevated in patients with advanced stages of pancreatic and breast cancers [41, 61]. Serum SP-A, SP-D, and KL-6 are also elevated in some infectious diseases such as pneumocystis and cytomegalovirus pneumonia [62, 63].

With regard to monitoring of clinical course, acute exacerbation is an extremely important phenomenon. We reported that the most common cause of death in Japanese IPF patients was acute exacerbation with a frequency of 40 % in a large-scale epidemiological survey [64]. It is important to promptly know about the occurrence of acute exacerbation and to start optimal therapy. High-resolution computed tomography (HRCT) is a reliable examination method for detecting acute

exacerbations; however, it is not always possible to be repeated at frequent intervals. The serum levels of these biomarkers increase without exception when patients with IPF develop respiratory failure due to acute exacerbation [13, 65]. In contrast, IPF patients developing respiratory failure due to bacterial infection seldom show high levels of these biomarkers. Therefore, the measurements of these biomarkers may support the differential diagnosis for causes of acute respiratory failure. Moreover, in many patients, the levels concomitantly decline promptly with clinical improvement, suggesting that these biomarkers may be reliable monitoring markers.

## 5.6 Utility as Biomarkers for Evaluating Disease Activity and Predicting Prognosis of Patients with IPF

It is an important role for biomarkers to predict prognosis because patients with IPF have considerable individual variability in clinical course of disease. Our study demonstrated that high levels of serum SP-A and SP-D were associated with mortality in patients with IPF. Fifty-two IPF patients were studied to evaluate the association between serum SP-A and SP-D and deterioration in pulmonary function and survival during 3 years of follow-up. The SP-D concentration, unlike that of SP-A, was related to the rate of deterioration per year in pulmonary function. The concentrations of SP-A and SP-D in patients who died within 3 years were significantly higher than in patients who were still alive after 3 years. Initial SP-A levels in non-survivors ($117.7 \pm 66.8$ ng/mL) were significantly higher than those in survivors ($68.8 \pm 40.4$ ng/L) ($p = 0.0125$). Initial SP-D levels in non-survivors ($453.7 \pm 290.3$ ng/mL) were also significantly higher than those in survivors ($248.0 \pm 176.4$ ng/mL) ($p = 0.0032$) [13]. In a study using Cox's proportional hazards model, Greene et al. found that the levels of serum SP-A (log of SP-A, HR, 1.73; $p = 0.031$) and SP-D (log of SP-D, HR, 2.04; $p = 0.003$) in patients with IPF ($n = 142$) were significant predictors of mortality after adjusting for smoking history and age [14]. These studies were performed before ATS/ERS consensus classification for the diagnosis of IPF and might have included patients with nonspecific interstitial pneumonia [2]. Kinder et al. found that serum SP-A levels (each increase of 48.7 ng/mL, HR, 3.27; $p = 0.003$) were associated with an increased risk of 1-year mortality after controlling for known clinical predictors. There was no significant association between SP-D level and mortality, although addition of SP-D to SP-A improved 1-year mortality prediction significantly (area under the curve, 0.89 vs 0.76; $p = 0.03$) [66].

Satoh et al. reported that patients with higher levels of KL-6 had increased risk of mortality in patients with ILD [67]. During the study period (1999–2005), 219 patients (152 patients with IIP and 67 patients with CVD- ILD) were enrolled in this study. On HRCT scan, 183 patients showed an IPF/usual IP pattern. The median follow-up period of the 219 patients was 20 months. Overall mortality was

26.5 %. Serum KL-6 levels in the 58 non-survivors (median, 1330 U/mL) were significantly higher than those of the 161 survivors (median, 823/U/mL) ($p = 0.0004$). On the basis of receiver operating characteristic (ROC) analysis, the optimal point on the ROC curves for discriminating between survivors and non-survivors corresponding to KL-6 was 1000 U/mL. When the optimal cutoff level of 1000 U/mL was applied, its sensitivity was 67.2 % and specificity was 60.2 %. Yokoyama et al. reported a correlation between serum KL-6 levels and survival [16]. Twenty-seven patients with IPF were assessed retrospectively. During the 3 years of observation, 10 of 27 patients died. On the basis of univariate logistic correlation analysis, both KL-6 and LDH had significant correlations with survival among the six variables (age, VC% predicted, $PaO_2$, C-reactive protein, LDH, and KL-6). Furthermore, multivariate analysis revealed that KL-6 but not LDH predicted prognosis. When the optimal cutoff level of 1000 U/mL was applied, survival was significantly different between the two groups (median survival, 36 months vs 18 months).

Song et al. hypothesized that a combination of biomarkers may be a more accurate predictor than any single biomarker alone [17]. In 118 patients with IPF, the predictive power of serum levels of biomarkers (SP-A, SP-D, KL-6, and MMP-7) and the predictive power of biomarkers in combination for clinical outcomes were shown. The data showed that blood levels of MMP-7 and SP-A are useful predictors of mortality and disease progression in IPF. The combination of both biomarkers yielded only marginally better prediction than clinical parameters alone; however, with addition of three biomarkers (MMP-7, SP-A, and KL-6), the improvement in predictability became statistically significant [17].

## 5.7 Relation Between HRCT Findings and Biomarkers

HRCT scanning is widely recognized to be a gold standard in determining disease activity and extent of pulmonary fibrosis. The HRCT pattern of IPF commonly shows patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities. There may be a variable amount of ground-glass opacity (GGO) and alveolar opacity (AO). In areas of more severe involvement, there is often reticular opacity, traction bronchiectasis (TBE), and subpleural honeycombing (HCMB). The GGO observed on HRCT in patients with IPF can be associated with alveolar inflammation, mild fibrotic thickening of alveolar septa, and intraluminal fibroblastic foci. Areas of GGO often progress to reticular opacity or HCMB on follow-up evaluation.

We evaluated HRCT findings from 49 IPF patients to assess the correlation between scoring of HRCT findings and serum SP-A and SP-D levels [13]. In this study, the extent of GGO correlated significantly with serum levels of SP-A and SP-D (SP-A, $\rho = 0.791$, $p < 0.0001$; SP-D, $\rho = 0.446$, $p < 0.0001$, $p = 0.0034$, when analyzed using Spearman's rank correlation test), whereas the extent of HMCB did not correlate with levels of either surfactant proteins. Next, we divided the IPF

subjects into two subgroups: GGO-dominant type and parenchymal collapse opacity (PCO), which was defined as air bronchiolograms with intense lung attenuation with parenchymal collapse, often accompanied by thickened vessels and traction bronchiectasis. PCO may reflect collapsed and fibrotic abnormalities in peripheral airspaces of alveoli and bronchioles. SP-A levels ($51.3 \pm 33.3$ ng/mL) in PCO-dominant type were significantly ($p = 0.0003$) lower than those ($98.3 \pm 55.8$ ng/mL) in the GGO-dominant type, whereas SP-D levels were not significantly different for two types (GGO-dominant type, $243.1 \pm 142.4$ ng/mL; PCO-dominant type, $266.6 \pm 161.1$ ng/mL). The sensitivity of SP-A (52 %) was inferior to SP-D (83 %) in the PCO-dominant group. This may explain why SP-D is superior to SP-A in detecting mild interstitial changes, and mechanisms of increases in these proteins may differ.

## 5.8 Mechanism and Significance for Dissociation Among Serum Biomarker Levels

Simultaneous measurement of the serum levels of SP-A, SP-D, and KL-6 in patients with IPF sometimes reveals a dissociation among these serum biomarkers. For instance, an increase in the serum levels of SP-A and SP-D even in early and mild lung injury is often observed, while serum KL-6 levels remain unchanged [68]. The increases in serum KL-6 mean a leakage of high molecular weight protein from the alveolar space into the bloodstream, and that indicates an intense destruction of the alveolar-capillary barrier. It is believed that the discrepancy between serum KL-6 and lung collectins reflects the difference in the extent of alveolar epithelium damage. As another mechanism for dissociation, the dissociation between KL-6 and collectins in patients with acute eosinophilic pneumonia (AEP) may be a good case. Serum SP-A and SP-D are present at quite high levels; however, serum KL-6 remains at low level in AEP patients [69]. Lung collectins are secretory proteins, while KL-6 is basically a structural component of the cell membrane and its extracellular domain binds to the cell surface. Therefore, the presence of some proteinase, such as ADAM17 or ADAM9, to cleave its extracellular domain, may be essential for liberation into the alveolar space. If enzyme activity is lacking, KL-6 will be limited on the cell surface even though severe interstitial damage exists. BALFs from IPF patients show high concentrations of KL-6; however, KL-6 in the BALFs from AEP patients are within normal range, suggesting the mechanism responsible for the difference may be associated with the secretion manner of these proteins.

SP-A and SP-D are proteins with high homology and similar molecular weight; however, patients often showed differences in serum levels for the two proteins. A recent study from this laboratory demonstrated that the difference in hydrophilicity of the two proteins could be the cause of their difference in migration from the air space into the bloodstream [70]. Most of the SP-A found in the alveolar space is

bound to DPPC, which is the main component of pulmonary surfactant. In contrast, SP-D remains in a lipid-free state in the alveolar space. SP-A decreases hydrophilicity by binding to DPPC, thus making it more difficult for SP-A to migrate to the bloodstream. Because SP-D leaks into the circulation more easily than SP-A, serum levels of SP-D may reflect pathological changes of the disease more sharply than those of SP-A.

In addition to the above mechanisms, the difference in half-life of these biomarkers in the bloodstream may also be related to dissociation.

## 5.9 Biomarkers for IPF Other Than SP-A, SP-D, and KL-6

Some studies have reported new candidates for biomarkers of IPF other than SP-A, SP-D, and KL-6. CCL18 is a chemotactic factor produced by alveolar macrophages and stimulates collagen production in pulmonary fibroblasts by TGF-β-signaling pathway in an independent manner. In interstitial pneumonia including IPF, the number of CCL18-positive macrophages increased. In 72 patients with IPF, it was demonstrated that baseline serum CCL18 levels predicted a change in TLC and FVC at 6-month follow-up [18]. ROC analysis revealed a significant relationship between survival and baseline CCL18 levels. The cutoff value with the highest diagnosis accuracy was defined as 150 ng/mL ($p < 0.0001$). The hazard proportional ratio adjusted for age, sex, and baseline pulmonary function data was 8.0. There was a higher incidence of disease progression in the group with high serum CCL18 levels. Therefore, serum CCL18 levels may be one of several useful prognostic biomarkers.

MMPs are a large family of zinc-containing metallopeptidases that degrade biological mediators and facilitate cell migration. MMPs are critically important in homeostasis of the ECM, expressed at low levels in healthy tissue, and upregulated in wound healing. MMPs are some of the most highly expressed genes in the lungs of IPF patients. In IPF-affected lungs, MMPs are primarily produced by activated alveolar type II cells; however, a few enzymes are produced by fibroblasts within the fibroblast foci. In 74 patients with IPF, serum MMP-1 and MMP-7 levels were significantly higher in IPF patients compared to healthy subjects [71]. MMP-1 and MMP-7 serum protein levels are also higher in IPF compared with subacute/chronic hypersensitivity pneumonia, sarcoidosis, and COPD. In addition, MMP-7 levels correlate with impairment of pulmonary function (FVC and DLco) in patients with IPF. In a large clinical trial cohort of IPF subjects ($n = 438$), MMP-7 was an independent predictor of survival in a model including clinical parameters (sex, FVC, DLco) and MUC5B genotype ($p = 0.04$).

## 5.10 Conclusion

IPF is a biologically heterogenous disease. Diversity is one of the features of this disease. In clinical practice for patients with IPF, the biomarkers are required in the following points: diagnosing the patients (diagnostic biomarkers), monitoring clinical course and therapeutic effect (monitoring or therapeutic biomarkers), and predicting prognosis (prognostic biomarkers). To date, there are no universally accepted biomarkers used in the clinical setting.

In Japan, SP-A, SP-D, and KL-6 are commonly used as serum markers of interstitial pneumonia, including IPF, in clinical settings. The mechanisms underlying serum elevation probably include a combination of epithelial injury and breakdown, together with increased accumulation of alveolar type II cells due to hyperplasia. Multiple studies have demonstrated the utility of these biomarkers for IPF. These markers are useful for diagnosing, monitoring, and predicting prognosis of patients with IPF. The serum levels of these biomarkers sometimes reveal a dissociation. It is believed that the dissociation between serum KL-6 and lung collectins reflects the difference of the extent of alveolar epithelium damage.

Some studies have reported new candidates for biomarkers of IPF other than SP-A, SP-D, and KL-6. These biomarkers could, in the near future, improve accuracy of diagnosis and predictability of prognosis and lead to optimal therapy.

## References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
2. American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med. 2000;161:646–64.
3. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2002;165:277–304.
4. Collard HR, Moore BB, Flaherty KR, Brown KK, Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176:636–43.
5. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012;126:355–61.
6. Kistler KD, Nalysnyk L, Rotella P, Esser D. Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. BMC Pulm Med. 2014;14:139.
7. Collard HR, King Jr TE, Bartelson BB, Vourlekis JS, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168:538–42.
8. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168:543–8.

9. Latsi PI, du Bois RM, Nicholson AG, Colby TV, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med. 2003;168:531–7.
10. Best AC, Meng J, Lynch AM, Bozic CM, et al. Idiopathic pulmonary fibrosis: physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology. 2008;246:935–40.
11. Lama VN, Flaherty KR, Toews GB, Colby TV, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168:1084–90.
12. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, et al. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J. 2005;25:96–103.
13. Takahashi H, Fujishima T, Koba H, Murakami S, et al. Serum surfactant proteins A and D as prognostic factors in idiopathic pulmonary fibrosis and their relationship to disease extent. Am J Respir Crit Care Med. 2000;162:1109–14.
14. Greene KE, King Jr TE, Kuroki Y, Bucher-Bartelson B, et al. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. Eur Respir J. 2002;19:439–46.
15. Kuroki Y, Tsutahara S, Shijubo N, Takahashi H, Shiratori M, et al. Elevated levels of lung surfactant protein A in sera from patients with idiopathic pulmonary fibrosis and pulmonary alveolar proteinosis. Am Rev Respir Dis. 1993;147:723–9.
16. Yokoyama A, Kondo K, Nakajima M, Matsushima T, et al. Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis. Respirology. 2006;11:164–8.
17. Song JW, Do KH, Jang SJ, Colby TV, et al. Blood biomarkers MMP-7 and SP-A: predictors of outcome in idiopathic pulmonary fibrosis. Chest. 2013;143:1422–9.
18. Prasse A, Probst C, Bargagli E, Zissel G, et al. Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;179 (8):717–23.
19. Day AJ. The C-type carbohydrate recognition domain (CRD) superfamily. Biochem Soc Trans. 1994;22:83–8.
20. Kuroki Y, Voelker DR. Pulmonary surfactant proteins. J Biol Chem. 1994;269:25943–6.
21. Crouch E, Persson A, Chang D, Heuser J. Molecular structure of pulmonary surfactant protein D (SP-D). J Biol Chem. 1994;269:17311–19.
22. Crouch E. Structure, biologic properties, and expression of surfactant protein D (SP-D). Biophys Biochim Acta. 1998;1408:278–89.
23. King RJ, Simon D, Horowitz PM. Aspects of secondary and quaternary structure of surfactant protein A from canine lung. Biochim Biophys Acta. 1989;1001:294–301.
24. Haagsman HP, Hawgood S, Sargeant T, Buckley D, et al. The major lung surfactant protein, SP 28–36, is a calcium-dependent carbohydrate-binding protein. J Biol Chem. 1987;262:13877–80.
25. Persson A, Chang D, Crouch E. Surfactant protein D is a divalent cation-dependent carbohydrate-binding protein. J Biol Chem. 1990;265:5755–60.
26. Kuroki Y, Akino T. Pulmonary surfactant protein A (SP-A) specifically binds dipalmitoylphosphatidylcholine. J Biol Chem. 1991;266:3068–73.
27. Childs RA, Wright JR, Ross GF, Yuen CT, et al. Specificity of Lung Surfactant Protein SP-A for both the carbohydrate and the lipid moieties of certain neutral glycolipids. J Biol Chem. 1992;267:9972–9.
28. Kuroki Y, Gasa S, Ogasawara Y, Shiratori M, et al. Binding specificity of lung surfactant protein SP-D for glucosylceramide. Biochem Biophys Res Commun. 1992;187:963–9.
29. Ogasawara Y, Kuroki Y, Akino T. Pulmonary surfactant protein D specifically binds to phosphatidylinositol. J Biol Chem. 1992;267:21244–9.
30. Takahashi H, Sano H, Chiba H, Kuroki Y. Pulmonary surfactant proteins A and D: innate immune functions and biomarkers for lung diseases. Curr Pharm Des. 2006;12:589–98.
31. Crouch EC. Collectins and pulmonary host defense. Am J Respir Cell Mol Biol. 1998;19:177–201.

32. Lawson PR, Reid KB. The roles of surfactant proteins A and D in innate immunity. Immunol Rev. 2000;173:66–78.
33. Tino MJ, Wright JR. Surfactant protein A stimulates phagocytosis of specific pulmonary pathogens by alveolar macrophages. Am J Physiol. 1996;270:L677–88.
34. Kudo K, Sano H, Takahashi H, Kuronuma K, et al. Pulmonary collectins enhance phagocytosis of Mycobacterium avium through increased activity of mannose receptor. J Immunol. 2004;172:7592–602.
35. Sano H, Sohma H, Muta T, Nomura S, et al. Pulmonary surfactant protein A modulates the cellular responses to smooth and rough lipopolysaccharides by interactions with CD14. J Immunol. 1999;163:387–95.
36. Murakami S, Iwaki D, Mitsuzawa H, Sano H, et al. Surfactant protein A inhibits peptidoglycan induced tumor necrosis factor-cc secretion in U937 cells and alveolar macrophages by direct interaction with Toil-like receptor 2. J Biol Chem. 2002;277:6830–7.
37. Seko A, Ohkura T, Ideo H, Yamashita K. Novel O-linked glycans containing 6′sulfoGal/GalNAc of MUC1 secreted from human breast cancer YMBS cells: possible carbohydrate epitopes of KL6 (MUC1) monoclonal antibody. Glycobiology. 2012;22:181–95.
38. Hirasawa Y, Kohno N, Yokoyama A, Kondo K. KL-6, a human MUC1 mucin is chemotactic for human fibroblasts. Am J Respir Cell Mol Biol. 1997;17:501–7.
39. Singh PK, Hollingsworth MA. Cell surface-associated mucins in signal transduction. Trends Cell Biol. 2006;16:467–76.
40. Hattrup CL, Gendler SJ. Structure and function of the cell surface (tethered) mucins. Annu Rev Physiol. 2008;70:431–57.
41. Kohno N, Akiyama M, Kyoizumi S, Tanabe M, et al. Detection of soluble tumor-associated antigens in sera and effusions using novel monoclonal antibodies, KL-3 and KL-6, against lung adenocarcinoma. Jpn J Clin Oncol. 1988;18:203–16.
42. Kohno N, Kyoizumi S, Awaya Y, Fukuhara H, et al. New serum indicator of interstitial pneumonitis activity. Sialylated carbohydrate antigen KL-6. Chest. 1989;96:68–73.
43. Thathiah A, Blobel CP, Carson DD. Tumor necrosis factor-alpha converting enzyme/ADAM17 mediates MUC1 shedding. J Biol Chem. 2003;278:3386–94.
44. Kondo K, Kohno N, Yokoyama A, Hiwada K. Decreased MUC1 expression induces E-cadherin-mediated cell adhesion of breast cancer cell lines. Cancer Res. 1998;58:2014–19.
45. Doi M, Yokoyama A, Kondo K, Ohnishi H, et al. Anti-tumor effect of the anti-KL-6/MUC1 monoclonal antibody through exposure of surface molecules by MUC1 capping. Cancer Sci. 2006;97:420–9.
46. Ohshimo S, Yokoyama A, Hattori N, Ishikawa N, et al. KL-6, a human MUC1 mucin promotes proliferation and survival of lung fibroblasts. Biochem Biophys Res Commun. 2005;338:1845–52.
47. Chida S, Phelps S, Soil RF, Taeusch HW. Surfactant proteins and anti surfactant antibodies in sera from infants with respiratory distress syndrome with and without surfactant treatment. Pediatrics. 1991;88:84–9.
48. Honda Y, Kuroki Y, Shijubo N, Fujishima T, et al. Aberrant appearance of lung surfactant protein A in sera of patients with idiopathic pulmonary fibrosis and its clinical significance. Respiration. 1995;62:64–9.
49. Kuroki Y, Takahashi H, Chiba H, Akino T. Surfactant protein A and D: disease markers. Biochim Biophys Acta. 1998;1408:334–45.
50. Robertson B, Curstedt T, Herting E, Sun B, et al. Alveolar-to-vascular leakage of surfactant protein A in ventilated immature newborn rabbits. Biol Neonate. 1995;68:185–90.
51. Kohno N, Awaya Y, Oyama T, Yamakido M, et al. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis. 1993;148:637–42.
52. Inoue Y, Barker E, Daniloff E, Kohno N, et al. Pulmonary epithelial cell injury and alveolar-capillary permeability in berylliosis. Am J Respir Crit Care Med. 1997;156:109–15.

53. Underhill DM, Ozinsky A, Hajjar AM, Stevens A, et al. The toll-like receptor 2 is recruited to macrophage phagosomes and discriminates between pathogens. Nature. 1999;401:811–15.
54. Shimazu R, Akahsi S, Ogata H, Nagai Y, et al. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor4. J Exp Med. 1999;189:1777–82.
55. da Silva CJ, Soldau K, Christen U, et al. Lipopolysaccharide is in close proximity to each of the proteins in its membrane receptor complex. J Biol Chem. 2001;276:21129–35.
56. Nagae H, Takahashi H, Kuroki Y, Honda Y, et al. Enzyme-linked immunosorbent assay using F(ab′)2 fragment for the detection of human pulmonary surfactant D in sera. Clin Chim Acta. 1997;266:157–71.
57. Honda Y, Kuroki Y, Matuura E, Nagae H, et al. Pulmonary surfactant protein D in sera and bronchoalveolar lavage fluids. Am J Respir Crit Care Med. 1995;152:1860–6.
58. Takahashi H, Imai Y, Fujishima T, Shiratori M, et al. Diagnostic significance of surfactant protein A and D in sera from patients with radiation pneumonitis. Eur Respir J. 2001;17:481–7.
59. Kobayashi J, Kitamura S. KL-6: a serum marker for interstitial pneumonia. Chest. 1995;108:311–15.
60. Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, et al. Circulating KL-6 levels in patients with drug induced pneumonitis. Thorax. 2003;58:872–5.
61. Tanaka S, Hattori N, Ishikawa N, Shoda H, et al. Krebs von den Lungen-6 (KL-6) is a prognostic biomarker in patients with surgically resected non small cell lung cancer. Int J Cancer. 2012;130:377–87.
62. Inoue Y, Nishimura K, Shiode M, Akutsu H, et al. Evaluation of serum KL-6 levels in patients with pulmonary tuberculosis. Tuber Lung Dis. 1995;76:230–3.
63. Shimizu Y, Sunaga N, Dobashi K, Fueki M, et al. Serum markers in interstitial pneumonia with and without *Pneumocystis jirovecii* colonization: a prospective study. BMC Infect Dis. 2009;22:47.
64. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190:773–9.
65. Yokoyama A, Kohno N, Hamada H, Sakatani M, et al. Circulating KL-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158:1680–4.
66. Kinder BW, Brown KK, McCormack FX, Ix JH, Kervitsky A, Schwarz MI, King Jr TE. Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. Chest. 2009;135:1557–63.
67. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. J Intern Med. 2006;260:429–34.
68. Nukiwa T. The role of biomarkers in management of interstitial lung disease: implication of biomarkers derived from type II pneumocytes. In: DuBois RM, Richeldi L, editors. The european respiratory monograph 46 interstitial lung disease. Leeds: Maney Publishing; 2009. p. 47–66.
69. Fujii M, Tanaka H, Kameda M, Fujii M, et al. Elevated serum surfactant protein A and D in a case of acute eosinophilic pneumonia. Intern Med. 2004;43:423–6.
70. Nishikiori H, Chiba H, Ariki S, Kuronuma K, et al. Distinct compartmentalization of SP-A and SP-D in the vasculature and lungs of patients with idiopathic pulmonary fibrosis. BMC Pulm Med. 2014;14:196.
71. Rosas IO, Richards TJ, Konishi K, Zhang Y, et al. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. PLoS Med. 2008;5, e93.

# Chapter 6
# High-Resolution Computed Tomography of Honeycombing and IPF/UIP

## To What Extent Can Honeycomb Lung Be Diagnosed by Imaging? To What Extent Can IPF Diagnosis Be Made by HRCT?

**Fumikazu Sakai**

**Abstract** Typical and atypical imaging findings, differential diagnosis, complications of disease itself and roles of imaging, and problems in diagnosis of idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) are described. Pathologic hallmarks of IPF/UIP are perilobular/periacinar fibrosis, temporal/spatial heterogeneity, advanced fibrosis, and small concentrated areas of nearly normal lung. Typical high-resolution computed tomographic (HRCT) features of IPF/UIP are subpleurally located reticular opacity or honeycomb lung in the dorsal aspect of bilateral lower lobes. Honeycomb lung (honeycombing) is a key finding in the diagnosis of IPF/UIP, but experienced radiologists sometimes disagree in judging honeycomb lung at HRCT. Early diagnosis of IPF/UIP requires establishment of diagnostic criteria other than honeycombing and investigation of HRCT findings that correspond with temporal and spatial heterogeneity.

**Keywords** Heterogeneity • Honeycomb lung • HRCT • Pathology • Perilobular fibrosis • Usual interstitial pneumonia

## 6.1 Introduction

Idiopathic pulmonary fibrosis (IPF), a form of idiopathic interstitial pneumonia (IIP), has no apparent cause, is observed most commonly in older male smokers, follows a progressive course, and offers a poor prognosis. Its pathological pattern is that of usual interstitial pneumonia (UIP).

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The 2011 international guideline for the diagnosis and treatment of IPF/UIP published by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) [1] and the 2013 international multidisciplinary classification of IIPs of the ATS and ER [2] emphasize the need for multidisciplinary discussion among clinicians, radiologists, and pathologists that integrates clinical, imaging, and pathological information to establish diagnosis except when disease manifests typical clinical findings.

Findings of HRCT are very important in diagnosing IPF/UIP. Diagnosis of IPF is possible without surgical lung biopsy when HRCT demonstrates a typical (definite) IPF/UIP pattern and causes of interstitial pneumonia remain unknown, but acquisition of pathological findings by surgical lung biopsy is necessary when HRCT findings are atypical or inconsistent with UIP/IPF.

Imaging findings presumed from pathologic features, differential diagnosis, and limitations and roles of imaging evaluation in the diagnosis and treatment of IPF/UIP will be described.

## 6.2 Honeycomb Lung (Honeycombing)

### *6.2.1 Definition of Honeycomb Lung*

Honeycomb lung is one of the most important findings of IPF/UIP. The term was originally used to describe a macroscopic finding of bronchiectasis and has been used to describe multiple cystic lesions in chronic fibrosing interstitial pneumonia (CFIP) since Liebow and coworkers organized the pathologic findings of interstitial pneumonia [3]. Most pathologists have adopted the term pathologic honeycombing to describe the dilatation of a small airway surrounded by infolded fibrotic alveolar wall and microscopic honeycomb to describe a constellation of cysts smaller than one to 2 mm in size with fibrosis (Fig. 6.1a, b). Honeycomb lung must be differentiated pathologically from the constellation of traction bronchiectasis (Fig. 6.2) and such destructive changes as pulmonary emphysema (Fig. 6.3a, b).

### *6.2.2 Disagreement Among Radiologists in Judging Honeycomb Lung*

According to Fleischner Society nomenclature, radiological honeycomb lung describes findings of a cluster of relatively thick-walled cysts (3–10-mm diameter and 1–3-mm cyst wall thickness) in peripheral (subpleural) regions of the lung that are most frequently seen in IPF/UIP [4]. These radiological findings correspond

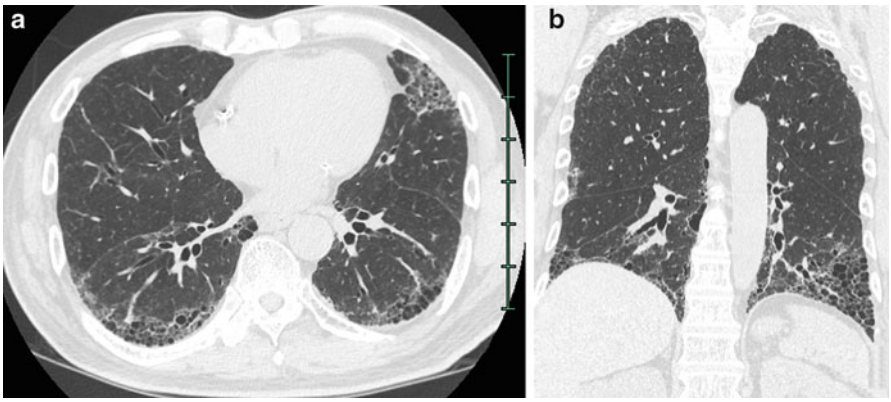


**Fig. 6.1** Typical honeycomb lung. (**a**) High-resolution computed tomography (HRCT) shows clustered multiple cysts of which walls are relatively thick. The diameter of each cyst is one cm or less. Honeycomb lung is located subpleurally. (**b**) Reformatted coronal image shows a constellation of multiple cysts located in the subpleural regions

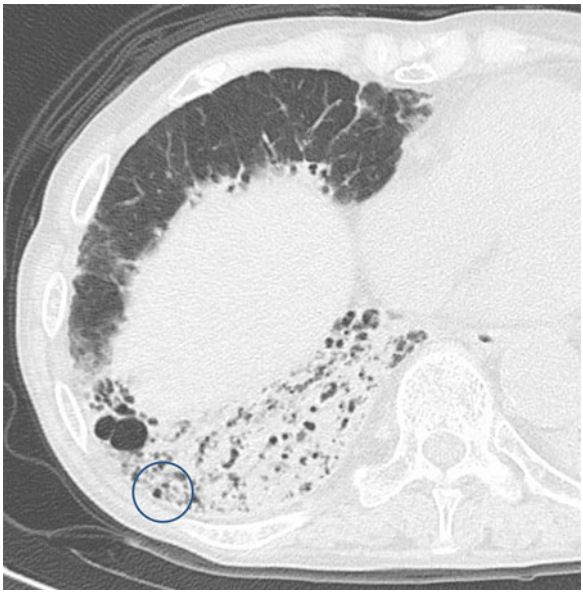

**Fig. 6.2** Traction bronchiectasis in advanced fibrotic nonspecific interstitial pneumonia (fNSIP). High-resolution computed tomography (HRCT) of advanced fNSIP shows a constellation of traction bronchiectasis in the right middle lobe, evidenced by the course of the dilated bronchi within the CT plane. In the right lower lobe, a multicystic shadow may represent a constellation of traction bronchiectasis when dilated bronchi are sliced in the transverse plane perpendicular to the axes of the bronchi or honeycomb lung (*circled*)

with pathologic features – cystic space with small dilated airway and thick cyst wall with infolded fibrotic pulmonary parenchyma – that definitely differ from such destructive change as that of pulmonary emphysema.

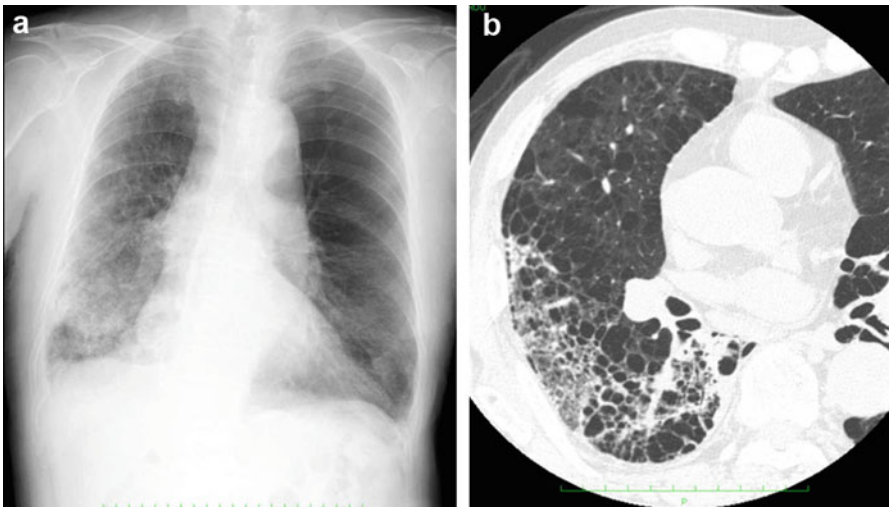


**Fig. 6.3** Pneumonia and emphysema (Swiss cheese appearance). (**a**) Chest x-ray shows overinflation of both lungs. Abnormal opacity is noted in the right middle to lower lung fields. (**b**) High-resolution computed tomography (HRCT) shows a multicystic shadow and ground-glass opacity/consolidation in the right lower lobe. Emphysema is evident in the lung fields without ground-glass opacity/consolidation

Because the limited spatial resolution of HRCT prevents observation of microscopic honeycomb lung, radiological description must be confined to macroscopic honeycombing, and the term honeycomb lung must be used with extreme caution. Even experienced radiologists may disagree in judging honeycomb lung [5], primarily because various pathologic processes mimic its appearance and the term is used to describe different entities in the fields of pathology and radiology.

Mimickers of honeycomb lung in emphysema include pneumonia and other disease processes with diffuse ground-glass opacity (GGO)/consolidation, though GGO/consolidation does not occur in the holes of emphysema, pneumonia that resembles Swiss cheese on HRCT (Fig. 6.3), and the multiple cysts frequently observed in pulmonary fibrosis concomitant with emphysema (Fig. 6.4a, b).

Constellated traction bronchiectasis may also simulate honeycomb lung when dilated bronchi are sliced in the transverse plane perpendicular to their axes (Fig. 6.2). The use of coronal/sagittal reconstructed images or 3-dimensional display may improve its differentiation from honeycombing. It is very confusing that traction bronchiectasis may intermingle with honeycombing and that a constellation of "pure" traction bronchiectasis may simulate honeycomb lung (Fig. 6.5a, b).

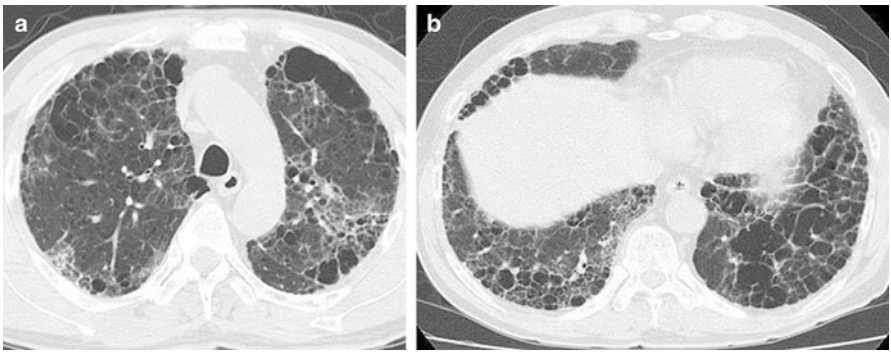


**Fig. 6.4** Pulmonary fibrosis concomitant with pulmonary emphysema. (**a**) Computed tomography (CT) of upper lung shows paraseptal and centrilobular emphysema mixed with ground-glass opacity and reticular opacity. (**b**) CT scan of lower lung shows multiple cysts including large thick-walled cysts that mimic honeycombing

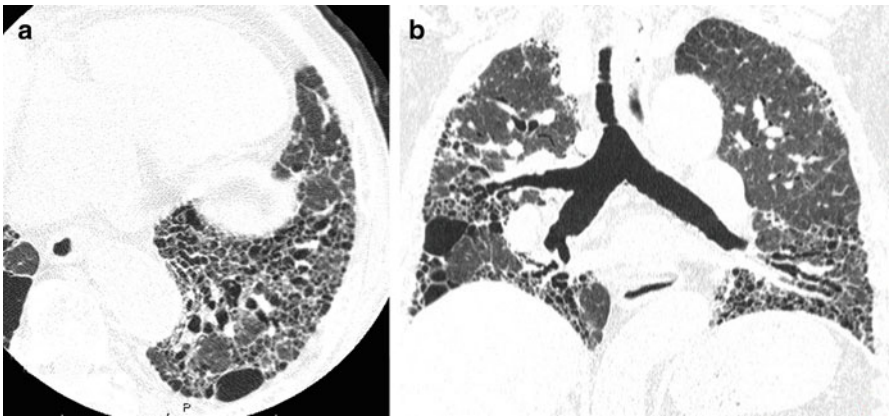


**Fig. 6.5** Advanced fibrotic nonspecific interstitial pneumonia (fNSIP). (**a**) High-resolution computed tomography (HRCT) of lower lung shows traction bronchiectasis mixed with multiple cysts that mimics honeycomb lung. (**b**) Reformatted coronal image shows most of cystic structures are constellation of traction bronchiectasis

## 6.3 Imaging Findings of Idiopathic Pulmonary Fibrosis/ Usual Interstitial Pneumonia

### *6.3.1 Pathologic Criteria of IPF/UIP*

Pathologic hallmarks of the UIP pattern include perilobular/periacinar fibrosis and spatial and temporal heterogeneity. Advanced fibrotic change, such as honeycombing, exists in close proximity with nearly normal lung tissue, typically

within the same pulmonary lobule, and the borders of fibrotic foci are very sharp and abruptly abut lung that is nearly normal [6].

Fibrosis with a UIP pattern may be seen in such diseases as secondary interstitial pneumonia of known cause, interstitial pneumonia with collagen vascular disease (CVD-IP), chronic hypersensitivity pneumonitis (CHP), sarcoidosis, and asbestosis. Pathologic findings of CVD-IP frequently show rich aggregated lymphatic follicles with germinal center, pleuritis, bronchiolitis, and other features. Typically, CHP shows airway-centered fibrosis and small granulomas related to airways, but these features may be absent. The multidisciplinary discussion to diagnose IPF/UIP must exclude these secondary IPs with a UIP pattern.

The 2011 international diagnostic guideline [1] classifies pathologic patterns as definite, probable, possible, and not UIP based on the combination of several pathologic findings.

A definite UIP pattern comprises marked fibrosis/architectural distortion with or without honeycomb lung located predominantly in subpleural and paraseptal regions, patchy involvement by fibrosis, fibroblastic foci, and absence of any finding that contraindicates the diagnosis of IPF/UIP. Findings that rule out IPF/UIP include hyaline membrane, organizing pneumonia, marked inflammatory cell infiltration, granulomas, predominant airway-centered change, and any other finding that suggests an alternative diagnosis.

A probable UIP pattern includes marked fibrosis/architectural distortion with or without honeycomb lung, absence of either patchy involvement or fibroblastic foci, and absence of any finding that contraindicates the diagnosis of IPF/UIP.

A possible UIP pattern demonstrates patchy involvement of the lung by fibrosis with or without honeycomb lung and absence of any finding that contraindicates the diagnosis of IPF/UIP.

The definite UIP pattern includes perilobular (subpleural and/or paraseptal)/periacinar fibrosis and temporal/spatial heterogeneity, but the probable and possible UIP patterns may include other pathologic patterns than those of IPF/UIP, such as fibrotic nonspecific interstitial pneumonia (fNSIP), interstitial pneumonia with collagen vascular disease, or chronic hypersensitivity pneumonia.

### *6.3.2 HRCT Criteria of IPF/UIP*

HRCT images must be included in the analysis of radiological findings of interstitial pneumonia [7–10]. Nishimura and associates described HRCT findings of IPF/UIP as perilobular fibrosis (abnormal opacities along the pleura, bronchial wall, large vessels, and interlobular septa) [11] (Fig. 6.6). Intralobular interstitial changes correspond with periacinar fibrosis along the intralobular veins. Fibrotic change is shown by reticular opacity or honeycomb lung. Honeycomb lung is a key finding of IPF/UIP and more extensive in UIP than NSIP [12–17] (Figs. 6.5 and 6.6).

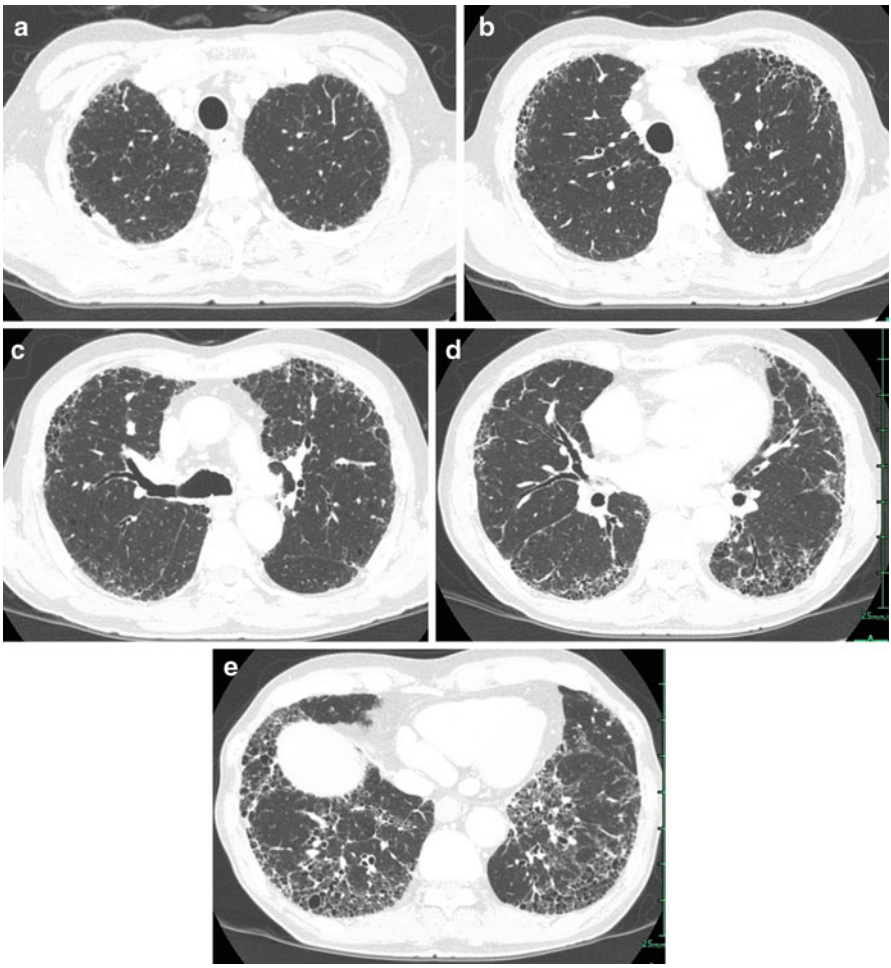


**Fig. 6.6** Idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP). (**a**) High-resolution computed tomography (HRCT) at the pulmonary apex shows small linear opacity abutting the chest wall that suggests perilobular (pleural surface, interlobular septa, and bronchovascular bundle) fibrosis. (**b**) HRCT at the level of the aortic arch shows inhomogeneous reticular opacity abutting the chest wall (subpleural regions). (**c**) HRCT at the level of the tracheal bifurcation shows inhomogeneous reticular opacity and honeycomb lung abutting the chest wall. Small linear opacity adjacent to the chest wall is also identified. (**d**) HRCT at the level of the pulmonary vein shows subpleurally located reticular opacity and honeycomb lung. Distribution of abnormal opacity is patchy and confined to subpleural regions. (**e**) HRCT at the level of the lung base shows patchy areas of reticular opacity and honeycomb lung in the subpleural regions. No findings contraindicate the diagnosis of IPF/UIP

Approximately one third of UIP diagnosed by video-assisted thoracoscopic surgery (VATS) mimics NSIP at HRCT [18, 19], probably because surgical lung biopsy is performed to diagnose IPF/UIP with atypical findings on radiology and

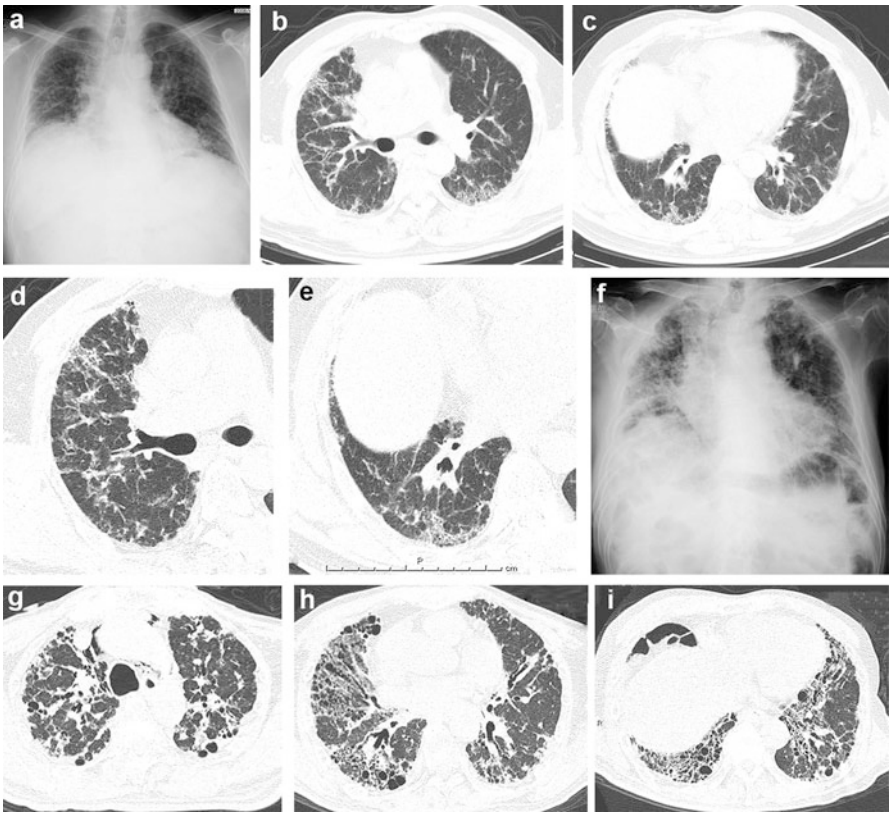


**Fig. 6.7** Chronic fibrosing interstitial pneumonia of unknown cause with definite usual interstitial pneumonia (UIP) pattern at pathology and atypical (inconsistent with) UIP pattern at high-resolution computed tomography (HRCT). (**a**–**g**) Images at surgical lung biopsy; (**f**–**i**) images were obtained 4 years later. (**a**) Chest x-ray shows volume loss in bilateral lungs with reticular opacity. (**b**) HRCT at the middle lung shows ground-glass opacity (GGO) and reticular opacity in the peribronchovascular regions in bilateral lungs. (**c**) GGO and reticular opacity predominant in basal regions. Abnormal opacity is identified in both subpleural and peribronchovascular regions. (**d**) HRCT at the middle lung shows peribronchovascular abnormal opacity that represents a pattern inconsistent with UIP. (**e**) HRCT at the level of the lung base shows abnormal opacity in both the peribronchovascular and subpleural regions. (**f**) Chest x-ray after 4 years shows progression of abnormal opacity and loss of volume in bilateral lungs. (**g**) HRCT at the level of the pulmonary apex shows peribronchovascular and subpleural foci consolidation with traction bronchiectasis. (**h**) HRCT at the level of the middle lung shows peribronchovascular-predominant reticular opacity with traction bronchiectasis that suggests a pattern of fibrotic nonspecific interstitial pneumonia (fNSIP). (**i**) In the lung base, HRCT shows peribronchovascular-predominant reticular opacity that includes traction bronchiectasis and cysts

not disease with typical features (Fig. 6.7). IPF/UIP may show an NSIP pattern during the course of disease [20, 21], and a UIP pattern may change to an NSIP pattern in the terminal stage of disease. The pattern of pathologically proven NSIP comorbid with pulmonary emphysema mimics a UIP pattern at HRCT [22].

#### 6.3.2.1 Categories of HRCT Patterns in the 2011 Guideline (Table 6.1)

The 2011 IPF/UIP guideline [1] categorizes the disease patterns of IPF/UIP based on HRCT criteria as definite UIP (Fig. 6.6), possible UIP (Fig. 6.8), and inconsistent with UIP (Fig. 6.7). Certainty of IPF/UIP diagnosis is achieved by combining the categories of HRCT and pathology.

A definite IPF/UIP pattern at HRCT consists of subpleural distribution of reticular opacity or honeycomb lung predominantly in the dorsal aspects of the lower lobes and absence of any of the below mentioned 7 findings noted that contraindicate a diagnosis of IPF/UIP. A possible IPF/UIP pattern demonstrates lower lobe predominance and subpleural distribution, reticular opacity, and lack of any of the 7 findings that contraindicate a diagnosis of IPF/UIP; the honeycombing of the definite IPF/UIP pattern is absent. A pattern that is inconsistent with IPF/UIP includes any of the 7 findings that contraindicate IPF/UIP, peribronchovascular-predominant distribution (Fig. 6.9), prominent GGO (wider than reticular opacity and honeycomb lung) (Fig. 6.10), upper lung predominance as pleuropulmonary fibroelastosis (PPFE) (Fig. 6.11), a large cyst away from honeycomb lung (Fig. 6.12), segmental distribution of shadow, profuse micronodules (Fig. 6.13), and diffuse mosaic appearance. These imaging findings may represent secondary

**Table 6.1** High-resolution computed tomography (HRCT) categories of disease patterns of usual interstitial pneumonia (UIP) of the 2011 international guideline for the diagnosis and treatment of idiopathic pulmonary fibrosis [1]

| HRCT criteria for UIP pattern | | |
|---|---|---|
| UIP pattern (all four features) | Possible UIP pattern (all three features) | Inconsistent with UIP pattern (any of the seven features) |
| Subpleural, basal predominance | Subpleural, basal predominance | Upper or mid-lung predominance |
| Reticular abnormality | Reticular abnormality | Peribronchovascular predominance |
| Honeycombing with or without traction bronchiectasis | Absence of features listed as inconsistent with UIP pattern (see third column) | Extensive ground-glass abnormality (extent > reticular abnormality) |
| Absence of features listed as inconsistent with UIP pattern (see third column) | | Profuse micronodules (bilateral, predominantly upper lobes) |
| | | Discrete cysts (multiple, bilateral, away from areas of honeycombing) |
| | | Diffuse mosaic attenuation/air trapping (bilateral, in 3 or more lobes) |
| | | Consolidation in bronchopulmonary segment(s)/lobe(s) |

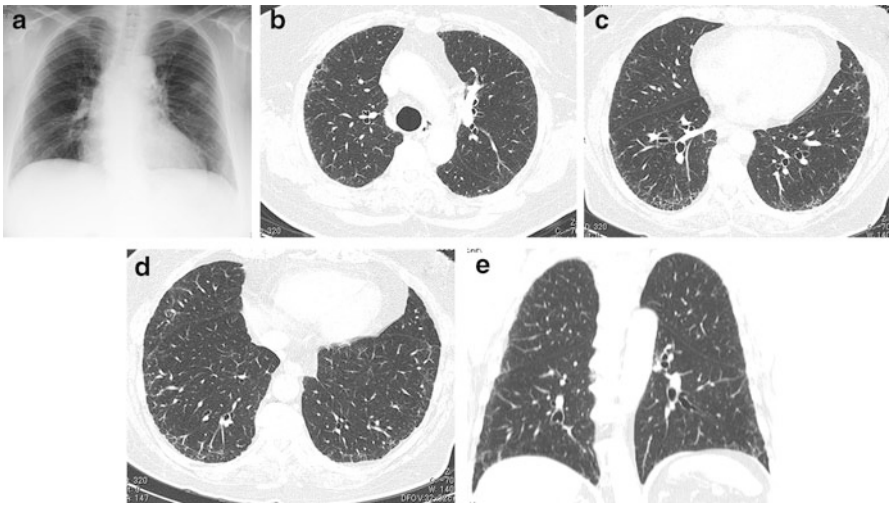


**Fig. 6.8** Possible usual interstitial pneumonia (UIP) pattern at high-resolution computed tomography (HRCT). (**a**) Chest x-ray shows ground-glass opacity predominantly in bilateral basal lungs. Nodular opacity in the left middle lung field suggests lung cancer. (**b**) HRCT at the upper lung shows subpleural inhomogeneous reticular opacity. (**c**) HRCT at the lower lung shows subpleurally located inhomogeneous reticular opacity. Reticular opacities distribute inhomogeneously. (**d**) HRCT at the lung base shows subpleurally distributed reticular opacity without honeycomb lung. (**e**) Coronal CT shows subpleural reticular opacity located predominantly in the lower lungs. No honeycombing is identified

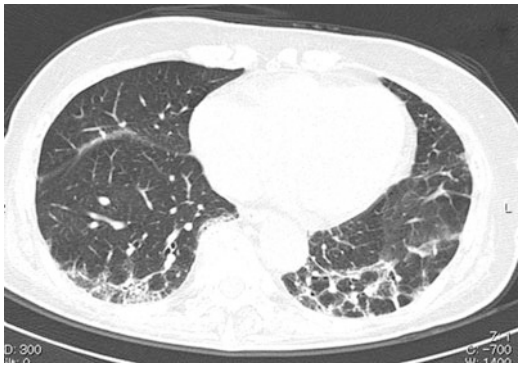

**Fig. 6.9** Interstitial pneumonia in a patient with dermatomyositis. Prominent peribronchovascular distribution. High-resolution computed tomography (HRCT) shows peribronchovascular consolidation that suggests acute lung injury (fibrosing organizing pneumonia [OP])

interstitial pneumonias with a UIP pattern that may be included in the differential diagnosis of IPF/UIP.

In IPF/UIP, HRCT findings of overlapping reticular and ground-glass opacity (GGO) combined with honeycombing demonstrate a wider area of fibrosis than

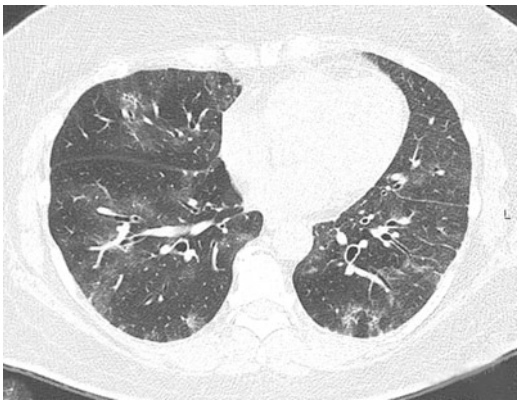

**Fig. 6.10** Cellular nonspecific interstitial pneumonia (NSIP) and prominent ground-glass opacity (GGO). High-resolution computed tomography (HRCT) shows widespread GGO without structural distortion that suggests cellular NSIP

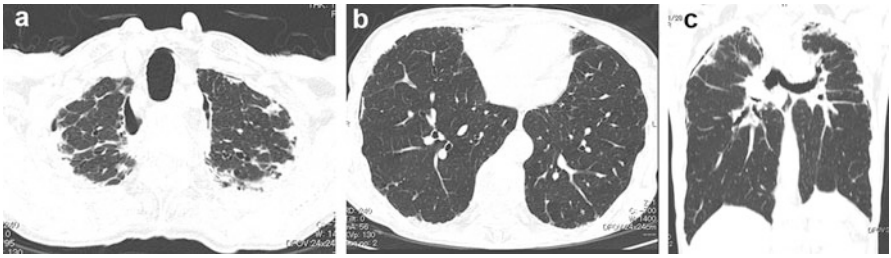


**Fig. 6.11** Pleuroparenchymal fibroelastosis (PPFE). (**a**) High-resolution computed tomography (HRCT) at the pulmonary apex shows subpleural atelectatic fibrosis. (**b**) HRCT at the pulmonary base shows subpleural fibrosis that suggests a usual interstitial pneumonia (UIP) pattern. (**c**) Reformatted coronal CT image shows marked volume loss in bilateral upper lobes with elevation of the pulmonary hili

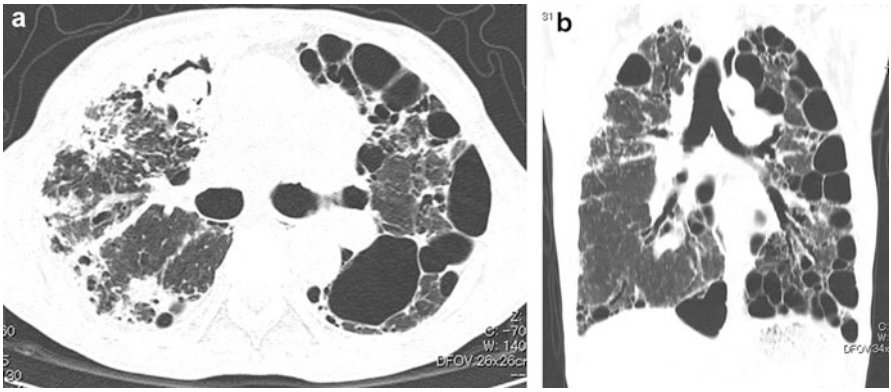


**Fig. 6.12** Chronic hypersensitivity pneumonia with large cyst. (**a**) High-resolution computed tomography (HRCT) image shows multiple large subpleural cysts. Fungal ball is noted in the right lung. (**b**) Reformatted coronal images show multiple large cysts in the subpleural region

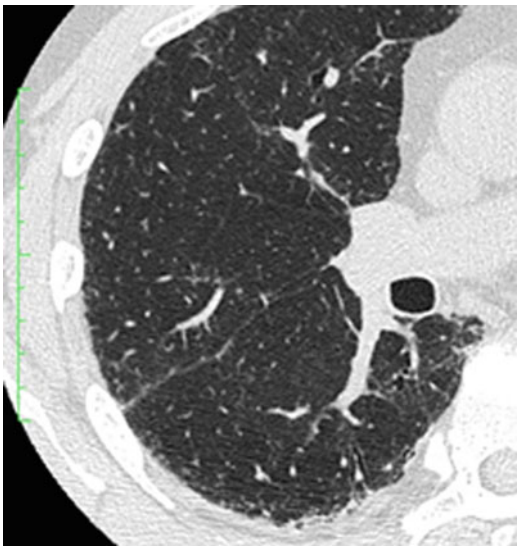

**Fig. 6.13** Profuse micronodules of respiratory bronchiolitis interstitial lung disease (RBILD). High-resolution computed tomography (HRCT) shows prominent centrilobular nodules

GGO. Prominent GGO suggests less fibrotic change. Profuse micronodules are frequently seen in chronic hypersensitivity pneumonia and sarcoidosis, and peribronchovascular-predominant abnormal opacity is typically seen in fibrotic NSIP. Absence of segmental consolidation is intended to exclude pneumonia. A large cyst is typically seen in complicated emphysema or cystic diseases, and predominant upper distribution is a hallmark of such inhalational diseases as pneumoconiosis and CHP. Diffuse mosaic appearance suggests airway disease, sometimes identified in CHP.

#### 6.3.2.2 Correlation of HRCT and Pathologic Findings (Figs. 6.6 and 6.8)

The 2011 diagnostic guideline for IPF/UIP [1] describes limited specific findings on HRCT and none that reflect temporal/spatial heterogeneity, and other forms of interstitial pneumonia, such as fibrotic NSIP (fNSIP), may manifest a pattern of possible UIP on HRCT. Pathologic hallmarks of the UIP pattern are perilobular/periacinar fibrosis and temporal/spatial heterogeneity. Fibrosis is assured by the presence of reticular opacity and/or honeycombing at HRCT, and perilobular fibrosis corresponds with the subpleural location of reticular opacity or honeycomb lung.

Though few articles in the English literature describe the heterogeneous CT appearance of IPF/UIP, HRCT findings that reflect the heterogeneous distribution of fibrosis must be investigated [23]. Potentially useful findings that suggest heterogeneity may include marked laterality of abnormal opacity, coexistence of advanced fibrosis (such as honeycombing) with normal-appearing lung parenchyma

packed in a very small area, and a normal-appearing area remaining within subpleural reticular opacity and/or honeycomb lung [24, 25].

Approximately one third of VATS-determined IPF/UIP shows an atypical CT appearance that mimics NSIP or unclassified patterns (which might represent secondary UIP), probably because surgical biopsy was not performed in recent cases of IPF/UIP that demonstrated a typical IPF pattern (definite UIP pattern) [18]. However, the prognosis is similar for IPF/UIP with atypical findings and IPF with a definite IPF/UIP appearance at HRCT [19].

#### 6.3.2.3 Honeycomb Lung in the Diagnosis of IPF/UIP (Table 6.1, Fig. 6.14)

Honeycomb lung is one of the most important findings of IPF/UIP [16, 26–29] and can be key in its diagnosis [1]. Definitive diagnosis of IPF/UIP is possible without surgical biopsy when HRCT shows a typical UIP pattern, but biopsy is necessary when imaging demonstrates a possible or inconsistent with UIP pattern. Honeycombing is the only finding different between the patterns of definite and

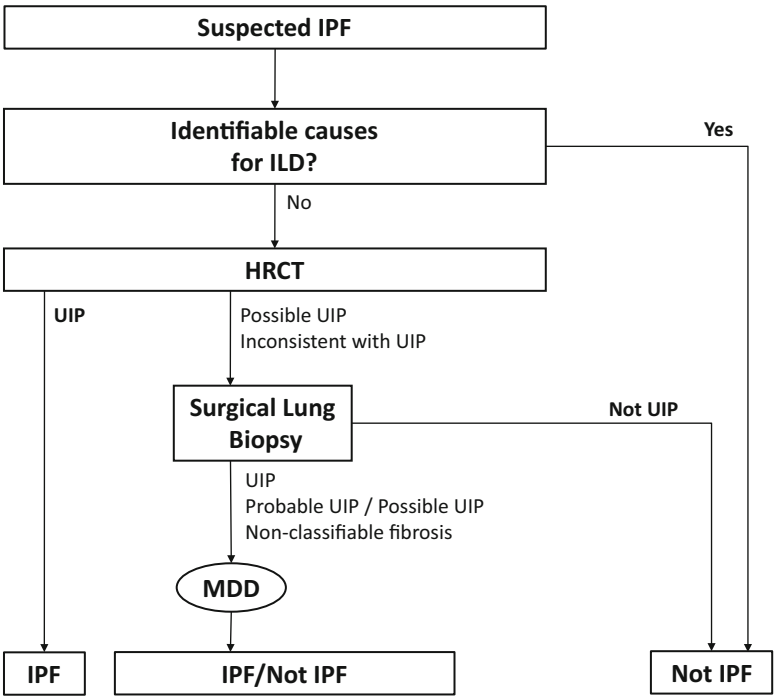


**Fig. 6.14** Approach of the 2011 international guideline for the diagnosis of idiopathic pulmonary fibrosis [1]

possible UIP, and difficulty in its discrimination on radiology findings, even among experienced chest radiologists [5], requires that surgical lung biopsy be performed. Heavy reliance on the observation of honeycombing to establish the diagnosis of IPF/UIP therefore can be problematic.

#### 6.3.2.4 Diagnosis of IPF/UIP in Early Stage

New drugs have recently been developed to treat IPF/UIP, and medical intervention might be more effective in the early stage of disease prior to honeycombing. Pathologic findings of IPF/UIP indicate that perilobular/periacinar fibrosis and temporal/spatial heterogeneity should be included in the diagnostic criteria of HRCT. Early recognition of these features in the disease process could improve treatment management.

## 6.4 Differential Diagnosis of IPF/UIP

### *6.4.1 Nonspecific Interstitial Pneumonia*

Satisfactory differentiation of subtypes of idiopathic interstitial pneumonias by HRCT has been reported generally [30]. NSIP is one the most important differential diagnoses of IPF/UIP [31, 32]. Its primary HRCT feature is peribronchovascular or patchy ground-glass opacity. Findings of intralobular reticular opacity, traction bronchiectasis within GGO, and honeycomb lung indicate progression of fibrosis and suggest a worse prognosis (Fig. 6.15) [17, 33–41]. According to Sumikawa and associates, IPF/UIP shows more extensive honeycombing than fNSIP [12].

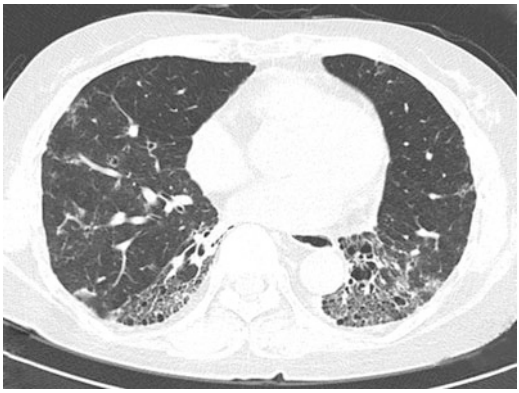

**Fig. 6.15** Fibrotic nonspecific interstitial pneumonia (fNSIP). High-resolution computed tomography (HRCT) at the lower lung shows marked volume loss in bilateral lower lobes. Reticular opacity and traction bronchiectasis are identified in bilateral lower lobes

Approximately one third of VATS-determined IPF/UIP appears atypical on HRCT, but the prognosis is similar for IPF/UIP with typical imaging features and disease with atypical features that requires surgical lung biopsy [19].

### 6.4.2 Desquamative Interstitial Pneumonia

HRCT findings of desquamative interstitial pneumonia (DIP) include subpleural or patchy panlobular ground-glass opacity. Usually reticular opacity is less prominent, and honeycomb lung is absent. Multiple cystic changes are observed within areas of GGO, especially after disappearance of GGO by treatment [42]. During long-term follow-up study, honeycombing can become apparent [43].

### 6.4.3 Respiratory Bronchiolitis Interstitial Lung Disease (Fig. 6.13)

Respiratory bronchiolitis interstitial lung disease (RBILD) is another form of idiopathic interstitial pneumonia closely related to cigarette smoking [44]. Its main feature on HRCT is abundant centrilobular nodules that reflect respiratory bronchiolitis; other findings include patchy ground-glass opacity and reticular opacity [45, 46].

### 6.4.4 Sarcoidosis

Pulmonary sarcoidosis may mimic IPF at HRCT [47]. Profuse micronodules with perilymphatic distribution suggest the diagnosis of sarcoidosis.

### 6.4.5 Chronic Hypersensitivity Pneumonia (Fig. 6.16)

Chronic hypersensitivity pneumonia is a secondary interstitial pneumonia that shows a UIP or NSIP pattern on pathologic specimens [48]. Its imaging features most frequently show a UIP pattern but include upper lobe predominance or generalized distribution in the craniocaudal direction, profuse centrilobular micronodules in the upper lungs that suggest bronchocentric fibrosis, bridging fibrosis that connects the centrilobular and perilobular regions, cyst formation in the upper lungs, atelectatic induration, and/or prominent ground-glass opacity

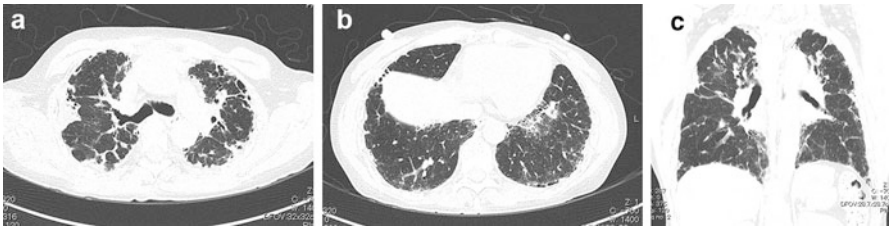


**Fig. 6.16** Chronic hypersensitivity pneumonitis (CHP). (**a**) High-resolution computed tomography (HRCT) at the pulmonary apex shows multiple subpleural areas of atelectatic induration abutting the chest wall. Small cysts are also identified. (**b**) HRCT of the lower lung shows interstitial pneumonia with a UIP pattern. (**c**) Coronal reformatted image shows that reticular opacity is confined to subpleural regions

[49]. Some CHP cases simulate IPF/UIP, lacking any findings contraindicating this diagnosis, so the diagnosis of CHP requires multidisciplinary discussion among specialists [50, 51].

### *6.4.6 Collagen Vascular Disease (CVD) (Fig. 6.17)*

Interstitial lung disease in patients with collagen vascular disease (CVD) most frequently shows an NSIP pattern, but a UIP pattern may be seen, especially in patients with rheumatoid arthritis [52–54]. Features of usual interstitial pneumonia with CVD (CVD-UIP) are somewhat atypical from those of IPF/UIP, and concomitant peribronchovascular abnormal opacity in addition to subpleural reticular opacity and/or honeycomb lung indicate concomitant UIP and NSIP patterns. On the other hand, Assayag's group described no difference between HRCT images of UIP complicated with rheumatoid arthritis and those of IPF/UIP [55].

Because NSIP is frequently complicated in patients with CVD, Kinder and colleagues suggested NSIP might be a lung complication in patients with undifferentiated connective tissue disease (UCTD) [56]. Though the prognoses differ distinctly between patients with UCTD and those with usual NSIP [57], no differences in HRCT findings have been reported.

Lung-dominant connective tissue disease (LD-CTD) [58] and autoimmune-featured interstitial lung disease (AFILD) [59] are reported to be interstitial pneumonias that do not satisfy the diagnostic criteria of specific collagen disease but have clinical and/or pathologic findings that suggest CVD.

Though CVDs most frequently complicate NSIP, approximately half of AFILD shows a UIP pattern. Some LD-CTD/AFILD shows an unclassifiable (mixed UIP and NSIP pattern) or UIP pattern at HRCT. Because interstitial pneumonia in patients with UCTD, LD-CTD, and AFILD is currently classified as idiopathic interstitial pneumonia, IPF/UIP may include these interstitial pneumonias with the "flavor of CVD."

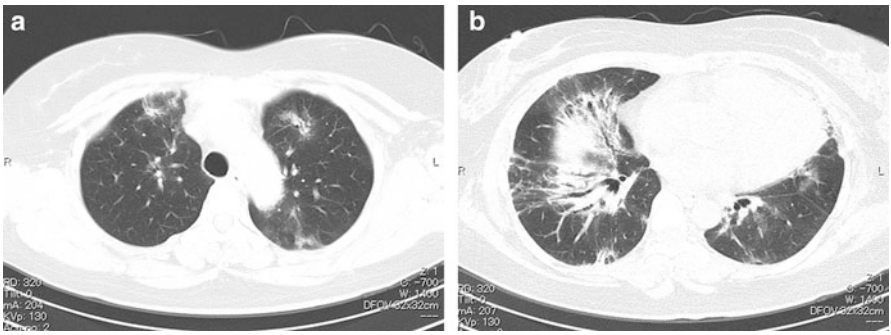


**Fig. 6.17** Interstitial pneumonia with collagen vascular disease (CVD-IP) (fibrosing nonspecific interstitial pneumonia [NSIP] pattern). (**a**, **b**) High-resolution computed tomography (HRCT) images show abnormal opacities located predominantly in the lower lungs that represent peribronchovascular ground-glass opacity and consolidation including traction bronchiectasis

### *6.4.7 Pneumoconiosis*

Asbestosis is bronchocentric fibrosis caused by asbestos fiber (2 or more asbestos bodies/one square cm in histologic section). Bronchocentric fibrosis extends to the perilobular regions and may show the fibrosis of a UIP pattern [60–62].

Imaging findings of asbestosis differ by disease stage. Early stage findings include small nodular centrilobular opacities that correspond with bronchocentric fibrosis, thickening of the intralobular interstitium, septal thickening, subpleural curvilinear opacity that corresponds with coalescent bronchocentric fibrosis, wedge-shaped abnormal opacity abutting the chest wall, and air trapping [63]. Advanced asbestosis shows honeycomb lung and atelectatic fibrosis [64–66].

Although asbestosis may show fibrosis with a UIP pattern [67], typical HRCT images of classical asbestosis can show centrilobular nodules, subpleural curvilinear opacity, transpulmonary band, and prominent air trapping and less frequent honeycomb lung and traction bronchiectasis than IPF/UIP [68].

Pleural plaque on chest x-ray (CXR)/CT and clinical history of asbestos exposure are also useful in diagnosing asbestosis. Mixed dust pneumoconiosis and hard metal lung may show a UIP pattern [69].

### *6.4.8 Combined Pulmonary Fibrosis and Emphysema and Smoking-Related Pulmonary Fibrosis (Fig. 6.18)*

Pulmonary fibrosis with emphysema is frequently seen in daily clinical practice. Since Cottin proposed the term combined pulmonary fibrosis and emphysema (CPFE) to describe pulmonary emphysema in the upper lung and pulmonary

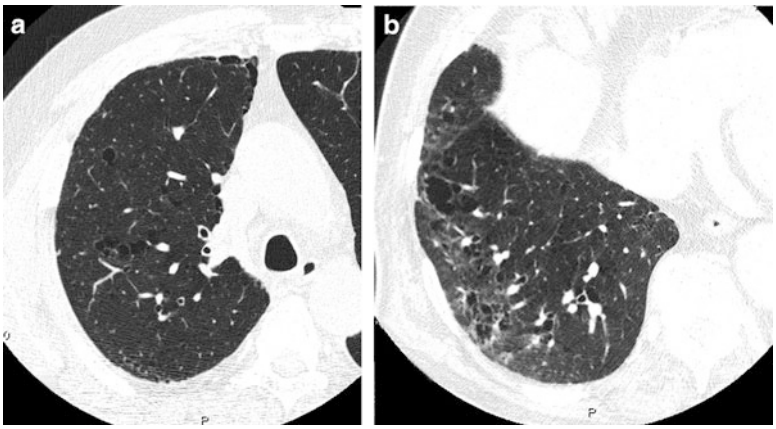


**Fig. 6.18** Combined pulmonary fibrosis and emphysema (CPFE). (**a**) High-resolution computed tomography (HRCT) at the upper lung shows centrilobular emphysema. (**b**) HRCT at the lower lung shows centrilobular cysts surrounded by reticular and ground-glass opacity, a pattern definitely different from that of usual interstitial pneumonia (UIP)

fibrosis in the lower lung as defined by clinical and imaging characteristics, there has been much controversy regarding the pathogenesis of interstitial pneumonia complicated with emphysema [70, 71].

The 2013 ATS/ERS consensus guideline for idiopathic interstitial pneumonia [2] defines CPFE as a state, not a disease. CPFE is thought to include emphysema and interstitial pneumonia coexistent with smoking-induced pulmonary fibrosis. CPFE may not be differentiated from idiopathic interstitial pneumonia based on imaging findings, but it may show destructive change, such as a large cyst. CPFE is thought to include heterogeneous disease from comorbid pulmonary emphysema and idiopathic interstitial pneumonia with smoking-induced pulmonary fibrosis [72–76].

Biopsy-proven NSIP concomitant with pulmonary emphysema can show a UIP pattern at HRCT as a result of pre-existing pulmonary emphysema [22].

## 6.5 Imaging Features of Complication of IPF/UIP

### *6.5.1 Acute Exacerbation (Fig. 6.19)*

Acute exacerbation of unknown cause is one of the most serious complications of IPF/UIP and one of the most frequent causes of death in patients with IPF in Japan. Approximately 40 % of patients with IPF/UIP experience this complication, possibly related to viral infection [77–80]. The surgical procedure, drug toxicity, and radiation exposure can exacerbate disease [81–84]. Acute respiratory failure after

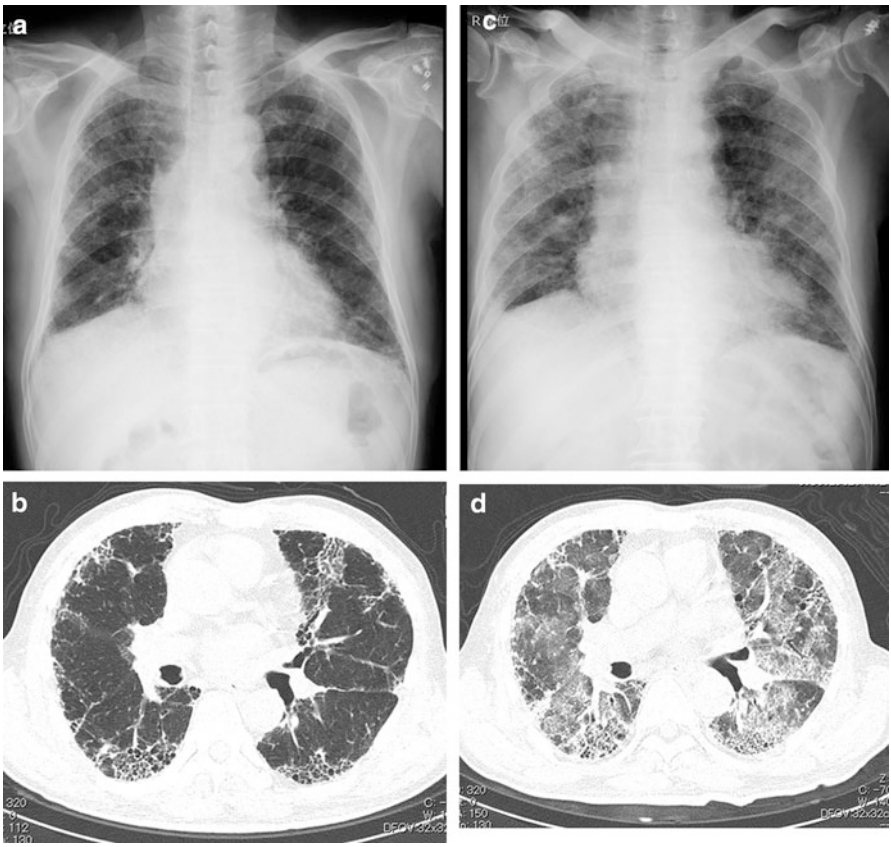


**Fig. 6.19** Acute exacerbation of IPF/UIP. (**a**) Chest x-ray shows volume loss in bilateral lungs with reticular opacity. (**b**) High-resolution computed tomography (HRCT) shows reticular opacity located predominantly in the subpleural region of lung base. (**c**) Chest x-ray at the onset of acute exacerbation shows widespread overlapping ground-glass opacity on pre-existing interstitial opacity. (**d**) HRCT shows widespread ground-glass opacity overlapping pre-existing interstitial pneumonia

surgical resection may be related to acute exacerbation of subclinical interstitial pneumonia [85, 86] (Fig. 6.20). Exacerbation by drug toxicity is considered to be drug-induced lung injury.

The pathology of acute exacerbation demonstrates diffuse alveolar damage (DAD) or an organizing pneumonia (OP) pattern. Imaging features of acute exacerbation of IPF/UIP include widespread ground-glass opacity or consolidation [85, 86].

Imaging findings are useful to predict the prognosis of acute exacerbation. Distribution of newly appeared GGO/consolidation is classified as diffuse, patchy, or peripheral. Prognosis is better for the peripheral pattern than the other two

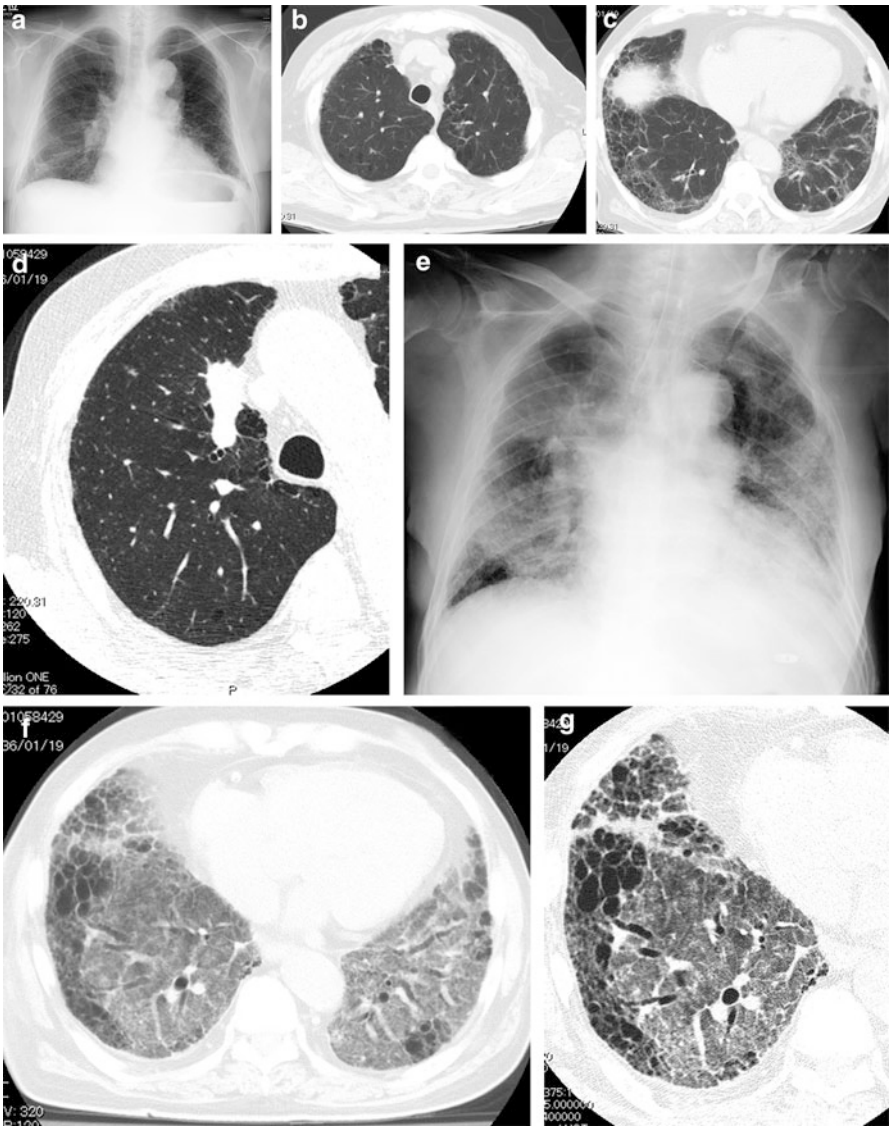


**Fig. 6.20** Postsurgical exacerbation of chronic fibrosing interstitial pneumonia with lung cancer. (**a**) Preoperative chest x-ray shows reticular opacity located predominantly in the bilateral lower lungs. The mass lesion is overlapped on the upper portion of the right hilum. (**b**) Computed tomography (CT) at the level of the upper lungs shows minimal emphysema. (**c**) CT at the level of the lung base shows reticular opacity and honeycomb lung in the subpleural regions. (**d**) High-resolution computed tomography (HRCT) of the right upper lobe shows nodular opacity, which is diagnosed as lung cancer by bronchoscopy. (**e**) Chest x-ray 4 days after right upper lobectomy shows widespread ground-glass opacity (GGO) and consolidation in bilateral lungs. (**f**) CT of the lower lungs shows diffuse GGO in the lungs. (**g**) HRCT of the right lower lobe shows diffuse GGO overlapping pre-existing interstitial pneumonia

patterns [87]. More extensive ground-glass opacity that includes traction bronchiectasis and honeycombing suggests a poor prognosis [88].

The differential diagnosis of acute exacerbation of IPF/UIP includes various infections, pulmonary edema by cardiac failure and following noninfectious disease, and acute exacerbation of other types of chronic fibrosing interstitial pneumonia, including acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), acute eosinophilic pneumonia, diffuse alveolar hemorrhage, and acute respiratory distress syndrome (ARDS).

### *6.5.2 Lung Cancer (Fig. 6.21)*

Lung cancer is more frequently identified in patients with IPF/UIP, and risk factors in these patients include older age, male gender, and history of smoking [89–91]. The frequencies of histological subtypes of lung cancer do not differ between

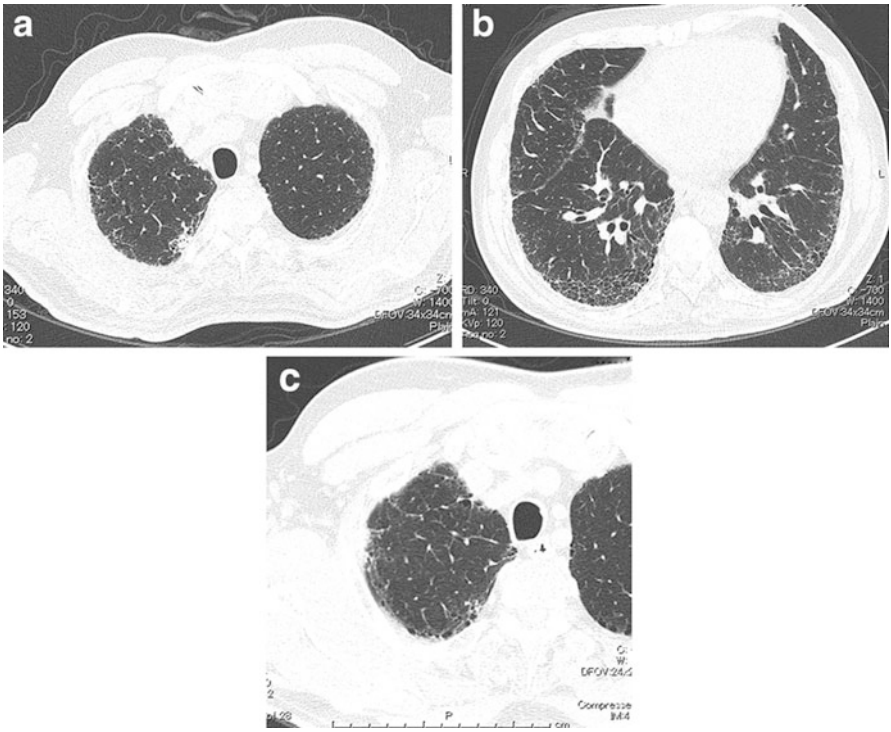


**Fig. 6.21** Lung cancer complicated with idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP). (**a**) High-resolution computed tomography (HRCT) shows lung cancer abutting the cyst wall in the right upper lobe. (**b**) HRCT of the lower lung shows UIP pattern fibrosis. (**c**) HRCT of the right upper lobe obtained one year before (**a**) shows a very subtle nodule abutting a small cyst

those with IPF/UIP and those without IPF [89–91]. Multiple lung cancer is not rare in cancer complicated by IPF/UIP [92].

Lung cancers with IPF/UIP frequently occur in fibrotic areas [93–95] and abutting cysts or interface between fibrotic areas and relatively normal lung [93]. Lung cancer in patients with IPF shows solid abnormal opacity formation even in early-stage disease, and early-stage lung cancer is indistinguishable from localized fibrotic shadow because of its small size and irregular shape.

### 6.5.3 *Infection (Figs. 6.12 and 6.22)*

Pneumonia is one of the most important differential diagnoses of acute exacerbation of IPF. Although infectious pneumonia usually shows segmental or lobar

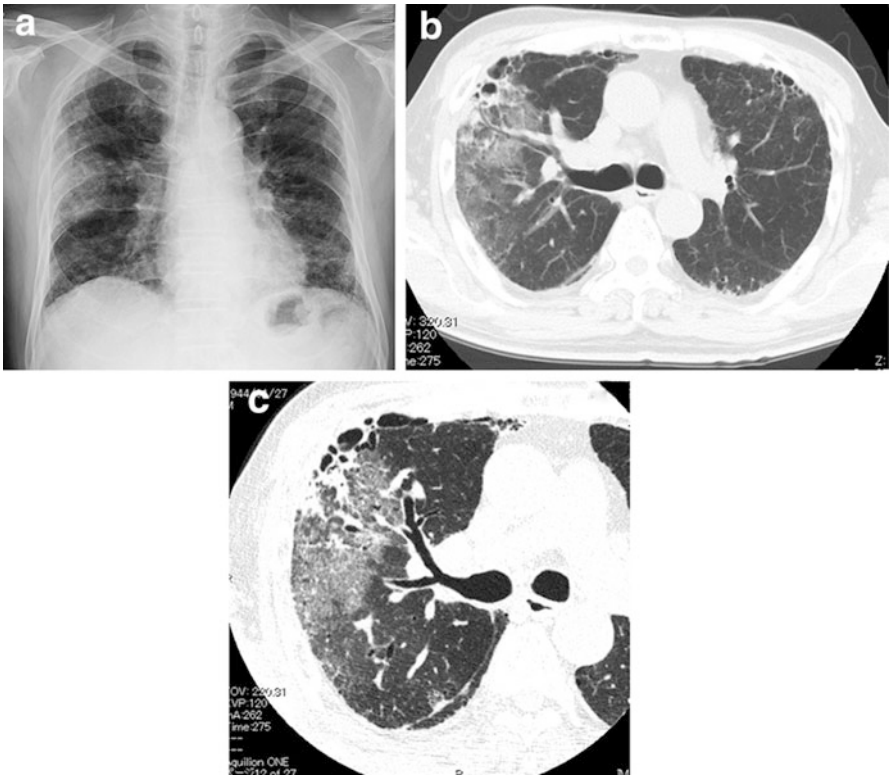


**Fig. 6.22** Pneumonia in a patient with idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP). (**a**) Chest x-ray shows reticular opacity in bilateral lower lungs and segmental consolidation in the lateral aspect of the right middle lung field. (**b**) High-resolution computed tomography (HRCT) shows scattered foci of reticular opacity and honeycombing in bilateral lungs. Segmental ground-glass opacity (GGO) including consolidation is noted in the right upper lobe. (**c**) HRCT shows GGO and consolidation in the right upper lobe more clearly

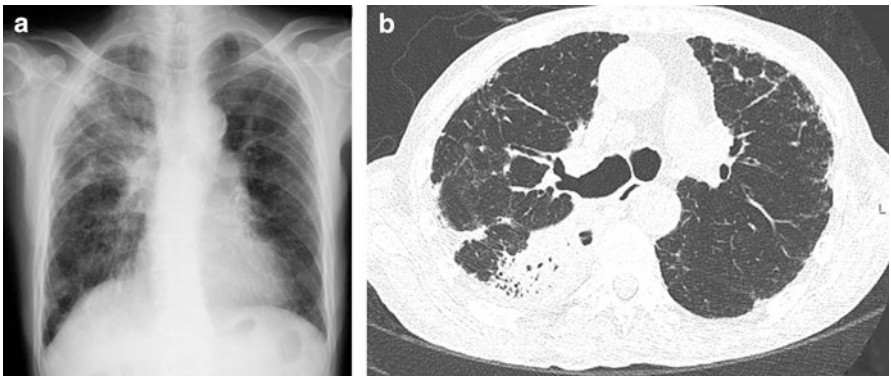


**Fig. 6.23** Tuberculosis in a patient with idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP). (**a**) Chest x-ray shows reticular opacity located predominantly in the lower lung fields. Radiopaque shadow is noted in the right upper to middle lung fields. (**b**) High-resolution computed tomography (HRCT) shows interstitial pneumonia with UIP pattern in the left lung and consolidation that suggests pneumonia in the right lung. Sputum examination shows acid-fast bacilli

distribution, nonbacterial infection, such as *Pneumocystis* pneumonia, shows diffuse ground-glass opacity that simulates acute exacerbation.

The appearance of mycobacterial infection complicated with IPF is atypical on CT.

It is more likely to appear as lobar/segmental consolidation instead of likely to show centrilobular nodular opacity/tree in bud [96, 97] that mimics bacterial or fungal pneumonia (Fig. 6.23).

## References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, et al. ATS/ERS/JRS/ALAT Committee on idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
2. Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D. ATS/ERS Committee on idiopathic interstitial pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
3. Arakawa H, Honma K. Honeycomb lung: history and current concepts. AJR Am J Roentgenol. 2011;196:773–82.
4. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner society: glossary of terms for thoracic imaging. Radiology. 2008;246:697–722.

5. Watadani T, Sakai F, Johkoh T, Noma S, Akira M, Fujimoto K, Bankier AA, Lee KS, Müller NL, Song JW, Park JS, Lynch DA, Hansell DM, Remy-Jardin M, Franquet T, Sugiyama Y. Interobserver variability in the CT assessment of honeycombing in the lungs. Radiology. 2013;266:936–44.
6. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157:1301–15.
7. Webb WR, Müller NL, Naidich DP. High-resolution CT of the lung. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 179–89, a Wolters Kluwer business.
8. Hansell DM, Lynch DA, McAdams HP, Bankier AA, editors. Imaging of diseases of the chest. 5th ed. Philadelphia: Mosby Elsevier; 2010. p. 564–72.
9. Elicker BM, Webb WR. Fundamentals of high-resolution lung CT: common findings, common patterns, common diseases, and differential diagnosis. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 150–9, a Wolters Kluwer business.
10. Kazerooni EA, Martinez FJ, Flint A, et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. AJR Am J Roentgenol. 1997;169:977–83.
11. Nishimura K, Kitaichi M, Izumi T, Nagai S, Kanaoka M, Itoh H. Usual interstitial pneumonia: histologic correlation with high-resolution CT. Radiology. 1992;182:337–42.
12. Sumikawa H, Johkoh T, Ichikado K, Taniguchi H, Kondoh Y, Fujimoto K, Tateishi U, Hiramatsu T, Inoue A, Natsag J, Ikemoto M, Mihara N, Honda O, Tomiyama N, Hamada S, Nakamura H, Müller NL. Usual interstitial pneumonia and chronic idiopathic interstitial pneumonia: analysis of CT appearance in 92 patients. Radiology. 2006;241:258–66.
13. Chan TY, Hansell DM, Rubens MB, du Bois RM, Wells AU. Cryptogenic fibrosing alveolitis and the fibrosing alveolitis of systemic sclerosis: morphological differences on computed tomographic scans. Thorax. 1997;52:265–70.
14. Müller NL, Miller RR, Webb WR, Evans KG, Ostrow DN. Fibrosing alveolitis: CT-pathologic correlation. Radiology. 1986;160:585–8.
15. Tung KT, Wells AU, Rubens MB, Kirk JM, du Bois RM, Hansell DM. Accuracy of the typical computed tomographic appearances of fibrosing alveolitis. Thorax. 1993;48:334–8.
16. Lynch DA, Godwin JD, Safrin S, Starko KM, Hormel P, Brown KK, Raghu G, King Jr TE, Bradford WZ, Schwartz DA, Richard WW, Idiopathic Pulmonary Fibrosis Study Group. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. Am J Respir Crit Care Med. 2005;172:488–93.
17. Elliot TL, Lynch DA, Newell Jr JD, et al. High-resolution computed tomography features of nonspecific interstitial pneumonia and usual interstitial pneumonia. J Comput Assist Tomogr. 2005;29:339–45.
18. Sverzellati N, Wells AU, Tomassetti S, et al. Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. Radiology. 2010;254:957–64.
19. Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, Kondoh Y, Ogura T, Arakawa H, Fujimoto K, Inoue A, Mihara N, Honda O, Tomiyama N, Nakamura H, Müller NL. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. Am J Respir Crit Care Med. 2008;177:433–9.
20. Silva CI, Müller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. Radiology. 2008;247:251–9.
21. Flaherty KR, Travis WD, Colby TV, Toews GB, Kazerooni EA, Gross BH, Jain A, Strawderman RL, Flint A, Lynch JP, Martinez FJ. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med. 2001;164:1722–7.
22. Akira M, Inoue Y, Kitaichi M, Yamamoto S, Arai T, Toyokawa K. Usual interstitial pneumonia and nonspecific interstitial pneumonia with and without concurrent emphysema: thin-section CT findings. Radiology. 2009;251:271–9.

23. Gruden JF, Panse PM, Leslie KO, Tazelaar HD, Colby TV. UIP diagnosed at surgical lung biopsy, 2000–2009: HRCT patterns and proposed classification system. AJR Am J Roentgenol. 2013;200:W458–67.
24. Johkoh T, Sakai F, Ogura T, et al. Idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) without honeycombing on CT: CT findings in 30 patients diagnosed by surgical lung biopsy. RSNA. 2014;CHS 257.
25. Johkoh T, Sumikawa H, Fukuoka J, et al. Do you really know precise radiologic-pathologic correlation of usual interstitial pneumonia? Eur J Radiol. 2014;83:20–6.
26. Hartman TE, Primack SL, Kang EY, et al. Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assessment with serial CT. Chest. 1996;110:378–82.
27. Mino M, Noma S, Kobashi Y, Iwata T. Serial changes of cystic air spaces in fibrosing alveolitis: a CT-pathological study. Clin Radiol. 1995;50:357–63.
28. Wells AU, Rubens MB, du Bois RM, Hansell DM. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR Am J Roentgenol. 1993;161:1159–65.
29. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. Radiology. 1993;189:687–91.
30. Johkoh T, Müller NL, Cartier Y, Kavanagh PV, Hartman TE, Akira M, Ichikado K, Ando M, Nakamura H. Idiopathic interstitial pneumonias: diagnostic accuracy of thin-section CT in 129 patients. Radiology. 1999;211:555–60.
31. Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol. 1994;18:136–47.
32. MacDonald SL, Rubens MB, Hansell DM, Copley SJ, Desai SR, du Bois RM, Nicholson AG, Colby TV, Wells AU. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology. 2001;221:600–5.
33. Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, Travis WD, Mumford JA, Murray S, Flint A, Lynch 3rd JP, Martinez FJ. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax. 2003;58:143–8.
34. Hartman TE, Swensen SJ, Hansell DM, Colby TV, Myers JL, Tazelaar HD, Nicholson AG, Wells AU, Ryu JH, Midthun DE, du Bois RM, Müller NL. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. Radiology. 2000;217:701–5.
35. Park JS, Lee KS, Kim JS, Park CS, Suh YL, Choi DL, Kim KJ. Nonspecific interstitial pneumonia with fibrosis: radiographic and CT findings in seven patients. Radiology. 1995;195:645–8.
36. Cottin V, Donsbeck AV, Revel D, Loire R, Cordier JF. Nonspecific interstitial pneumonia. Individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med. 1998;158:1286–93.
37. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J. 1998;12:1010–19.
38. Johkoh T, Müller NL, Colby TV, Ichikado K, Taniguchi H, Kondoh Y, Fujimoto K, Kinoshita M, Arakawa H, Yamada H, et al. Nonspecific interstitial pneumonia: correlation between thin-section CT findings and pathologic subgroups in 55 patients. Radiology. 2002;225:199–204.
39. Nishiyama O, Kondoh Y, Taniguchi H, Yamaki K, Suzuki R, Yokoi T, Takagi K. Serial high resolution CT findings in nonspecific interstitial pneumonia/fibrosis. J Comput Assist Tomogr. 2000;24:41–6.
40. Akira M, Inoue Y, Arai T, Okuma T, Kawata Y. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. Thorax. 2011;66:61–5.
41. Tsubamoto M, Müller NL, Johkoh T, Ichikado K, Taniguchi H, Kondoh Y, Fujimoto K, Arakawa H, Koyama M, Kozuka T, et al. Pathologic subgroups of nonspecific interstitial

pneumonia: differential diagnosis from other idiopathic interstitial pneumonias on high-resolution computed tomography. J Comput Assist Tomogr. 2005;29:793–800.
42. Hartman TE, Primack SL, Swensen SJ, Hansell D, McGuinness G, Müller NL. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. Radiology. 1993;187:787–90.
43. Kawabata Y, Takemura T, Hebisawa A, Sugita Y, Ogura T, Nagai S, Sakai F, Kanauchi T, Colby TV, Desquamative Interstitial Pneumonia Study Group. Desquamative interstitial pneumonia may progress to lung fibrosis as characterized radiologically. Respirology. 2012;17:1214–21.
44. Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology. 2004;45:275–82.
45. Remy-Jardin M, Remy J, Gosselin B, Becette V, Edme JL. Lung parenchymal changes secondary to cigarette smoking: pathologic-CT correlations. Radiology. 1993;186:643–51.
46. Holt RM, Schmidt RA, Godwin JD, Raghu G. High resolution CT in respiratory bronchiolitis-associated interstitial lung disease. J Comput Assist Tomogr. 1993;17:46–50.
47. Padley SP, Padhani AR, Nicholson A, Hansell DM. Pulmonary sarcoidosis mimicking cryptogenic fibrosing alveolitis on CT. Clin Radiol. 1996;51:807–10.
48. Ohtani Y, Saiki S, Kitaichi M, et al. Chronic bird fancier's lung: histopathological and clinical correlation. An application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. Thorax. 2005;60:665–71.
49. Silva CI, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology. 2008;246:288–97.
50. Lynch DA, Newell JD, Logan PM, King Jr TE, Müller NL. Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonary fibrosis? AJR Am J Roentgenol. 1995;165:807–11.
51. Pérez-Padilla R, Salas J, Chapela R, et al. Mortality in Mexican patients with chronic pigeon breeder's lung compared with those with usual interstitial pneumonia. Am Rev Respir Dis. 1993;148:49–53.
52. Hwang JH, Misumi S, Sahin H, Brown KK, Newell JD, Lynch DA. Computed tomographic features of idiopathic fibrosing interstitial pneumonia: comparison with pulmonary fibrosis related to collagen vascular disease. J Comput Assist Tomogr. 2009;33:410–15.
53. Song JW, Do KH, Kim MY, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. Chest. 2009;136:23–30.
54. Corte TJ, Copley SJ, Desai SR, Zappala CJ, Hansell DM, Nicholson AG, Colby TV, Renzoni E, Maher TM, Wells AU. Significance of connective tissue disease features in idiopathic interstitial pneumonia. Eur Respir J. 2012;39:661–8.
55. Assayag D, Elicker BM, Urbania TH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology. 2014;270:583–8.
56. Kinder BW, Collard HR, Koth L, Daikh DI, Wolters PJ, Elicker B, Jones KD, King Jr TE. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med. 2007;176:691–7.
57. Suda T, Kono M, Nakamura Y, et al. Distinct prognosis of idiopathic nonspecific interstitial pneumonia (NSIP) fulfilling criteria for undifferentiated connective tissue disease (UCTD). Respir Med. 2010;104:1527–34.
58. Fischer A, West SG, Swigris JJ, Brown KK, duBois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. Chest. 2010;138:251–6.
59. Vij R, Noth I, Strek ME, et al. Autoimmune-featured interstitial lung disease: a distinct entity. Chest. 2011;140:1292–9.
60. Tossavainen A. Asbestos, asbestosis, and cancer: the Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health. 1997;23:311–6.

61. American Thoracic Society. Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med. 2004;170:691–715.
62. Roggli VL, Gibbs AR, Attanoos R, Churg A, Popper H, Cagle P, Corrin B, Franks TJ, Galateau-Salle F, Galvin J, Hasleton PS, Henderson DW, Honma K. Pathology of asbestosis – an update of the diagnostic criteria: report of the asbestosis committee of the College of American Pathologists and Pulmonary Pathology Society. Arch Pathol Lab Med. 2010;134:462–80.
63. Akira M, Yokoyama K, Yamamoto S, et al. Early asbestosis: evaluation with high-resolution CT. Radiology. 1991;178:409–16.
64. Akira M, Yamamoto S, Yokoyama K, et al. Asbestosis: high-resolution CT-pathologic correlation. Radiology. 1990;176:389–94.
65. Aberle DR, Gamsu G, Ray CS, Feuerstein IM. Asbestos-related pleural and parenchymal fibrosis: detection with high-resolution CT. Radiology. 1988;166:729–34.
66. al-Jarad N, Strickland B, Pearson HC, Rubens MB, Rudd RM. High resolution computed tomographic assessment of asbestosis and cryptogenic fibrosing alveolitis: a comparative study. Thorax. 1992;47:645–50.
67. Copley SJ, Wells AU, Sivakumaran P, et al. Asbestosis and idiopathic pulmonary fibrosis: comparison of thin-section CT features. Radiology. 2003;229:731–6.
68. Akira M, Yamamoto S, Inoue Y, Sakatani M. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 2003;181:163–9.
69. Arakawa H, Johkoh T, Honma K, et al. Chronic interstitial pneumonia in silicosis and mix-dust pneumoconiosis: its prevalence and comparison of CT findings with idiopathic pulmonary fibrosis. Chest. 2007;131:1870–6.
70. Cottin V, Cordier JF. The syndrome of combined pulmonary fibrosis and emphysema. Chest. 2009;136:1–2.
71. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier JF. Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26:586–93.
72. Kawabata Y, Hoshi E, Murai K, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course. Histopathology. 2008;53:707–14.
73. Churg A, Hall R, Bilawich A. Respiratory bronchiolitis with fibrosis-interstitial lung disease: a new form of smoking-induced interstitial lung disease. Arch Pathol Lab Med. 2015;139 (4):437–40.
74. Reddy TL, Mayo J, Churg A. Respiratory bronchiolitis with fibrosis. High-resolution computed tomography findings and correlation with pathology. Ann Am Thorac Soc. 2013;10:590–601.
75. Katzenstein AL. Smoking-related interstitial fibrosis (SRIF): pathologic findings and distinction from other chronic fibrosing lung diseases. J Clin Pathol. 2013;66:882–7.
76. Katzenstein AL. Smoking-related interstitial fibrosis (SRIF), pathogenesis and treatment of usual interstitial pneumonia (UIP), and transbronchial biopsy in UIP. Mod Pathol. 2012;25 Suppl 1:S68–78.
77. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest. 1993;103:1808–12.
78. Collard HR, Moore BB, Flaherty KR, et al. Idiopathic Pulmonary Fibrosis Clinical Research Investigators. Acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2007;176:636–43.
79. Kondoh Y, Taniguchi H, Katsuta T, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27:103–10.
80. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63.

81. Sato T, Kondo H, Watanabe A, Nakajima J, Niwa H, Horio H, Okami J, Okumura N, Sugio K, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Kondo T, Date H. A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients. Gen Thorac Cardiovasc Surg. 2014;63:164–72.
82. Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, Fujii Y, Mitsudomi T, Yoshimura M, Maniwa T, Suzuki K, Kataoka K, Sugiyama Y, Kondo T. Date H; Japanese Association for Chest Surgery. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014;147:1604–11.
83. Chida M, Kobayashi S, Karube Y, Hayama M, Tamura M, Ishihama H, Oyaizu T. Incidence of acute exacerbation of interstitial pneumonia in operated lung cancer: institutional report and review. Ann Thorac Cardiovasc Surg. 2012;18:314–17.
84. Sugiura H, Takeda A, Hoshi T, Kawabata Y, Sayama K, Jinzaki M, Kuribayashi S. Acute exacerbation of usual interstitial pneumonia after resection of lung cancer. Ann Thorac Surg. 2012;93:937–43.
85. Saito H, Minamiya Y, Nanjo H, Ito M, Ono T, Motoyama S, Hashimoto M, Ogawa J. Pathological finding of subclinical interstitial pneumonia as a predictor of postoperative acute respiratory distress syndrome after pulmonary resection. Eur J Cardiothorac Surg. 2011;39:190–4.
86. Chida M, Ono S, Hoshikawa Y, Kondo T. Subclinical idiopathic pulmonary fibrosis is also a risk factor of postoperative acute respiratory distress syndrome following thoracic surgery. Eur J Cardiothorac Surg. 2008;34:878–81.
87. Akira M, Kozuka T, Yamamoto S, Sakatani M. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178:372–8.
88. Fujimoto K, Taniguchi H, Johkoh T, et al. Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. Eur Radiol. 2012;22:83–92.
89. Mizushima Y, Kobayashi M. Clinical characteristics of synchronous multiple lung cancer associated with idiopathic pulmonary fibrosis. A review of Japanese cases. Chest. 1995;108:1272–7.
90. Park J, Kim DS, Shim TS, et al. Lung cancer in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2001;17:1216–19.
91. Nagai A, Chiyotani A, Nakadate T, Konno K. Lung cancer in patients with idiopathic pulmonary fibrosis. Tohoku J Exp Med. 1992;167:231–7.
92. Sakai S, Ono M, Nishio T, Kawarada Y, Nagashima A, Toyoshima S. Lung cancer associated with diffuse pulmonary fibrosis: CT-pathologic correlation. J Thorac Imaging. 2003;18:67–71.
93. Kishi K, Homma S, Kurosaki A, Motoi N, Yoshimura K. High-resolution computed tomography findings of lung cancer associated with idiopathic pulmonary fibrosis. J Comput Assist Tomogr. 2006;30:95–9.
94. Yoshida R, Arakawa H, Kaji Y. Lung cancer in chronic interstitial pneumonia: early manifestation from serial CT observations. AJR Am J Roentgenol. 2012;199:85–90.
95. Matsushita H, Tanaka S, Saiki Y, et al. Lung cancer associated with usual interstitial pneumonia. Pathol Int. 1995;45:925–32.
96. Park SW, Song JW, Shim TS, et al. Mycobacterial pulmonary infections in patients with idiopathic pulmonary fibrosis. J Korean Med Sci. 2012;27:896–900.
97. Hwang HJ, Kim MY, Shim TS, Kim DS. Nontuberculous mycobacterial pulmonary infection in patients with idiopathic interstitial pneumonias: comparison with patients without idiopathic interstitial pneumonias. J Comput Assist Tomogr. 2014;38:972–8.

# Chapter 7
# Pathology of IPF

## Why Does the Pathological Classification of IIPs Vary Among Pathologists?

**Yoshinori Kawabata**

**Abstract** The pathological pattern of usual interstitial pneumonia (UIP) is defined as temporal and topological heterogeneous chronic interstitial pneumonia with a peripheral lobular distribution. The natural history of UIP is unclear, but attempts have been made to elucidate it. The complication of acute and subacute worsening or exacerbation has been discussed as an important part of the natural history of UIP. The major differential diagnoses of UIP are nonspecific interstitial pneumonia, desquamative interstitial pneumonia, and airspace enlargement with fibrosis. In a significant number of cases, analyses of pathological materials have just led to a diagnosis of chronic interstitial pneumonia not otherwise specified (an important component of unclassifiable interstitial pneumonia). Various diseases and other factors cause UIP, including idiopathic, collagen vascular diseases; chronic hypersensitivity pneumonia; occupational exposure, especially to asbestos; and the administration of certain drugs. The role of pulmonary pathologists is to make a pathological diagnosis of UIP or another diagnosis and to look for etiological findings, like epithelioid cell granuloma and asbestos bodies. In this chapter, recent pathological advances in UIP are critically discussed, and I consider the reason why the pathological classification of IIPs varies among pathologists.

**Keywords** Usual interstitial pneumonia • Chronic interstitial pneumonia • Surgical lung biopsy • Pathology • Natural history

### 7.1 Introduction

In 2002, the histological patterns of idiopathic interstitial pneumonias (IIPs) were classified into usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), (bronchiolitis obliterans) organizing pneumonia (BOOP/OP), diffuse

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alveolar damage (DAD), respiratory bronchiolitis (RB), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia [1]. To me, DAD, NSIP, UIP, and DIP comprise the main idiopathic and secondary interstitial pneumonias. I exclude (BO) OP because of alveolar pneumonia [2] and RB/RB interstitial lung disease (RB-ILD) because only smoking causes RB and RB does not show histological features of ordinarily identified interstitial pneumonia. Katzenstein et al. divided IIPs into four types histologically (UIP, DIP/RB-ILD, NSIP, and DAD [3]). Katzenstein et al. also excluded OP because of intra-alveolar processes. The recent ATS/ERS Committee classified IIPs into three groups, namely, acute and subacute (DAD, OP), smoking related (DIP, RB), and chronic (UIP, NSIP) [4].

In this chapter, various features of UIP and its differential diagnosis are mainly discussed; the term UIP is used just to refer to the pathological pattern, not to a specific disease. I wish to emphasize papers written in Japanese (mainly by my research group).

## 7.2 Previous Understanding of Usual Interstitial Pneumonia (UIP) and Its Recent Histological Criteria

### *7.2.1 Previous Understanding*

Liebow et al. reported that UIP is characterized by honeycombing and muscular tissue proliferation, which occurs in one of five chronic interstitial pneumonias; they also thought that DAD is the first step of UIP [5, 6]. The superimposition of DAD on UIP at autopsy was identified, which is why the pathological features were a mixture of DAD and UIP and the early pathology was supposed to be DAD. In 1978, Carrington et al. for the first time established the histological features of modern UIP through open lung biopsy [7]. A highly variegated structure was stressed, but the presence of fibroblastic focus (FF) was not stated. In 1988, Myers et al. first reported the presence of FF at the top of dense fibrosis of UIP [8], and, in 1998, Katzenstein et al. stressed that FF is necessary for the diagnosis of UIP in addition to the above definition of Carrington [3].

### *7.2.2 Recent Histological Criteria of UIP*

Recently, idiopathic pulmonary fibrosis (IPF) and UIP have been redefined [1, 4, 9, 10]. In addition to structural/topological heterogeneity (normal lung to dense fibrosis with structural remodeling), (a) temporal heterogeneity (presence of FF), (b) peripheral lobular distribution, and (c) the absence of suspicion of other diseases were added (Fig. 7.1). Katzenstein et al. do not require peripheral lobular

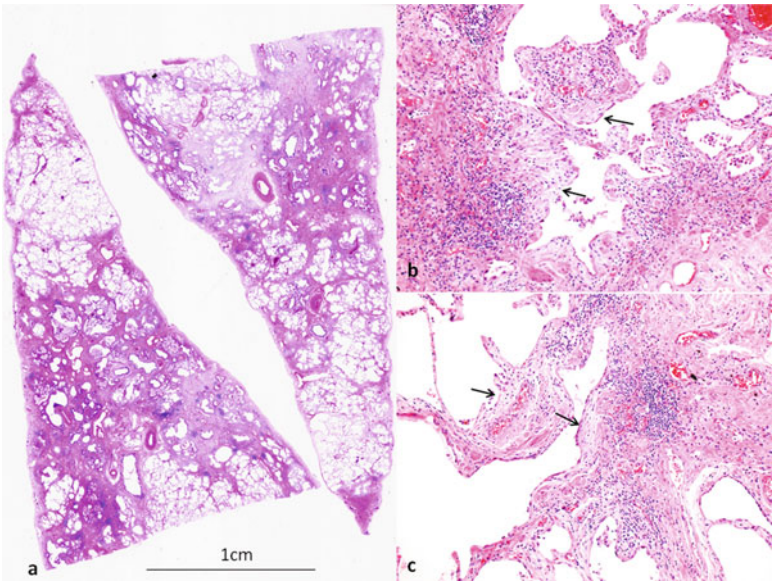


**Fig. 7.1** Histology of UIP. (**a**) Panoramic view. Patchy involvement and perilobular dense fibrosis with structural remodeling. Bar: 1 cm. Hematoxylin-eosin staining (HE). (**b**, **c**) Fibroblastic focus on dense fibrosis (*arrow*). ×10. HE

distribution [11, 12]. I personally prefer and use Katzenstein's definition, but here I will follow the official definition [1, 4, 9, 10] concerning UIP.

Now (in 2011), we can understand that UIP (HRCT and/or histology) of unknown etiology is IPF [10]. In 2000, IPF was defined as follows: (a) unknown etiology, (b) abnormal pulmonary function (decreased vital capacity and/or impaired gas exchange) with decreased diffusing capacity, and (c) abnormality on conventional chest radiographs or high-resolution computed tomography (HRCT) (bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT) when surgical lung biopsy (SLB) proved UIP [9]. Clinical criteria of IPF without SLB were defined separately. Recently, typical HRCT findings (honeycombing) have been stressed (previous criteria [9] including dyspnea and abnormal pulmonary function were eliminated), and SLB was recommended when HRCT is not typical [10]. In the latter cases [10], complicated combinations of HRCT and SLB can diagnose IPF as definite, possible, or inconsistent. Histopathological criteria for UIP were divided into (a) definite (fulfills the four criteria: marked fibrosis with structural remolding predominantly located peripheral lobule, patchy involvement, FF, and no alternative diagnosis), (b) probable (marked fibrosis but lacking either patchy involvement or FF and no alternative diagnosis), (c) possible (marked fibrosis and no alternative diagnosis), and (d) not UIP [10].

Not UIP includes the presence of any of six criteria: (a) hyaline membranes, (b) organizing pneumonia, (c) granulomas, (d) marked inflammatory cell infiltration away from honeycombing, (e) predominant airway-centered changes, and

(f) features suggestive of an alternative diagnosis. Features suggestive of an alternative diagnosis can include silicotic nodules, asbestos bodies, substantial other inorganic dust deposits, and marked eosinophilia [1].

## 7.3 Natural History of UIP, Emphasizing the Early Stage and Exacerbation

Natural history of UIP will be presented in Fig. 7.2 and will be explained later. In short, its continuous gradual progression and acute and subacute exacerbation will take place at any stages of UIP. Clinical IPF is the last stage.

### *7.3.1 Definition of IPF*

It is unclear to me whether IPF without dyspnea is admitted into the new classification [10], though many Japanese specialists believe so. In order to avoid confusion, here I wish to use the terms subclinical (asymptomatic stage but sufficiently

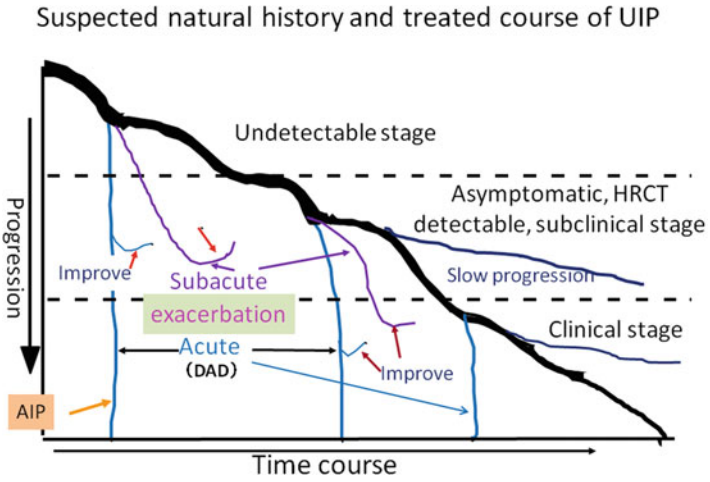


**Fig. 7.2** Suspected natural history and treated course of UIP. Natural history of UIP (*thick line*) is divided into three stages: (1) undetectable stage; (2) asymptomatic, HRCT-detectable, subclinical stage; and (3) symptomatic, clinical stage. Acute exacerbation (*blue*) can be seen at any stage and some cases respond to corticosteroid therapy (*red arrow*). When acute exacerbation is seen at the undetectable stage, it is called acute interstitial pneumonia or idiopathic DAD (*yellow arrow*). Subacute exacerbation (*purple*) can be seen at any stage and most cases respond to corticosteroid therapy (*red arrow*). Slower progression than expected is also seen (*dark blue*) (Modified from Modern Physician (Ref. [38]), Internal Medicine [43], and Kokyu [49] with permission)

detectable by HRCT) IPF and clinical (symptomatic stage, ordinarily) IPF when the cause of UIP is unknown.

## *7.3.2 Natural History of UIP*

### 7.3.2.1 Stage

I suspect that UIP starts with microscopic dense fibrosis with FF generally located in the base of the lower lobe subpleurally (Fig. 7.3a, b). Gradually, this fibrosis extends upward and to the inner lung continuously or discontinuously until HRCT can detect it (Fig. 7.3c, d).

I personally defined the UIP stages as follows: (a) microscopic stage, when macroscopically undetectable; (b) mild macroscopic stage, macroscopically detectable but up to 1 cm in depth from the pleura; and (c) extensive macroscopic stage, more than 1 cm in depth from the pleura by macroscopic examination of resected

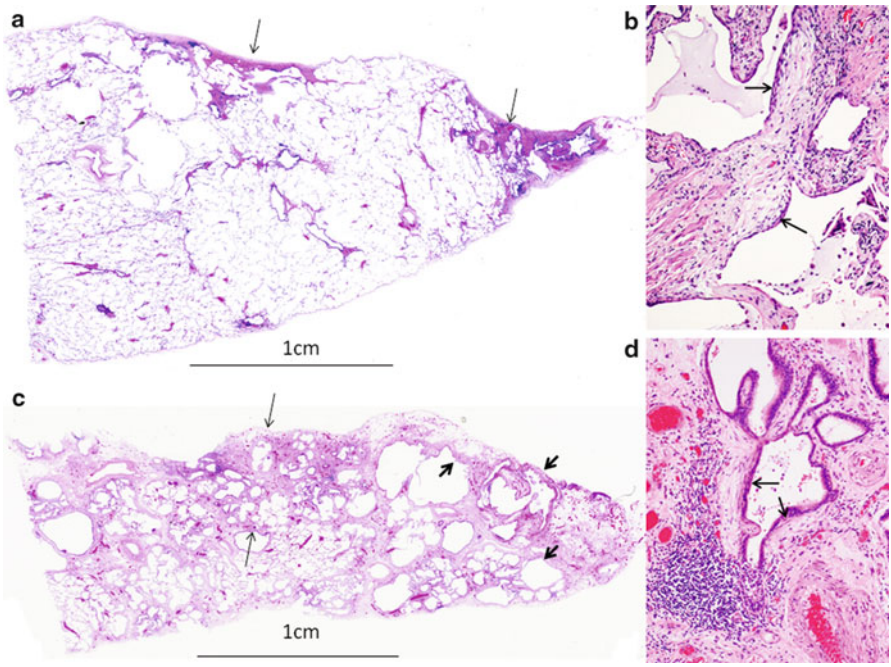


**Fig. 7.3** Histology of early UIP. a.c. Costophrenic edge on the right side. (**a**) Microscopic UIP showing dense fibrosis with/without structural remodeling (*arrow*). Bar: 1 cm. Panoramic view. HE. (**b**) Fibroblastic focus on dense fibrosis (*arrow*). ×10. HE. (**c**) Histology of macroscopic mild UIP showing dense fibrosis of 4.5 mm thickness from the pleura (between *arrows*) with honeycombing (*thick arrows*). Panoramic view. HE. (**d**) Fibroblastic focus on dense fibrosis (*arrow*). ×10. HE

lung [13–15]. The mild macroscopic stage roughly correlates with the HRCT-detectable stage when there are faint or clear, sufficient reticular shadows and/or honeycombing. When bilateral lower lobe reticular shadows or honeycombing are clearly seen within 1 cm in depth, it is subclinical IPF. The extensive macroscopic stage might be roughly clinical IPF.

#### 7.3.2.2 Incidence and Time Course

It is unclear how many years are required to progress from onset until the mild macroscopic stage, although 10 to 20 years has been suggested by me. The incidence of macroscopically detectable mild- and extensive-staged UIP was more than 20 % in more-than-moderate smokers and 3.5 % in nonsmokers in lungs subjected to lobectomy for lung cancer [14]. The incidence of mild macroscopic UIP increases with age (0 %, <40 years; 3 %, 50–60; 14.1 %, 70–80; 28 %, >80) [13]. It seems that mild macroscopic UIP begins approximately at the age of the 40s. The rate of subclinical interstitial pneumonia (mainly subclinical IPF) was 9.7 % [16] in Japan. In addition, a rate of bilateral lower lobe reticular shadows of 8 % was reported, as determined by HRCT in asymptomatic smokers [17]. I suppose that both variously typed interstitial pneumonias and airspace enlargement with fibrosis (AEF) [14] are included in this 8 %. As for progression, Nagai et al. reported that routine chest X-ray-screened, pathologically proven UIP cases became symptomatic 1000 days later [18]. Fukushima et al. followed up 127 microscopic and macroscopic mild UIP cases for 4 years; 4 % showed acute exacerbation and 6 % showed chronic progression [19]. It is necessary to follow up cases that show HRCT-detected reticular shadows and macroscopically detected UIP lesions found by lobectomy to determine how many years are required for progression to clinical IPF.

### *7.3.3 Acute Exacerbation of UIP*

#### 7.3.3.1 Historical Understanding

DAD superimposed of UIP is clinically called acute exacerbation [20–30], whether UIP is idiopathic or secondary. Liebow might have been the first to report acute exacerbation of IPF [5]. In Japan, idiopathic interstitial pneumonia was divided into the acute form (idiopathic DAD) and the chronic form (IPF) in 1976 following Liebow's concept because of the common complication of DAD in UIP. Yoshimura et al. reported acute exacerbation of IPF for the first time in 1984 [20]. Thirty-five cases suffered 43 episodes of acute exacerbation, and 97.1 % had died one month after the episode. They proposed diagnostic criteria of acute exacerbation. Kondo and Saiki published the first English paper in 1989 [21]: (a) clinical study (among 155 IPF cases, 89 (57 %) showed acute exacerbation) and (b) pathological study

(among 22 SLB-proved IPF cases, four showed acute exacerbation, and pathological examination confirmed hyaline membrane formation (one type of DAD) on UIP in all of these four cases).

#### 7.3.3.2 General Risk Factors and Incidences

Papers on acute exacerbation were mainly reported from the northeast of Asia, and the incidence of acute exacerbation varied, but was around 10 % per year [20, 22–25]. Risk factors were infection, reduction of corticosteroid dose, and various types of surgery, among others [15, 20–22, 25]. The reported incidences of acute exacerbation of clinical and subclinical IPF following lobectomy for lung cancer are 15 % (collective data of nine papers) [26] and 15.8 % (11 papers) [27]. The incidences of acute exacerbation of microscopic and macroscopic mild and extensive UIP cases just after lobectomy were 1.6, 6, and 10.6 % [15]. The incidence of acute exacerbation following SLB was reported to be low in Europe and America [28, 29].

#### 7.3.3.3 Extension of Acute e Exacerbation to the Milder Cases and Mortality

Generally, the concept of acute exacerbation has been used for clinical IPF. We reported acute exacerbation of macroscopic mild UIP cases following lobectomy in 2001 [13] and again in 2005 [15], in the same year as the report of Chida et al. [30], as well as a case report in 2011 [31]. We also reported acute exacerbation of the microscopic-staged cases [15, 32].

The mortality rate of acute exacerbation varies [20–22, 25, 27], from 20 to 100 %. Kondoh et al. reported three SLB cases of acute exacerbation without death [33].

#### 7.3.3.4 The Pathological Risk Factors

The pathological risk factors of acute exacerbation have not been well clarified. Fukushima et al. compared a thick-walled, small-sized honeycombing ($4.3 \pm 0.5$ mm in diameter) cases and a thin-walled, variously sized honeycombing ($10.0 \pm 1.6$ mm in diameter) cases. The former cases showed a higher incidence of acute exacerbation, as well as higher rates of women, nonsmokers, and those with a lower smoking index [34]. We also confirmed that the former cases showed a higher incidence of acute exacerbation, in addition to extent by another trial [15]. Histological factors related to acute exacerbation was the presence of active inflammatory changes: (a) degree of interstitial inflammation continuous with dense fibrosis, (b) amount of granulation tissue in and next to dense fibrosis (FF), (c) quantification of interstitial inflammatory change with granulation tissue apart from dense fibrosis,

and (d) quantification of acute interstitial inflammatory change with fibrin exudation seen in the lobectomy UIP area [35]. In addition, a microscopic organized membranous organization pattern of DAD, which will be described later, was seen only in the acute exacerbation cases [35].

#### 7.3.3.5 Two Histological Types of DAD

According to my experience, two histological patterns of DAD are observed. One is extensive epithelial erosion and hyaline membrane formation with subsequent membranous or ring organization (hyaline membrane was replaced by membranous granulation tissue due to activation of fibroblast) over the orifice ring of the alveolar wall (Fig. 7.4), and the other is epithelial erosion and massive exudation of fibrin following subsequent obstructive and incorporated-type intraluminal organization (Fig. 7.5) [36]. I named these as follows: (a) membranous organization pattern and (b) luminar organization pattern (somewhat resembling OP) in 1992 and 1994 [37, 38] (Figure 7.6 with permission from Kokyu and Modern Physician).

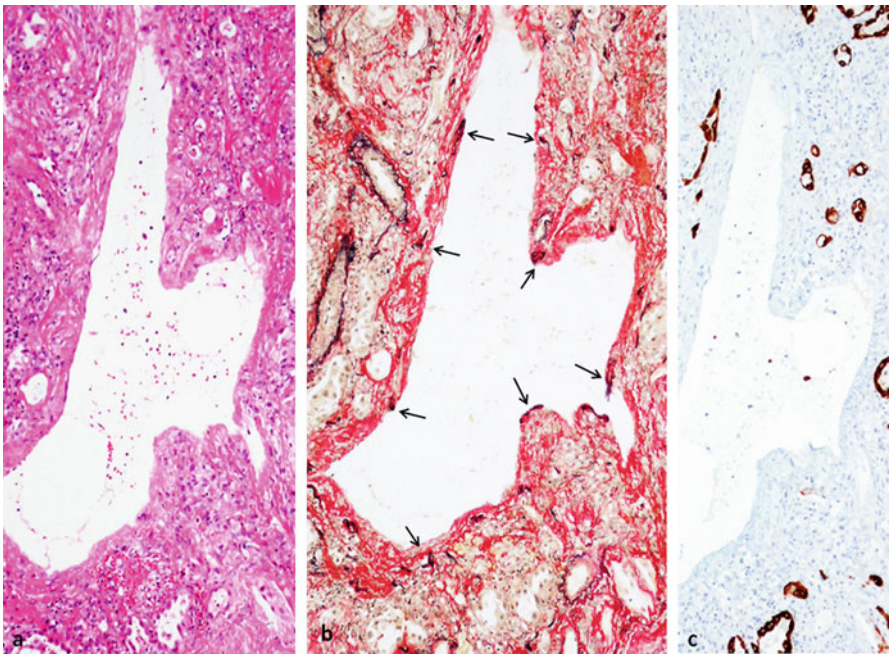


**Fig. 7.4** Organizing DAD, membranous organization. ×10. (**a**) Membranous or ring organization and dilated space. HE. (**b**) Alveolar orifice (*arrows*, portion of *black dot*) is embedded in the membranous organization and alveolar lumina are markedly collapsed. Dilated space is alveolar sac or duct. Elastica-van Gieson staining (EvG). (**c**) Remaining tiny airspace (mainly collapsed alveolar lumen) is lined by regenerative epithelium but no epithelialization on sac or duct. Immunostaining with AE1/AE3 for epithelium

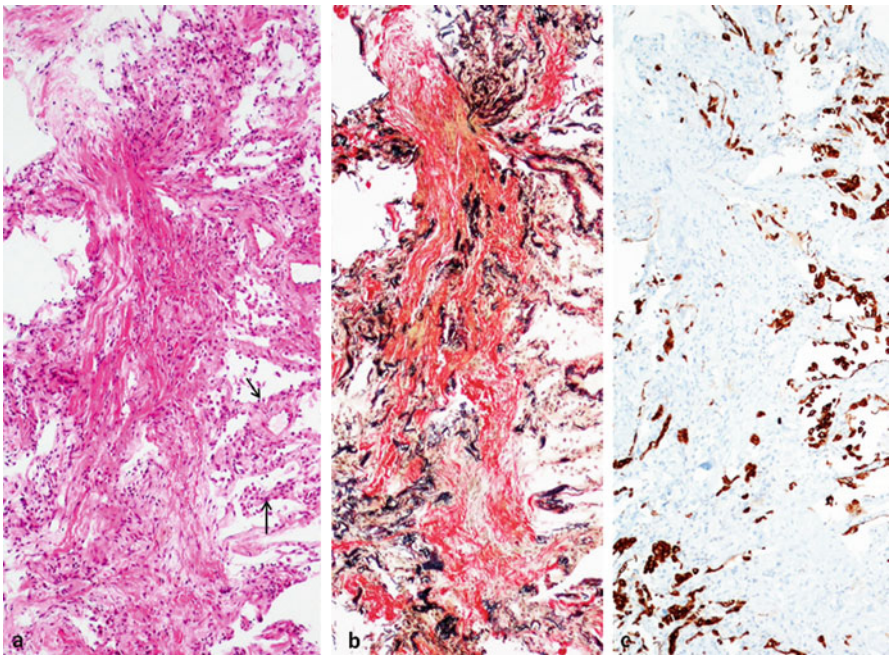


**Fig. 7.5** Organizing DAD, luminar organization. ×10. (**a**) Longitudinal organization in the center and thick-walled surrounding alveolar wall with cuboidal metaplasia (*arrow*). HE. (**b**) Many collapsed obliterated alveoli are trapped in the organization (obstructive-type organization). EvG. (**c**) No epithelialization in the organization, but surrounding alveolar wall is lined by cuboidal cells. Immunostaining with AE1/AE3 for epithelium. Figures 7.4 and 7.5 are of the same case. A 66-year-old female complained of exertional dyspnea and diffuse ground-glass opacities (GGO) within 1 month. Transbronchial lung biopsy showed luminal organization. Later, necropsy showed both membranous organization and luminal organization. The type of DAD changed or progressed

Frequently, both patterns and mixed pathology are seen in autopsy lungs, especially cases without a fulminant course, and the luminar organization pattern is older than the membranous organization pattern. DAD pathology as reported by Kondoh et al. was a luminar organization pattern [33]. Mandal et al. reported that DAD with organizing pneumonia showed greater survival than DAD without it (67 % versus 33 %) [39]. A luminal organization pattern and DAD with organizing pneumonia might involve nearly the same pathology. Parambil et al. reported seven cases showing DAD (six cases) and OP (one case) with 86 % mortality [40]. Churg et al. reported 12 cases showing DAD (four cases), OP (five cases), and giant fibroblastic foci (three cases), ten cases of which survived due to therapy [41].

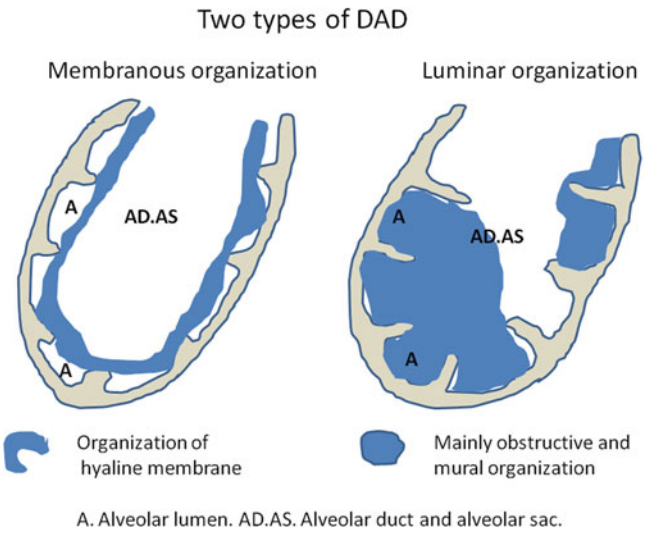


**Fig. 7.6** Two types of DAD. Membranous organization begins with hyaline membrane formation covering the surface of the alveolar orifice, and then hyaline membrane undergoes organization, resulting in a membranous or ring organization. Luminar organization begins with massive exudation to the alveoli, and obstructive and mural organization firmly attached to the alveolar wall

#### 7.3.3.6 Three Histological Features of Acute Exacerbation and Histological Differences Might Be Related to Prognosis

Before writing about pathology of acute exacerbation, I wish to discuss acute lung injury patterns (ALI/P). ALI/P was proposed by Katzenstein including DAD and BOOP in 1997 [42]. As far as my understanding from English literatures, the distinction between organizing DAD (luminal organization pattern) and OP is not so clear to me. The intraluminal organization seen in DAD is obstructive and incorporated mural pattern with an unclear lung structure, and the intraluminal organization in OP is mainly of the polypoid type with a preserved lung structure. Histologically, differential diagnosis between DAD and OP is clear, but there is a transitional-typed organization between DAD and OP. I named this ALI/P not otherwise specified (NOS). Katou et al. also reported this type of acute exacerbation [43]. Table 7.1 presents the histological features and prognosis of the two types of DAD and ALI/P NOS. Nowadays, above three comprise pathological features of acute exacerbation.

As stated before, the mortality rate of acute exacerbation ranges from 0 to 100 %. This difference in the mortality rate might mainly depend on different histology, in addition to recent advanced therapy, and other factors.

**Table 7.1** Histological features and prognosis of acute exacerbation

| | Early, acute stage | Organizing stage | Prognosis |
|---|---|---|---|
| DAD membranous organization | Mainly hyaline membrane formation | Membranous/ring fibrosis on hyaline membrane with remodeled lung structure | Poor, mostly fatal |
| | Epithelial denudation | Atypical epithelial regeneration including stratified squamous cells | |
| | Fibrin exudation | | |
| | Hemorrhage | | |
| DAD luminar organization | Mainly fibrin exudation | Obstructive and mural organization with unclear lung structure | Frequently favorable |
| | Epithelial denudation | Atypical epithelial regeneration | |
| | Myxomatous swelling of the alveolar wall | | |
| ALI/P NOS | Not clear | Various types and degrees of organization with unclear or preserved lung structure | Favorable |
| | | Diffuse interstitial inflammation | |
| | | Epithelial regeneration | |

Abbreviations: *DAD* diffuse alveolar damage, *ALI/P NOS* acute lung injury pattern not otherwise specified

### *7.3.4 Subacute Exacerbation of UIP*

We reported on female-dominant subacute interstitial pneumonia (SIP) [44] with 1 month to 6 months of increasing dyspnea, which shows a favorable prognosis following steroid treatment in 1995, 1 year after the NSIP paper [45]. Histologically, SIP resembles cellular and fibrosing NSIP (c- & f-NSIP) [45], but differs from organizing pneumonia [2]. I wish to propose the descriptive pathological term "organizing interstitial pneumonia" (organizing IP; interstitial pneumonia with various degreed and types of luminar organization) for SIP pathology. In addition, there was the frequent complication of UIP subpleurally together with SIP (15 cases, age $62.4 \pm 9.3$) (Fig. 7.7) in the same slide, which showed worse prognosis than SIP alone (35 cases, age $58 \pm 11$) in spite of no clinical and radiological differences between two groups [46]. This resembles subacute exacerbation of UIP cases. There are also reports on discordant UIP, namely, the presence of UIP and NSIP in different lobes, which follows the prognosis of IPF and has a worse prognosis than NSIP alone [47, 48].

### *7.3.5 Scheme of the Natural History of UIP*

Katou et al. and I proposed schemes of the natural history of UIP in 1994 and 1995 [38, 43, 49], and now I wish to present a modified natural history and treated course

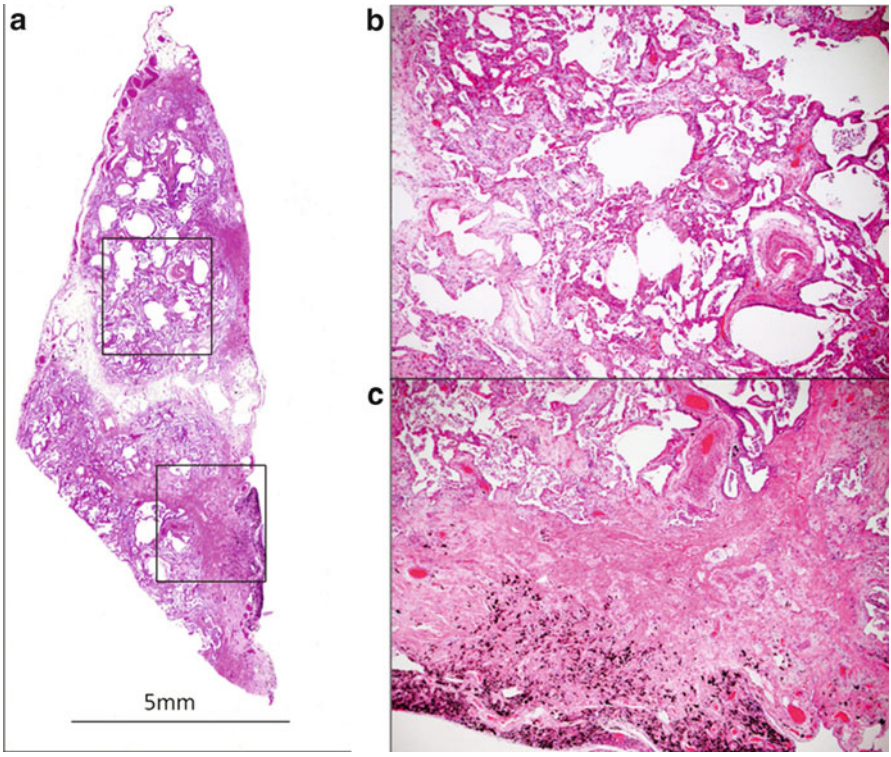


**Fig. 7.7** Combined fibrosing IP and UIP seen in a SLB slide. (**a**) Diffuse involvement of the lung tissue. Panoramic view. HE. (**b**) Inflammatory thick alveolar wall due to incorporation of organization into interstitium and new luminar organization (*upper box*). ×10. HE. (**c**) About 2-mm-thick, dense subpleural fibrosis with muscle tissue proliferation of UIP feature (*lower box*). ×10. HE

of UIP, with permission from the publishers (Modern Physician, Internal Medicine, and Kokyu) of references [38, 43, 49] (Fig. 7.2). Namely, it is divided into undetectable stage, subclinical stage, and clinical stage, as stated before. At any stage, acute exacerbation can take place. Araya et al. reported fatal [32], but Katou et al. reported improved acute exacerbation at the undetectable stage [44]. When acute exacerbation occurs at the undetectable stage, it is difficult to differentiate from idiopathic DAD (so-called acute interstitial pneumonia). We reported that the incidence of acute exacerbation at the undetectable stage following lobectomy is 1.6 % [15]. We also suspect that subacute exacerbation can take place at any stage (Fig. 7.7). Slower progression than expected is also experienced. The suspected progression pattern is shown in Fig. 7.8, namely, chronic, subacute, and acute (with permission from Modern Physician: [38]). Chronic progression comprises FF and local interstitial pneumonia with organization next to or adjacent to dense fibrosis. Subacute progression comprises two types of subacute exacerbation (c- & f-NSIP and organizing IP) and may be cellular NSIP (c-NSIP) apart from dense fibrosis.

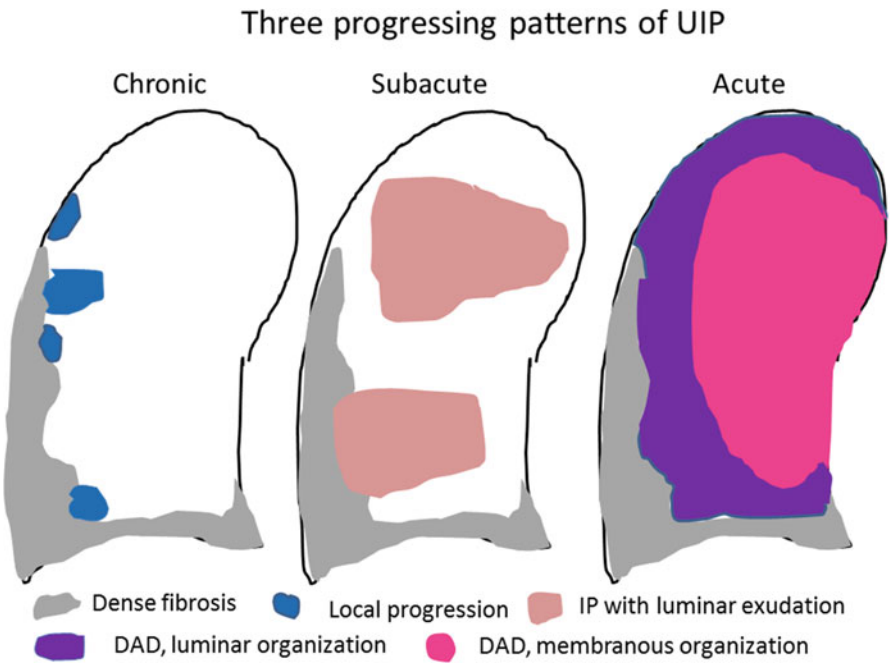


**Fig. 7.8** Three patterns of UIP progression. Generally, UIP progression is chronic, characterized by fibroblastic focus formation and other injury patterns next to fibrosis or the nearby perilobular area. Subacute progression sometimes takes place, showing interstitial pneumonia with some luminar organization apart from dense fibrosis. Acute exacerbation shows both luminar organization and membranous organization of DAD or ALI/P NOS. Generally, luminar organization takes place first, followed by membranous organization. In fulminant cases, only hyaline membrane formation occurs, and death occurs without membranous organization (Modified from Modern Physician (Ref. [38]), with permission)

The complication of two types of DAD, AIP/P NOS, c-NSIP, c- & f-NSIP, and organizing IP might be an integral part of UIP (concept of stable or inactive phase of UIP when there is UIP only and unstable or active phase of UIP when there is UIP + another interstitial pneumonia).

### *7.3.6 Early HRCT Detection of UIP Can Prepare for Acute Exacerbation and Early Therapy*

CT and HRCT features of IPF were reported [50, 51]. Johkoh et al. recently reported the HRCT features of clinical IPF without honeycombing [52]. However, we do not know about the HRCT features of subclinical IPF. Close pathological and radiological correlation is needed using lung subjected to lobectomy showing macroscopic mild UIP or subclinical IPF. It would be useful to understand the characteristic HRCT features of subclinical IPF, so we can prepare for acute and

subacute exacerbation, especially choosing therapy methods for lung cancer and introducing prompt timely therapy. I used to report to clinicians on whether lobectomized UIP cases had a risk of acute exacerbation or not by checking the activity of UIP as described before within 1 week, since most postoperative acute exacerbations occur around 1 week after surgery (unpublished data).

As discussed before, many of acute exacerbations are suspected to begin with luminar organization-typed DAD or ALI/P NOS; then early vigorous therapy can be effective.

## 7.4 Differential Diagnosis of UIP and Etiological Approach Through Histology

### *7.4.1 Classification of Interstitial Pneumonias*

The classification of interstitial pneumonias is an artificial one, and there was no complete classification. We thus have to look for a more suitable classification that shows the clinical-radiological-pathological correlation and indicates the constant effect of therapy.

Carrington et al. proved the differences in the natural history and treated course between UIP and DIP [7]. However, DIP was interpreted as the early stage and UIP as the late stage of IPF in 1976 [53], which was officially corrected in 2002 [1].

In my opinion, interstitial pneumonias of various etiologies can be classified into three types: acute interstitial pneumonia (using just the pathological pattern, not the specific disease) within 1 month, SIP with a course of 1–6 months of symptoms, and chronic interstitial pneumonia with a course of more than 6 months of symptoms or radiological findings [37, 49, 54]. Acute interstitial pneumonia can be histologically divided into membranous organization and luminar organization of DAD and ALI/P NOS. SIP can be histologically divided into organizing IP, c-NSIP, and c- & f-NSIP (overlap each other). Chronic interstitial pneumonia can be histologically divided into UIP, c- & f-NSIP, fibrosing NSIP (f-NSIP), DIP, and just chronic interstitial pneumonia unclassifiable.

Various types of SIP can be reversible. The challenge to the pathologists is chronic interstitial pneumonia; each histology has its own course and therapy response. Differentiation is essential for the selection of therapy.

### *7.4.2 Histological Heterogeneity of UIP and Selection of SLB Site*

#### 7.4.2.1 Histological Heterogeneity

As stated before, Flaherty et al. reported that, among 109 cases (either UIP or NSIP), biopsied multiple lobes showed UIP-UIP in 47 %, UIP-NSIP in 26 %, and

NSIP-NSIP in 27 % [47]. Monaghan et al. reported that among 64 previously diagnosed IPF cases, 12.5 % showed UIP-NSIP, 39.1 % showed UIP-UIP, and 48.4 % showed NSIP-NSIP [48]. I wonder whether the UIP-NSIP group showed pure UIP-pure NSIP without mixed features in one slide. In both studies, the age of UIP-NSIP cases was intermediate between those of UIP-UIP cases and NSIP-NSIP cases. Our SIP + UIP cases are old (not statistically significant) compared with SIP only. I suspect that, in the UIP-NSIP group, UIP might have a macroscopic mild extent and NSIP might be complicated, which could explain why the patients are younger than those with UIP-UIP and show symptoms. Katzenstein et al. also stated that focal NSIP was frequently seen in UIP [11, 12]. The data indicate that mixed histological patterns frequently exist, even in one disease, and the complication of NSIP can be understood as chronic exacerbation of UIP/stepwise progression of it or subacute exacerbation.

#### 7.4.2.2 Effect of Therapy

Treatment also affects histological features. Matsushima reported that SLB-proved DIP following treatment showed NSIP by later lobectomy for lung cancer [55]. Generally, at an advanced stage, each pathological pattern loses its characteristic or specific features and becomes nonspecific with/without therapy.

#### 7.4.2.3 Selection of Biopsy Site and Management

In order to make a pathological diagnosis, clinicians have to avoid far-advanced areas and should choose mildly to moderately affected areas, including normal-looking lung or early-stage areas. If possible, clinicians should select two portions showing different features on HRCT. In addition, the tip of the middle lobe or lingula should be avoided because of many nonspecific changes. Afterward, SLB staple should be removed and formalin should be injected, until the pleural surface becomes smooth, through the staple-removed area, in order to avoid injection of formalin into a fibrotic portion and interlobular septum.

### *7.4.3 Differential Diagnosis of UIP*

Smoking affects the pathological features of UIP in various ways. According to our current understanding, the concept of combined pulmonary fibrosis and emphysema is affected by smoking [56]. The complication of AEF [14] on UIP sometimes makes the interpretation of UIP difficult [57]. Smoking seems to affect the size of honeycombing. As stated before, Fukushima et al. divided UIP into a thick-walled honeycombing group (4.5 mm) and a thin-walled, variously sized honeycombing group (10.0 mm). The smoking ratio and smoking index were significantly higher in

the latter [34]. Flaherty et al. also began to look for smoking-related changes in SLB specimens [58].

UIP is complicated by other histological patterns, and smoking causes additional features and affects UIP itself, so the differential diagnosis is sometimes difficult.

#### 7.4.3.1 f-NSIP

NSIP was first reported by Katzenstein et al. [45] and incorporated into IIPs [1, 4].

Recent criteria of f-NSIP consisted of interstitial thickening by uniform fibrosis of the same age, usually preserving the alveolar architecture with varying amounts of cellular inflammation [4, 59]. Katzenstein et al. stressed the presence of paucicellular fibrosis with minimal or mild inflammation [11, 12], which indicates that they thought that this represents a more advanced stage than in the international criteria [1, 4]. When temporal and spatial uniformity was disturbed, the distinction between UIP and NSIP became impossible, and chronic interstitial pneumonia unclassifiable might be a better classification.

When a mixture of UIP and f-NSIP was seen in one slide, distinction became impossible, and a classification of chronic interstitial pneumonia with UIP and f-NSIP might be better. Clinical follow-up can resolve whether this is one type of UIP (UIP + α) or not.

#### 7.4.3.2 DIP

There is much controversy concerning the nature of DIP. Carrington et al. stressed that DIP progresses to end-stage fibrosis with honeycombing, but has a more favorable prognosis (70 % survival rate) than UIP [7]. Travis et al. reported a 10-year survival rate of 100 % [60]. The pathological criteria of DIP are as follows: (a) uniform involvement of lung parenchyma, (b) prominent accumulation of alveolar macrophages, (c) mild to moderate fibrotic thickening of the alveolar septa, and (d) mild interstitial chronic inflammation with lymphoid aggregate [1], and DIP was categorized into smoking-related IIPs akin to RB [4]. Katzenstein et al. also classified DIP and RB-ILD into a single category and limited this to only mild inflammation and fibrosis of the alveolar wall [11, 12]. We reported that DIP is an immunological disorder characterized by increased erythrocyte sedimentation rate and serum immunoglobulin and increased eosinophils and neutrophils in bronchoalveolar lavage fluid [61]. We think DIP has no relationship to smoking. Craig et al. reported that the smoking rate of DIP is 60 % [62]. The etiological and pathological features of DIP and RB are shown in Table 7.2. We confirmed that DIP progresses radiologically and shows honeycombing by a long-term follow-up [63], like Carrington et al. reported [7]. Via therapy and over a long course, the DIP pathology becomes nonspecific [55, 62, 64]. Early-stage DIP is easy to diagnose, but fibrotic-stage DIP is difficult to differentiate, especially from f-NSIP (Fig. 7.9) and sometimes from UIP (our personal experience).

**Table 7.2** Etiological and pathological features of DIP and RB

| | DIP | RB |
|---|---|---|
| Cause | Idiopathic, CVD, organ-specific autoimmune diseases, asbestosis, among others | Smoking only |
| Lobe | Lower lobe predominance | Upper lobe predominance |
| Distribution | Confluent panlobular, diffuse | Centrilobular, airway centered |
| Interstitial inflammation | Plasma cells, lymphocytes, eosinophils, and lymphoid follicles. Undergoes continuous fibrosis with structural remodeling | Paucicellular and hyalinous RB and alveolar wall with preserved structure |
| Alveolar epithelium | Diffuse cuboidal metaplasia | Occasional bronchiolarization |
| Alveolar lumina | Packed with Mφ and small numbers of eosinophils and neutrophils | Only Mφ |
| Character of Mφ | Large eosinophilic-collared cytoplasm, vesicular nuclei, and nucleoli | Small, brown-collared cytoplasm, condensed nuclei without nucleoli |

Abbreviations: *DIP* desquamative interstitial pneumonia, *RB* respiratory bronchiolitis, *RB* respiratory bronchiole, *CVD* collagen vascular disease, *Mφ* macrophage

#### 7.4.3.3 Pulmonary Upper Lobe Fibrosis, Pulmonary Upper Lobe Predominant Fibrosis, and Pleuroparenchymal Fibroelastosis

In 1992, Amitani et al. reported 13 cases (with one autopsy, three SLB, and five transbronchial lung biopsy) of idiopathic pulmonary upper lobe fibrosis (IPUF), vigorously excluding old tuberculosis, old nontuberculous mycobacteriosis, ankylosing spondylosis, and sarcoidosis, among others which show upper lobe fibrosis [65]. The histology is completely identical to that of apical scar. The macroscopic features include peripleural zonal atelectatic induration in the upper lobe beginning at the apex radiologically, and the histological feature is fibroelastosis with marked collapse. The coexistence of interstitial pneumonia in the lower lobe was excluded, so their criteria are strict. Clinically, the patients are not old and thinly built. In 1999, Shiota et al. reported seven cases of pulmonary upper lobe-predominant fibrosis confirmed by pathology that allows the coexistence of various types of interstitial pneumonia (mainly UIP) in the lower lobe [66]. Five years later, exactly the same category was reported under the name of idiopathic pleuroparenchymal fibroelastosis (IPPF) [67]. This name is inappropriate because the pleura do not show elastosis and pleural fibrosis is just an associated lesion. In addition, some cases are not idiopathic. We think that pulmonary upper lobe fibrosis or pulmonary upper lobe-predominant fibrosis is suitable as the general term, but the term IPPF was adopted [4]. I feel sorry about this as a Japanese person because Amitani et al. proposed the original concept in a review and Shiota et al. expanded this concept as an original paper. Histologically, upper lobe (predominant) fibrosis shows peripleural dense fibrosis with fibroblastic focus at the edge facing the normal lung. However, by elastic staining, the lung structure in the dense fibrosis

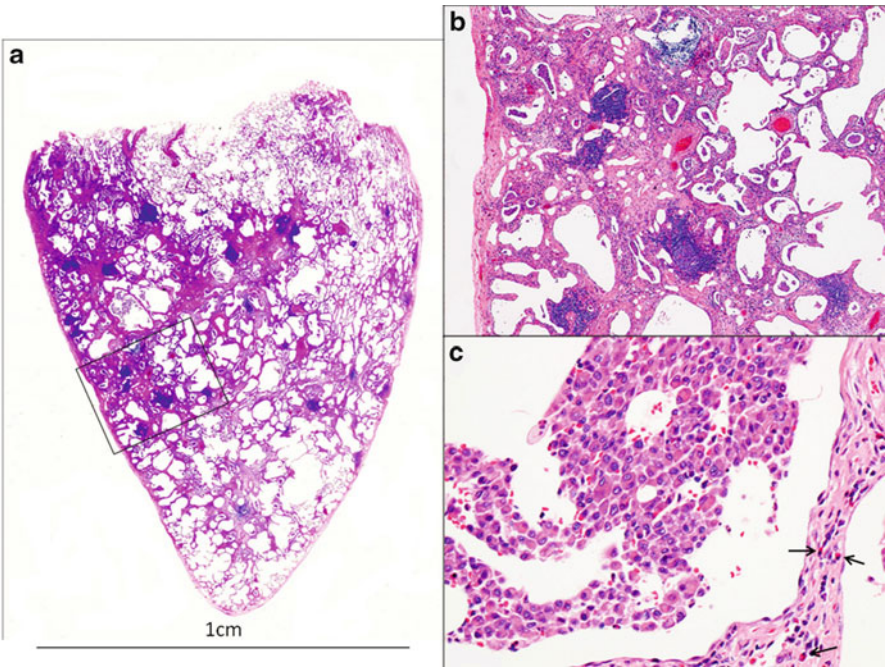


**Fig. 7.9** Suspected fibrotic-stage DIP. A 53-year-old male smoker with diffuse lobule-based ground-glass opacity and 26 % eosinophils and 28 % neutrophils by bronchoalveolar lavage. (**a**) SLB specimen. Rather diffuse involvement with various types of interstitial fibrosis and lymphoid follicles. Bar: 1 cm. Panoramic view. HE. (**b**) Lung structure was lost because of intraluminal organization. *In box*. ×4. HE. (**c**) Marked accumulation of large-sized, eosinophilic-colored macrophages in the alveoli and eosinophils in the interstitium (*arrow*). This comes from another slide of this case. ×40, HE. Pathological differential diagnosis with f-NSIP is impossible. Clinical information helped in reaching the final diagnosis

is preserved, which is completely different from UIP, in addition to different locations (upper lobe predominance versus lower lobe predominance).

#### 7.4.3.4 Airspace Enlargement with Fibrosis

In 2007, Yousem separated nine cases of respiratory bronchiolitis-associated interstitial lung disease with fibrosis as a disease from f-NSIP by the reevaluation of SLB slides [68]. In 2008, we found 100 AEF lesions through the examination of lungs subjected to lobectomy for lung cancer [14]. Katzenstein et al. also reported nine lesions named smoking-related interstitial fibrosis by examination of 23 lungs subjected to lobectomy [69]. Reddy et al. reported seven lesions named respiratory bronchiolitis with fibrosis [70]. The histological features of the above four papers are similar, except for the multiple thin-walled cysts in our work. The histological findings are (a) fibrous (frequently hyalinized) interstitium with structural

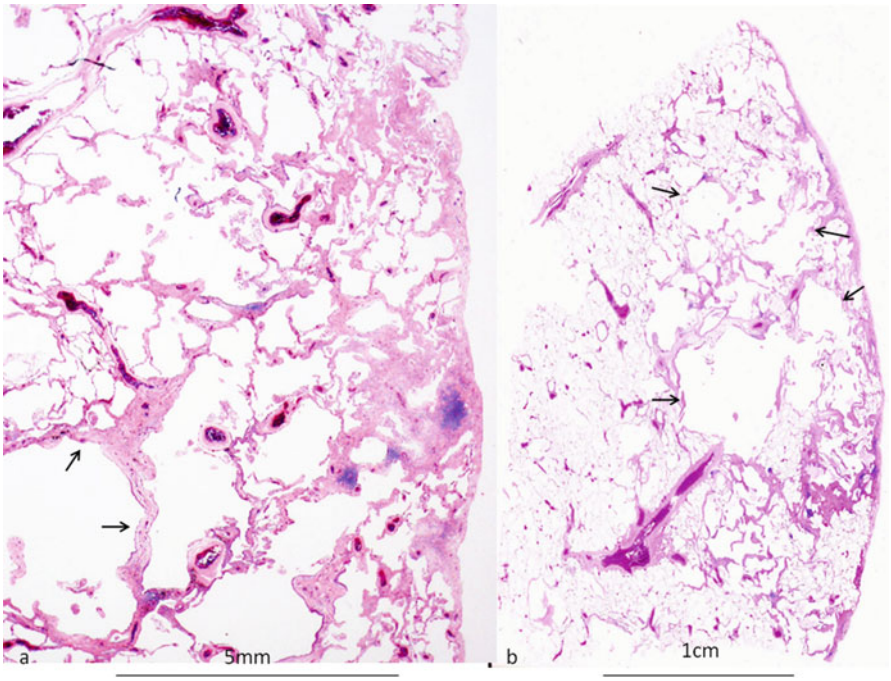


**Fig. 7.10** AEF from lobectomy lung. (**a**) Subpleural interstitial hyalinous thickening with mild emphysematous change and cystic change at the inner area (*arrow*). *Bar*: 5 mm. ×1, HE. (**b**) Multiple thin-walled cysts (*arrow*). Bar: 1 cm. Panoramic view, HE

remodeling, (b) emphysematous change, (c) frequently a bronchiolocentric location, and (d) general absence of FF. One example is hyalinous fibrous lesion (Fig. 7.10a) and another is fibrous cysts (Fig. 7.10b). Yamada et al. reported that the wall of the honeycomb ($2.1 \pm 0.3$ mm) is thicker than the cyst wall of AEF ($0.9 \pm 0.3$ mm) [71].

We used a descriptive term because nonsmokers with an occupational history also showed the same lesion, but most lesions are smoking related.

### *7.4.4 Etiological Approach Through Histology*

Generally, pathologists cannot decide on the disease or etiology. Collagen vascular disease (CVD), chronic hypersensitivity pneumonia (CHP), and occupational exposure also cause UIP. The role of a pathologist is only to suggest the probability of secondary UIP. Only the clinician can decide on the disease.

#### 7.4.4.1 CVD-Related UIP

Rheumatoid arthritis and Sjögren's syndrome, among others, cause UIP. In addition to ordinally UIP, plasma cell infiltration in the fibrotic area, lymphoid follicle with germinal center, various types of airway inflammation including follicular bronchiolitis, various types of pleuritis, and inflammatory thickening of the lymphatic routes are frequently seen (Fig. 7.11). However, the presence of the above features alone does not mean that UIP is associated with CVD. Song et al. reported that the germinal center score was the best distinguishing feature, but also reported the pathological resemblance between autoantibody-positive IPF and CVD [72]. Some cases of IPF and ANCA-positive UIP also show the same features. When pathologists see such features, they can suggest the possibility/probability of CVD to the clinician.

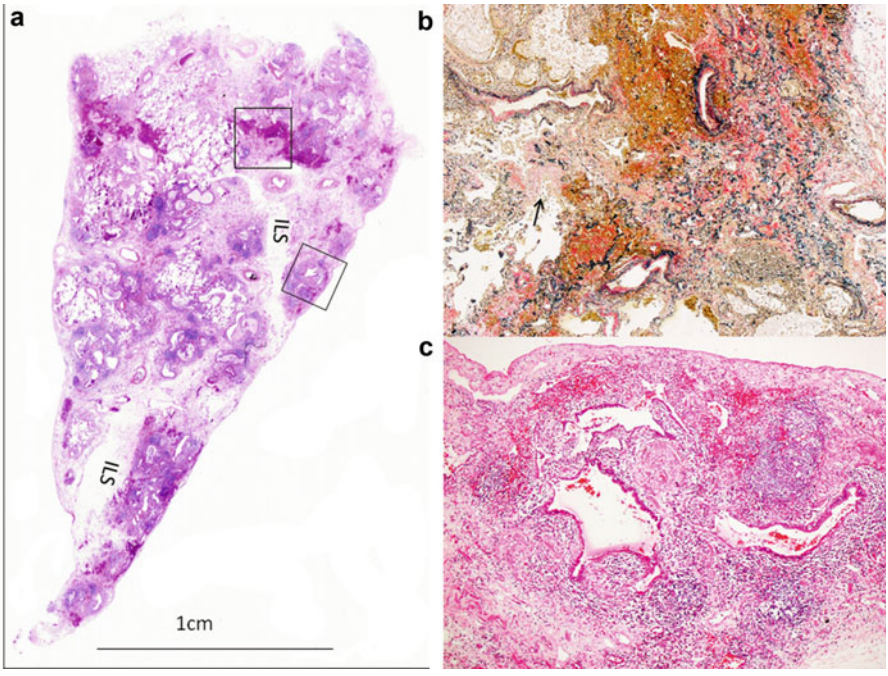


**Fig. 7.11** UIP-type CVD lung. A 75-year-old female with CREST syndrome showing honeycombing and ground-glass opacity by CT with increase of GGO or reticular shadow within 1 year. (**a**) SLB specimen. The costophrenic edge of the lower lobe shows rather diffuse involvement. ILS means dilated interlobular septum due to formalin. Bar: 1 cm. Panoramic view. HE. (**b**) Perilobular dense fibrosis and intraluminal young organization in the central area (*arrow*). *Upper box*, ×4. EvG. (**c**) Marked inflammatory cell infiltration and germinal center around bronchiole. *Lower box*, ×5. HE. Histology is typical of active UIP showing improvement by steroid semi-pulse therapy

#### 7.4.4.2 UIP-Type CHP

Churg et al. reported that most cases of UIP-type CHP showed more peribronchiolar fibrosis than one would expect in IPF and showed 88 % giant cells, granulomas, or Schaumann bodies by SLB [73]. Takemura et al. reported that bronchiolitis, centrilobular fibrosis, bridging fibrosis, organizing pneumonia, granulomas, giant cells, and lymphocytic alveolitis were significantly more common among patients with clinically confirmed CHP than among patients with IPF; however, the frequency of subpleural collapse did not differ between CHP and IPF cases, using SLB specimens [74]. In addition, Akashi et al. reported that centrilobular fibrosis and bridging fibrosis were significantly more conspicuous in the cases with clinically confirmed and treated CHP than in those with IPF by autopsy examination [75].

Some degree of centrilobular fibrosis and bridging fibrosis together with granulomas seems to be an indicator of UIP-type CHP. When the above features are found, pathologists can suggest the probability of CHP to the clinician. When the causative antigen is found, this is beneficial for patients. Figure 7.12 shows UIP seen in CHP that is identical to that of IPF.

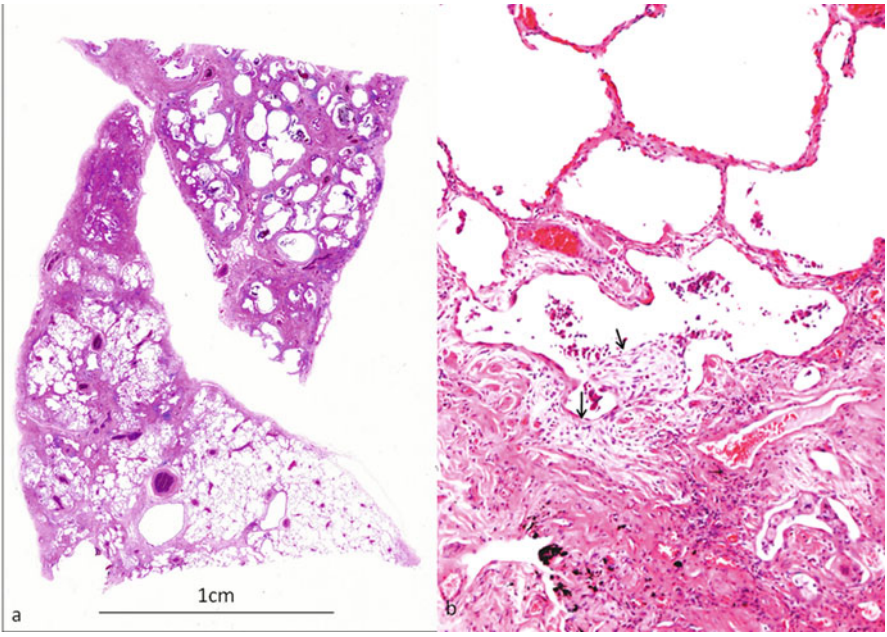


**Fig. 7.12** UIP-type CHP. A 65-year-old male with clinically confirmed bird fancier's lung underwent lobectomy for lung cancer. (**a**) The costophrenic edge showed dense fibrosis with honeycombing. Bar: 1 cm. Panoramic view. HE. (**b**) Fibroblastic focus on top of dense fibrosis (*arrow*). ×10. HE. There was no centrilobular fibrosis, bridging fibrosis, or epithelioid cell granuloma

#### 7.4.4.3 Occupational Exposure-Related UIP

Various types of mild to moderate occupational exposure cause a significant rate of UIP [76–78]. When a silicotic lesion is found, the case is pneumoconiosis-related UIP [76]. When asbestos bodies (fewer than 2/cm$^2$) are found, the case is asbestos-related UIP [79] (Fig. 7.13). Yamamoto reported that some asbestosis cases did not have pleural fibrosis or adhesion and were indistinguishable from IPF, apart from the asbestos bodies [80]. Therefore, a vigorous search for asbestos bodies by iron staining is required, even with only mild to moderate occupational asbestos exposure history. When typical bizarre giant cells with emperipolesis are found in the alveoli, the case might be UIP-type hard metal disease [81]. Metal analysis using electron probe microanalyzers is needed to confirm etiology.

In both CHP and occupational exposure, the level of exposure is up to moderate, and the duration of exposure is long.

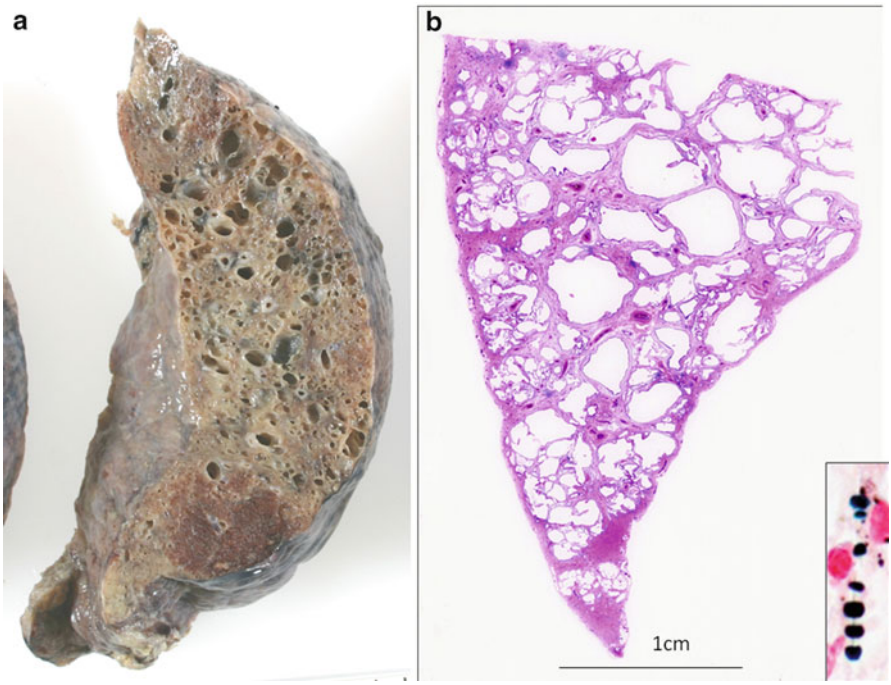


**Fig. 7.13** Asbestos-related UIP. A 74-year-old male with a history of construction work for 30 years and pleural plaque underwent lobectomy for lung cancer. (**a**) Basal area of the lower lobe showing diffuse fibrosis with traction ectasis and honeycombing. Macroscopic feature. (**b**) The costophrenic edge showed typical UIP with patchy involvement and honeycombing. *Bar*: 1 cm. Panoramic view. HE. *Box*. Typical asbestos body by iron staining. One asbestos body was found per glass slide, but this does not fulfill the criteria of asbestosis

#### 7.4.4.4 Not UIP/P

Not UIP/P [10] is an intriguing concept and does not exclude UIP or even IPF. The presence of hyaline membrane means acute exacerbation. The presence of OP can indicate subacute exacerbation. Marked interstitial inflammatory cells away from honeycombing seem to be subacute exacerbation or chronic exacerbation and also suggest UIP-type CVD or CHP. Granuloma can be seen in IPF, but upon combination with centrilobular fibrosis and bridging fibrosis, UIP-type CHP is strongly suggested. Predominant airway-centered changes suggest UIP-type CHP and occupation-related UIP. Even the presence of fewer than 2/cm$^2$ asbestos bodies means asbestos-related UIP. I think UIP is just a pathological term, not a disease (IPF).

### *7.4.5 Diagnostic Dilemma*

Unfortunately, the pathological diagnosis of the pattern and etiological suggestion is not a science, but rather an art. There are no definite boundaries, but instead significant overlaps between pathological patterns and etiological findings. Significant interobserver variation or difference has also been noted, even among specialists [82, 83]. When we follow the diagnostic criteria too strictly, many cases might be unclassifiable, while upon too loose application of these criteria, most cases would be classified.

## 7.5 Conclusion

The natural course of UIP is relentless progression, including acute, subacute, and even chronic exacerbation, and UIP histology complicates the two types of DAD, ALI/P NOS, organizing IP, and various NSIPs. This complication makes UIP diagnosis especially difficult. It is inevitable that the pathological classification of IIPs varies among pathologists.

**Acknowledgment** I wish to dedicate this article to my teacher, the late Dr. Charles B. Carrington. This article includes much of our works since I left Stanford University, USA, in 1983.

## References

1. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165:277–304.

2. Epler GR, Colby TV, McLoud C, Carrington CB, Gaensler E. Bronchiolitis Obliterans Organizing Pneumonia. N Engl J Med. 1985;312:152–8.
3. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis. Clinical relevance of pathologic classification. Am J Respir Crit Care Med. 1998;157:1301–15.
4. Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
5. Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, editors. Frontiers of pulmonary radiology. New York: Grunn & Stratton; 1968. p. 102–41.
6. Liebow AA. Definition and classification of interstitial pneumonias in human pathology. In: Basset F, Georges R, editors. Alveolar interstitium of the lung. Progress in respiratory research, vol. 8. Basel: Karger; 1975. p. 1–33.
7. Carrington CB, Gaensler EA, Coutu RE, Gupta RG, FitzGerald MX. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med. 1978;298:801–9.
8. Myers JL, Katzenstein AL. Epithelial necrosis and alveolar collapse in the pathogenesis of usual interstitial pneumonia. Chest. 1988;94:1309–11.
9. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. Am J Respir Crit Care Med. 2000;161:646–64.
10. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
11. Katzenstein AL, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Hum Pathol. 2008;39:1275–94.
12. Myers JL, Katzenstein AL. Beyond a consensus classification for idiopathic interstitial pneumonias: progress and controversies. Histopathology. 2009;54:90–103.
13. Kawabata Y, Fukushima K, Uchiyama T, Sugita H, Kimura B. A focal usual interstitial pneumonia lesion: an important risk factor in diffuse alveolar damage—acute exacerbation of a focal usual interstitial pneumonia patient. Nihon Kokyuki Gakkai Zasshi. 2001;39:316–21 (with English abstract).
14. Kawabata Y, Hoshi E, Murai M, Ikeya K, Takahashi N, Saitou Y, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to post operative course. Histopathology. 2008;53:707–14.
15. Kawabata Y, Aoyama K, Hoshi H, Ubukata M, Takayanagi N, Sugita Y. Pathological study of usual interstitial pneumonia in patients with lung cancer resection: with special reference to its relationship to subsequent acute exacerbation. Jpn J Lung Cancer (Haigann). 2005;45:115–21 (with English abstract).
16. Saito H, Minamiya Y, Nanjo H, Ito M, Ono T, Motoyama S, et al. Pathological finding of subclinical interstitial pneumonia as a predictor of postoperative acute respiratory distress syndrome after pulmonary resection. Eur J Cardiothorac Surg. 2011;39:190–4.
17. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364:897–906.
18. Nagai S, Nagao T, Kitaichi M, et al. Clinical courses of asymptomatic cases with idiopathic pulmonary fibrosis and a histology of usual interstitial pneumonia [abstract]. Eur Respir J. 1998;11:131s.
19. Fukushima K, Kawabata Y, Uchiyama T, Nakajima Y. Prognosis of possible development into diffuse interstitial pneumonia for 127 patients with localized usual interstitial pneumonia. Nihon Kokyuki Gakkai Zasshi. 1999;37:177–82 (with English abstract).
20. Yoshimura K, Nakatani T, Nakamori Y, Chonabayashi N, Tachibana A, Nakata K, et al. Acute exacerbation in idiopathic interstitial pneumonia. Nihon Kokyuki Gakkai Zasshi. 1984;22:1012–20 (with English abstract).

21. Kondo A, Saiki S. Acute exacerbation in idiopathic interstitial pneumonia (IIP). In: Harasawa M, Fukuchi Y, Morinari H, editors. Interstitial pneumonia of unknown etiology, Japan Intractable Diseases Research Foundation Publication no. 27. Tokyo: University of Tokyo Press; 1989. p. 33–42.
22. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27:143–50.
23. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest. 2005;128:1475–82.
24. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–7.
25. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63.
26. Watanabe A, Kawaharada N, Higami T. Postoperative acute exacerbation of IPF after lung resection for primary lung cancer. Pulm Med. 2011;2011:960316. doi:10.1155/2011/960316.
27. Chida M, Kobayashi S, Karube Y, Hayama M, Tamura M, Ishihama H, et al. Incidence of acute exacerbation of interstitial pneumonia in operated lung cancer: institutional report and review. Ann Thorac Cardiovasc Surg. 2012;18:314–17.
28. Utz JP, Ryu JH, Douglas WW, Hartman TE, Tazelaar HD, Myers JL, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. Eur Respir J. 2001;17:175–9.
29. Plönes T, Osei-Agyemang T, Elze M, Palade E, Wagnetz D, Loop T, et al. Morbidity and mortality in patients with usual interstitial pneumonia (UIP) pattern undergoing surgery for lung biopsy. Respir Med. 2013;107:629–32.
30. Chida M, Takahashi H, Yamanaka H, Suda H, Maeda S, Kondo T. Analysis of acute exacerbation from focal usual interstitial pneumonia following to lung cancer resection. Kyobu Geka. 2005;58:22–5 (with English abstract).
31. Goto T, Maeshima A, Akanabe K, Oyamada Y, Kato R. Acute exacerbation of idiopathic pulmonary fibrosis of microscopic usual interstitial pneumonia pattern after lung cancer surgery. Ann Thorac Cardiovasc Surg. 2011;17:573–6.
32. Araya J, Kawabata Y, Jinho P, Sugita Y, Ogata H, Uchiyama T, et al. Clinically occult subpleural fibrosis with acute interstitial pneumonia (AIP), precursor to idiopathic pulmonary fibrosis? Respirology. 2008;13:408–12.
33. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis: analysis of clinical and pathologic findings in three cases. Chest. 1993;103:1808–12.
34. Fukushima K, Kawabata Y, Uchiyama T, Sugita H. Clinicopathologic study of 50 autopsy cases of idiopathic pulmonary fibrosis and non-diffuse usual interstitial pneumonia. Nihon Kokyuki Gakkai Zassi. 2005;43:569–77 (with English abstract).
35. Kawabata Y, Hoshi E, Ubukata M, Takayanagi N, Sugita Y, Aoyama K, et al. Histological changes are background factors in acute exacerbation of usual interstitial pneumonia pattern_lesions following lung resection. Jpn J Lung Cancer (Haigann). 2006;46:329–36 (with English abstract).
36. Travis WD, Colby TV, Koss MN, Rosaso-de-Christenson ML, Muller NL, King TE. Diffuse alveolar damage and acute interstitial pneumonia. In: Non-neoplastic disorders of the lower respiratory tract. Washington, DC: AFIP; 2002. p. 89–105.
37. Kawabata Y. How to think interstitial pneumonias and proposal of pathological reclassification. Kokyu. 1992;11:734–43 (in Japanese).
38. Kawabata Y. What is acute exacerbation of chronic interstitial pneumonia? Mod Physician. 1994;14:117–20 (in Japanese).
39. Mandal RV, Mark EJ, Kradin RL. Organizing pneumonia and pulmonary lymphatic architecture in diffuse alveolar damage. Hum Pathol. 2008;39:1234–8.
40. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest. 2005;128:3310–15.

41. Churg A, Muller NL, Silva CI, Wright JL. Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. Am J Surg Pathol. 2007;31:277–84.
42. Katzenstain AL. Acute lung injury patterns: DAD and BOOP. In: Katzenstain AL, editor. Katzenstein and Askin's surgical pathology of non-neoplastic lung disease. 3rd ed. Philadelphia: WB Saunders; 1997. p. 14–47.
43. Katou T, Ohishi T, Ikuta N, Kawabata Y, Takagi K, Hayakawa T. A rapidly progressed case of interstitial pneumonia. Intern Med. 1995;34:388–92.
44. Kawabata Y, Umino T, Taniguchi H, Takagi K, Mieno T, Yamaguchi T, et al. Clinical features of subacute interstitial pneumonia-clinico-pathological study based on open lung biopsy findings. Nihon Kyoub Sikkann Gakkai Zassi. 1995;33:705–14 (with English abstract).
45. Katzenstein AL, Fiorelli RF. Non-specific interstitial pneumonia/fibrosis, histologic features and clinical significance. Am J Surg Pathol. 1994;18:136–47.
46. Kawabata Y, Kanazawa M, Ogura T, Fujita J, Tada S, Mieno T, et al. Prognosis of subacutely progressive interstitial pneumonia depends on the presence of focal usual interstitial pneumonia. Nihon Kokyuki Gakkai Zasshi. 2001;39:82–8 (with English abstract).
47. Flaherty KR, Travis WD, Colby TV, Toews GB, Kazerooni EA, Gross BH, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med. 2001;164:1722–7.
48. Monaghan H, Wells AU, Colby TV, du Bois RM, Hansell DM, Nicholson AG. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonias. Chest. 2004;125:522–6.
49. Kawabata Y. Classification of interstitial pneumonias following response to therapy. Chronic Kokyu. 1996;15:244–50.
50. Muller NL, Miller RR, Webb WR, Evans KG, Ostrow DN. Fibrosing alveolitis: CT pathologic correlation. Radiology. 1986;160:585–8.
51. Nishimura K, Kitaichi M, Izumi T, Nagai S, Kanaoka M, Itoh H. Usual interstitial pneumonia: histologic correlation with high-resolution CT. Radiology. 1992;182:337–42.
52. Johkoh T, Sumikawa H, Fukuoka J, Tanaka T, Fujimoto K, Takahashi M, et al. Do you really know precise radiologic-pathologic correlation of usual interstitial pneumonia? Eur J Radiol. 2014;83:20–6.
53. Crystal RG, Fulmer JD, Roberts WC, Moss ML, Line BR, Reynolds HY. Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. Ann Intern Med. 1976;85:769–88.
54. Kawabata Y. Classification of interstitial pneumonias following response to therapy, acute and subacute. Kokyu. 1996;15:132–7 (in Japanese).
55. Matsushima H, Takayanagi N, Sakamoto T, Kawata I, Motegi I, Ubukata M, et al. Pathologic findings both before and after steroid therapy in a case of desquamative interstitial pneumonia. Nihon Kokyuki Gakkai Zasshi. 2001;39:609–14 (with English abstract).
56. Cottin V, Hunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26:586–93.
57. Watanabe Y, Kawabata Y, Hoshi H, Kanauchi T, Kurashima K, Koyama K, et al. Multiple, thin-walled cysts are characteristic HRCT features of airspace enlargement with fibrosis. EJR 2015;54986–92.
58. Flaherty KR, Fell C, Aubry MC, Brown K, Colby T, Costabel U, et al. Smoking-related idiopathic interstitial pneumonia. Eur Respir J. 2014;44:594–602.
59. Travis WD, Hunninghake G, King Jr TE, Lynch DA, Colby TV, Galvin JR, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med. 2008;177:1338–47.
60. Travis WD, Matsui K, Moss J, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual

interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol. 2000;24:19–33.
61. Kawabata Y, Takemura T, Hebisawa A, Ogura T, Yamaguchi T, Kuriyama T, et al. Increased eosinophils in bronchoalveolar lavage fluid and lobule-based histologic lesions are characteristic features of desquamative interstitial pneumonia. Histopathology. 2008;52:194–202.
62. Craig PJ, Wells AU, Doffman S, Rassl D, Colby TV, Hansell DM, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology. 2004;45:275–82.
63. Kawabata Y, Takemura T, Hebisawa A, Sugita Y, Takashi Ogura T, et al. Desquamative interstitial pneumonia progresses to lung fibrosis, radiologically. Respirology. 2012;17:1214–21.
64. Tazelaar HD, Wright JL, Churg A. Desquamative interstitial pneumonia. Histopathology. 2011;58:509–16.
65. Amitani R, Niimi A, Kuze F. Idiopathic pulmonary upper lobe fibrosis. Kokyu. 1992;11:693–9.
66. Shiota S, Shimizu K, Suzuki M, Nakatani Y, Sakamoto K, Iwase A, et al. Seven cases of marked pulmonary fibrosis in the upper lobe. Nihon Kokyuki Gakkai Zasshi. 1999;37:87–96.
67. Frankel SK, Cool CD, Lynch DA, Brown KK. Idiopathic pleuroparenchymal fibroelastosis. Description of a novel clinicopathologic Entity. Chest. 2004;126:2007–13.
68. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. Mod Pathol. 2006;19:1474–9.
69. Katzenstein AL, Mukhopadhyay S, Zanardi C, Dexter E. Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens. Hum Pathol. 2010;41:316–25.
70. Reddy TL, Mayo J, Churg A. Respiratory bronchiolitis with fibrosis: high resolution CT findings and correlation with pathology. Ann Am Thorac Soc. 2013;10:590–601.
71. Yamada T, Nakanishi Y, Homma T, Uehara K, Mizutani T, Hoshi E, et al. Airspace enlargement with fibrosis shows characteristic histology and immunohistology different from usual interstitial pneumonia, nonspecific interstitial pneumonia, and centrilobular emphysema. Pathol Int. 2013;63:206–13.
72. Song JW, Do KH, Kim MY, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. Chest. 2009;136:23–30.
73. Churg A, Sin DD, Everett D, Brown K, Cool C. Pathologic patterns and survival in chronic hypersensitivity pneumonitis. Am J Surg Pathol. 2009;33:1765–70.
74. Takemura T, Akashi T, Kamiya H, Ikushima S, Ando T, Oritsu M, et al. Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis / usual interstitial pneumonia. Histopathology. 2012;61:1026–35.
75. Akashi T, Takemura T, Ando N, Eishi Y, Kitagawa Y, Takizawa T, et al. Histopathologic analysis of sixteen autopsy cases of chronic hypersensitivity pneumonitis and comparison with idiopathic pulmonary fibrosis / usual interstitial pneumonia. Am J Clin Pathol. 2009;131:405–15.
76. Honma K, Chiyotani K. Diffuse interstitial fibrosis in nonasbestos pneumoconiosis – a pathological study. Respiration. 1993;60:120–6.
77. Brichet A, Tonnel AB, Brambilla E, Devouassoux G, Rémy-Jardin M, Copin MC, et al. Chronic interstitial pneumonia with honeycombing in coal workers. Sarcoidosis Vasc Diffuse Lung Dis. 2002;19:211–19.
78. Arakawa H, Johkoh T, Honma K, Saito Y, Fukushima Y, Shida H, et al. Chronic interstitial pneumonia in silicosis and mix-dust pneumoconiosis: its prevalence and comparison of CT findings with idiopathic pulmonary fibrosis. Chest. 2007;131:1870–6.
79. Kawabata Y, Shimizu Y, Hoshi A, Murai K, Kanauchi T, Kurashima K, Sugita Y. Asbestos exposure increases the incidence of usual interstitial pneumonia. Histopathology (Accepted).

80. Yamamoto S. Histopathological features of pulmonary asbestosis with particular emphasis on the comparison with those of usual interstitial pneumonia. Osaka City Med J. 1997;43:225–42.
81. Tanaka J, Moriyama H, Terada M, Takada T, Suzuki E, Narita I, et al. An observational study of giant cell interstitial pneumonia and lung fibrosis in hard metal lung disease. BMJ Open. 2014;4(3), e004407.
82. Nicholson AG, Addis BJ, Bharucha H, Clelland CA, Corrin B, Gibbs AR, et al. Inter-observer variation between pathologists in diffuse parenchymal lung disease. Thorax. 2004;59:500–5.
83. Flaherty KR, Andrei AC, King Jr TE, Raghu G, Colby TV, Wells A, et al. Idiopathic interstitial pneumonia: do community and academic physicians agree on diagnosis? Am J Respir Crit Care Med. 2007;175:1054–60.

# Chapter 8
# Differential Diagnosis of IPF

## What Should We Particularly Keep in Mind in the Differential Diagnosis?

**Hidehiro Watanabe**

**Abstract** The idiopathic pulmonary fibrosis (IPF) guidelines were announced in the 2011 ATS/ERS/JRA/ALAT statement, and 6 items were listed as Summary Conclusions. Diagnosis is described in item 2, and both exhibiting a UIP pattern on high-resolution computed tomography (HRCT) scans, and that finding being consistent with the SLB findings are said to be necessary. The factors that are suspected of being associated with IPF and are important to the differential diagnosis have also been sorted out, and we consider them to mainly consist of three categories of factors and miscellaneous other factors. The first category is chronic hypersensitivity pneumonitis (CHP)/Feather duvet lung (FDL) caused by environmental factors. The second category is autoimmune-featured interstitial lung disease (AIF-ILD) in which lung lesions are observed first. The third category consists of PF that develops after a certain period of time has passed in patients treated with molecularly targeted drugs, anti-arrhythmia drugs, etc. The rest consist of PF caused by persistent infection. Because the time that has passed (sometimes as much as several years) after the corresponding episode is long, and the HRCT findings and SLB findings resemble the findings in a usual interstitial pneumonia (UIP), differentiation is difficult even when a diagnosis of PF has been made. A wide variety of possibilities are suspected when PF is encountered, and it is necessary to confirm the detail of past medical history and base on it to perform special tests (e.g., lymphocyte stimulation tests, antibody tests, virus DNA tests) in addition.

**Keywords** Chronic hypersensitivity pneumonitis (CHP) • Feather duvet lung (FDL) • Autoimmune-featured interstitial lung disease (AIF-ILD) • Molecularly targeted drugs • Anti-arrhythmia drugs • Persistent infection

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## 8.1 Introduction

The American Thoracic Society/European Respiratory Society (ATS/ERS) proposed the 2002 International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias [1]. When a surgical lung biopsy (SLB) has not been performed, four major criteria and three minor criteria are needed to be fulfilled to make a diagnosis of idiopathic pulmonary fibrosis (IPF). IPF has the highest incidence among the idiopathic interstitial pneumonias (IIPs), and it consists of nonbacterial chronic inflammation primarily of the alveolar interstitium and not intra-alveolar inflammation. The fibrosing of the lungs progresses until the lungs become irreversibly honeycombed, and it destroys the lungs. IPF has a poor prognosis. The average median survival time after the diagnosis of IPF is about 3–5 years, during which patients' quality of life deteriorates as a result of their diminishing pulmonary function. Since the ATS/ERS Classification was proposed in 2002, drug-induced lung injury, environmental factors, collagen-disease associations, etc. have been important in the differential diagnosis. However, with the passage of time, problems have come to light in regard to these diagnostic criteria for IPF. Major criterion 2, i.e., respiratory function; minor criterion 2, i.e., slow progression; and minor criterion 3, i.e., disease duration, are important in terms of prognostic factors for IPF, but they do not seem to be IPF specific. There is even a report that in some cases of IPF in which SLB reveals a usual interstitial pneumonia (UIP) pattern the pathology progresses despite pulmonary function being normal [2]. Moreover, there is a possibility that factors, such as smoking, etc., influence the slow progression of IPF, and acute IPF can be ruled out by disease duration in minor criterion 3. It was against this background that the IPF guidelines were announced in the 2011 ATS/ERS/JRA/ALAT statement, and 6 items were listed as its Summary Conclusions [3, 4] (Table 8.1). Diagnosis is described in item 2, and both exhibiting a UIP pattern on high-resolution computed tomography (HRCT) scans and that finding being consistent with the SLB findings are said to be necessary. Then, "the major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated."

The factors that are suspected of being associated with IPF and are important to the differential diagnosis have also been sorted out [5], and we consider them to mainly consist of three categories of factors and miscellaneous other factors. The first category of the factors consists of environmental factors, including pneumoconiosis and asbestos lung, and chronic hypersensitivity pneumonitis, including bird breeder's disease and farmer's lung. The second category consists of collagen-disease-related pulmonary lesions, and the third category consists of drug-induced pulmonary lesions caused by the latest anti-arrhythmia drugs, anticancer drugs, and molecularly targeted drugs. The miscellaneous other environmental factors are microbial pathogens (e.g., special pathogens including viruses that cause infection-induced pulmonary lesions). Naturally, it is thought that the factor of a smoking also may play a certain role in the manifestation of interstitial lung diseases (ILD), although the mechanisms are not still solved. The study of last decade has reported that a smoking participates in the manifestation of ILD other than chronic obstructive

**Table 8.1** ATS/ERS/JRA/ALTA statement

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|---|---|---|
| 1. | IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP | |
| 2. | The diagnosis of IPF requires | |
| | (a) | Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) |
| | (b) | The presence of a UIP pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy |
| | (c) | Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy |
| | | *The major and minor criteria proposed in the 2000 ATS/ERS Consensus Statement have been eliminated* |
| 3. | The accuracy of the diagnosis of IPF increases with multidisciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD | |
| 4. | IPF is a fatal lung disease; the natural history is variable and unpredictable | |
| | (a) | Most patients with IPF demonstrate a gradual worsening of lung function over years; a minority of patients remain stable or decline rapidly |
| | (b) | Some patients may experience episodes of acute respiratory worsening despite previous stability |
| 5. | Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death | |
| 6. | Patients with IPF may have subclinical or overt comorbid conditions including pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnea, obesity, and emphysema. The impact of these conditions on the outcome of patients with IPF is unclear | |

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pulmonary disease [4, 6]. However, according to study of large-scale for lung cancer using high-resolution computed tomography (HRCT), interstitial lung abnormalities are observed in the several percent of asymptomatic smokers [7–9]. At present, it needs to be evaluated in future studies through discovering the smoking-related ILD by screening tests such as a lung cancer.

In order to make all of these differentiations, it is important, first and foremost, to listen to the patient's past medical history with these differentiations in mind. In this chapter I will summarize the key points to bear in mind regarding these factors associated with IPF when making the differential diagnosis.

## 8.2 Chronic Hypersensitivity Pneumonitis (CHP)/Feather Duvet Lung (FDL)

Hypersensitivity pneumonitis used to be classified into acute, subacute, and chronic, but because of difficulty in defining "subacute" [10], it is now classified into acute and chronic. Acute hypersensitivity pneumonitis has a characteristic history, clinical picture, and course, and it appears to be relatively easy to make

the diagnosis. However, because the clinical picture and course of CHP are similar to the clinical picture and course of IPF and fibrotic nonspecific interstitial pneumonia (fNSIP), it is difficult to diagnose. In a prospective case-cohort study by Morell F. et al. [11], 20 (43 %) of 46 patients initially diagnosed as IPF were later diagnosed as CHP. None of the patients had a medical history of that included an occupational history of farming, mushroom growing, painting, etc., and there were no associations with residential humidity or humidifiers. The patients had just been using ordinary feather bedding. They appeared to have had feather duvet lung (FDL), and it seems very important to differentiate FDL from IPF.

Associations between feathers and respiratory tract lesions began to be reported around 1960 when there was a report of dyspnea developing in workers engaged in duck and goose feather processing [12], and in 1992 Haitjema T. et al. [13] reported the case of a 31-year-old female with CHP caused by a feather duvet. The event had developed in a nonsmoker during the 4th year of using a feather duvet. A chest x-ray showed reticulonodular shadows in both lower lung fields. After feather duvets came into widespread use worldwide, the pathological features of FDL/CHP became clear. In 2003, Inase et al. [14] reported a case of FDL/CHP in a 73-year-old woman. The patient had started using a feather duvet 8 years before, and she had a chronic course of illness that had developed 3 years before. The HRCT findings consisted of scattered consolidation, micronodules, and peribronchial ground-glass opacities. In 2008, Morell F. et al. [15] reported analyzing 86 cases of bird fancier's lung and that 17 % were the chronic type and 3 cases were FDL/CHP. In 2010, Koschel D. et al. [16] analyzed 13 cases of FDL. In one case the patient had used only a feather pillow, and in the other 12 cases, the patients had either used a feather duvet or both a feather pillow and a feather duvet. The results of their analysis showed: "in all patients specific IgG antibodies to goose and/or duck feathers were detected. Pulmonary function tests revealed a moderate to severe reduced diffusion capacity and a mild restrictive pattern." In 6 of the 11 cases in which HRCT was performed, the images revealed a PF pattern, and in one of the 9 cases in which an SLB was performed, it showed UIP. Based on these reports, cases that have been diagnosed as IPF have included a certain number of FDL/CHP cases. FDL/CHP pursues a chronic course and is slowly progressive and difficult to differentiate from IPF, but differential aspects have been pointed out based on both the HRCT and SLB findings.

Akashi T. et al. [17] assessed 16 autopsy cases of CHP and reported that the predominance of honeycombing in the lower lung fields resembled the findings in IPF/UIP, but that honeycombing that predominated in the upper lung fields and asymmetry of the honeycomb lesions were more common in CHP. They also reported that when there is centrilobular fibrosis in UIP, it is important to conduct a thorough investigation of the possibility of antigen exposure. Takemura T. et al. [18] compared 22 cases of CHP accompanied by UIP and 13 cases of IPF/UIP in which SLB had been performed. They reported that "bronchiolitis, centrilobular fibrosis, bridging fibrosis, organizing pneumonia, granulomas, giant cells and lymphocytic alveolitis were significantly more frequent among patients with CHP than among patients with IPF (all $P < 0.01$)." Silva C. I. et al. [19] described the HRCT image characteristics of CHP, thus: "The CT features that best

differentiated CHP were lobular areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower-zone predominance of abnormalities."

The values of the interstitial pneumonia markers KL-6 and SPD are both high in FDL and reflect disease activity, but they are not FDL specific. However, Ohnishi H. et al. [20] reported that the KL-6 levels were high in winter in bird-related HP (close to FDL) and that seasonal fluctuations in KL-6 values are a valid basis for making the diagnosis. The presence of specific IgG antibodies to goose feathers is useful for making the diagnosis of FDL [21], but evaluation is difficult when it is the chronic type. Antigen-induced lymphocyte proliferation in peripheral blood or bronchoalveolar lavage cells is positive in FDL. Its specificity is high, and it is said to be useful in making the diagnosis [22].

Cordeiro C. R. et al. [23] reported a case of CHF that was impossible to differentiate from IPF because the patient had clinical manifestations, including shortness of breath, which are common to IPF, and because testing was negative for parakeet-specific antibody, and because the SLB pathology findings were those of UIP. There were no significant findings in the pathological diagnosis or specific antibodies in their case. Nevertheless, the patient "had regular exposure to a parakeet and poultry," and "chest imaging showed subpleural cystic lesions and traction bronchiectasis with a right side and upper level predominance." The pathological findings in SLB specimens and the results of specific antibody testing do not always provide answers, and careful assessment of the medical history and findings is all that can be done.

## 8.3 Collagen-Disease-Antecedent PF and Collagen-Related Diseases

Collagen-related diseases and PF that precedes collagen disease present problems in making the differential diagnosis. Cases of interstitial lung disease (ILD) in which there is suspicion of a collagen disease have been debated by the American College of Rheumatology (ACR), and thus far three concepts have been proposed. Diseases that do not fulfill the diagnostic criteria established for collagen diseases have been classified as unclassified connective tissue disease (UCTD) [24–26], cases with meager systemic findings other than lung lesions have been classified as lung-dominant connective tissue disease (LD-CTD) [27, 28], and cases with some sort of autoimmune abnormality that do not fulfill the diagnostic criteria for collagen disease have been classified as autoimmune-featured interstitial lung disease (AIF-ILD) [29]. Lung diseases associated with them consist of many cases of NSIP in UCTD, ILD as a whole in LD-CTD, and many cases of UIP in AIF-ILD. Thus, there seems to be a high degree of need to differentiate AIF-ILD from IPF. In 2011, Vij et al. [29] conducted a comparative study in which, based on replies to a questionnaire and the results of serologic tests, they divided 200 ILD cases into three groups: an AIF-ILD group (63 cases, 32 %), an ordinary IPF group (58 cases, 29 %), and a so-called collagen-disease-lung lesion (connective tissue

disease – interstitial lung disease [CTD-ILD]) group that had already been diagnosed with collagen disease (37 cases, 19 %). HRCT revealed a classic UIP pattern in 62 % of the AIF-ILD cases, and in 81 % of the cases in which an SLB had been performed, it showed a UIP pattern. Moreover, the outcome of the AIF-ILD cases was the same as the outcome of the IPF cases. Based on the findings they reported to have obtained in these cases by HRCT and SLB, which are important tools in making the diagnosis, it is impossible to reliably distinguish between AIF-ILD and IPF. Points that have been cited to differentiate AIF-ILD from IPF have been as follows: female gender; in terms of clinical manifestations, dry eye, gastroesophageal reflux disease (GERD), foot swelling, joint pain, and the Raynaud phenomenon; and in terms of clinical laboratory test findings, the presence of antinuclear antibody (ANA) and rheumatoid factor (RF).

In research conducted on IPF, Kono et al. [30] reported a study in which they followed up 111 IPF cases for a mean period of 6.4 years. The result was the discovery that a definite collagen disease had developed in ten (9 %) of the cases, and the collagen diseases consisted of rheumatoid arthritis (RA) in four cases, microscopic polyangiitis (MPA) in four cases, and systemic sclerosis (SSc) in one case. There were two factors at the time the diagnosis of IPF was made that were important predictors of the future onset of a collagen disease: female gender and biopsy specimen histology showing the presence of lymph follicles with germinal centers. In addition, the outcome of the IPF accompanied by collagen disease was significantly better than that of the IPF not accompanied by collagen disease. Thus, whether or not a collagen disease will develop in IPF in the future appeared to be a factor related to the prognosis. In research conducted on RA, Lee et al. [31] assessed 18 cases of ILD associated with RA. In 3 of the 18 cases, the pulmonary lesions developed first. In two of the three cases, they were UIP lesions, and in one case they were NSIP lesions. However, the pulmonary lesions had developed 1.6–7 years in advance, earlier than the 1.1–4.3 years in the report by Kono et al. [30]. Ultimately, they may fall into the AIF-ILD category before a definitive diagnosis is made.

## 8.4 Drug-Induced PF

A drug-induced type of PF caused by anticancer drugs (e.g., bleomycin) is known. Since an underlying disease is present, when treatment with one of the drugs that fall into this category is considered necessary, it is possible to make the differential diagnosis of ILD that develops relatively soon after starting the drug. However, development of a wide variety of drugs is proceeding, and the drug situation has been changing. The problem is PF that develops after treating patients with molecularly targeted drugs, anti-arrhythmia drugs, etc., and a certain period of time has passed.

### 8.4.1 *Infliximab (Antitumor Necrosis Factor-Alpha Monoclonal Antibody)*

Hagiwara et al. [32] reported observing cases in which ILD/IPF developed from 3 weeks to 51 months after starting treatment of rheumatism with infliximab. All seven patients in whom infliximab was added during maintenance-dose methotrexate therapy developed ILD, not IPF according to the strict definition. The incidence of ILD appears to start to increase with the third course of infliximab therapy [33–35].

### 8.4.2 *Gefitinib (Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor)*

Ando et al. [36] reported observing the development of ILD in 70 of 1976 patients being treated for non-small cell lung cancer with gefitinib. Although not IPF in the strict sense in this report either, ILD developed an average of 31 days (18–50 days) after the start of treatment with gefitinib, and risk factors were male gender, history of smoking, and presence of ILD. The ILD sideration ratio in a gefitinib treatment had a difference between regenerates, and the ratio in Japanese was significantly higher than that in American [37].

### 8.4.3 *Amiodarone (Antiarrhythmic Agent)*

In research on patients being treated with amiodarone for arrhythmias, Ernawati D. K. et al. [38] assessed 237 cases of amiodarone lung injury and reported that at the age of 60 years and over, a duration of treatment of 6−12 months and cumulative doses of 101–150 g were high risk factors. Kang I. S. et al. [39] observed 7 cases of lung injury among 34 amiodarone therapy cases, and in 6 of them, the lung injury was PF. Furthermore, the cumulative dose in the cases that developed lung injury was 449.6 g ± 191.4 g, and the duration of treatment was 2206.7 days ± 1207.4 days. Since their results showed a higher cumulative dose and longer duration of treatment than in the report by Ernawati D. K. et al. [38], they considered regular HRCT follow-up examinations to be necessary to detect the onset of PF.

All of the above were drug therapies for an underlying disease, but, with the exception of gefitinib, if the onset occurred several years after treatment, then the differential diagnosis is not easy. Follow-up in the form of regular HRCT examinations and observation of KL-6 and SPD values before treatment as a baseline are considered effective means of detecting the onset of drug-induced PF [40, 41].

## 8.5 Infection-Induced PF

Herpesvirus involvement, in particular, has been pointed out among cases of PF caused by persistent infection by viruses and other pathogens [42]. Hepatitis C virus [43], adenovirus [44], human cytomegalovirus (HCMV) [45], and Epstein-Barr virus (EBV) [46] have also been associated with the development of PF. These viruses cause persistent latent infections and do not produce any clear clinical manifestations of an infection. Dworniczak S. et al. [45] compared newly diagnosed PF patients and 16 healthy volunteers and tested their alveolar lavage fluid cells for the presence of HCMV DNA. Both groups tested positive for HCMV DNA, but the number of DNA copies in the PF group was significantly higher. Endoplasmic reticulum (ER) stress has been hypothesized to increase as a result of persistent infection and induce alveolar epithelial-cell apoptosis [47]. Lawson et al. [48] discovered that the markers of endoplasmic reticulum (ER) stress were elevated in alveolar epithelial cells lining areas of the fibrosing portion of IPF using the immunostain. They also discovered the antigen proteins of three herpesviruses (EBV, CMV, or HHV-8) to the same area seen with the same distribution for the ER stress markers. These findings were the interesting reports which suggest the hypothesis implicating alveolar epithelial-cell apoptosis in the pathogenesis of PF. There was also a report of PF being observed in an SLB 1 year after *Mycoplasma pneumoniae* pneumonia [49], and there is a possibility of PF developing as a result of a pathogen that causes a latent infection. However, there were some reports which were not able to discover the antigen of herpesviruses from the tissue of PF [50, 51]. It is still unknown that the infection of viruses and others may play the role to IPF. The relationship between latent infections (such as viruses and others) and IPF will be probably confirmed in the near future.

## 8.6 Conclusion

I think that there are three major categories of conditions plus infections that require differentiation from IPF (Table 8.2). The first category is CHP/FDL caused by environmental factors. The second category is AIF-IDL in which lung lesions are observed first. The third category consists of PF that develops after a certain period of time has passed in patients treated with molecularly targeted drugs, anti-arrhythmia drugs, etc. The rest consist of PF caused by persistent infection. Because the time that has passed (sometimes as much as several years) after the corresponding episode is long, and the HRCT findings and SLB findings resemble the findings in UIP, differentiation is difficult even when a diagnosis of PF has been made. Special tests also are impossible without postulating the differential diagnosis. A wide variety of possibilities are suspected when PF is encountered, and it is necessary to confirm the detail of past medical history and base on it to perform special tests (e.g., lymphocyte stimulation tests, antibody tests, virus DNA tests) in addition.

**Table 8.2** Differential diagnosis of IPF

| Differential diagnosis | Long period to diagnosis | Characteristic factor | Laboratory findings | References |
|---|---|---|---|---|
| CHP/FDL | 3–8 years | Lobular areas with decreased attenuation and vascularity, centrilobular nodules, and absence of lower-zone predominance of abnormalities | Regular HRCT examinations | [11–22] |
| | | | Specific IgG antibodies to goose feathers | |
| | | | Antigen-induced lymphocyte proliferation test | |
| AIF-ILD | 1–7 years | Female gender, dry eye, gastroesophageal reflux disease (GERD), foot swelling, joint pain, Raynaud phenomenon, antinuclear antibody (ANA), rheumatoid factor (RF) | Regular HRCT examinations, autoimmune antibody tests | [29–31] |
| | | | UIP (62 % by HRCT; 81 % by SLB) | |
| Drug-induced PF | Molecularly targeted drugs (Infliximab) 3 weeks–51 months | Infliximab | Regular HRCT examinations, KL-6 and SPD values before treatment as a baseline | [32–37], [40, 41] |
| | (Gefitinib)18–50 days | After 3 courses, ILD (Gefitinib) | | |
| | | Male gender, smoking, presence of ILD | | |
| | Antiarrhythmic agent (Amiodarone) 6–12 months vs 2206.7 ± 1207.4 days | Over 60 years old, cumulative doses of 101–150 g vs 449.6 ± 191.4 g | | [38, 39] |
| Infection-induced PF | Persistent latent infections, Herpesvirus, HCV, Adenovirus, HCMV, EBV, *Mycoplasma pneumoniae* | Chronic low level of lung inflammation | Regular HRCT examinations, Virus DNA copies & virus DNA tests | [42–51] |

*CHP/FDL* hypersensitivity pneumonitis/feather duvet lung, *AIF-ILD* autoimmune-featured interstitial lung disease,*HCV* hepatitis C virus, *HCMV* human cytomegalovirus, *EBV* Epstein-Barr virus. [] is related reference

## References


1. American Thoracic Society; European Respiratory Society: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277–304.
2. Kondoh Y, Taniguchi H, Ogura T, Johkoh T, Fujimoto K, Sumikawa H, Kataoka K, Baba T, Colby TV, Kitaichi M. Disease progression in idiopathic pulmonary fibrosis without pulmonary function impairment. Respirology. 2013;18(5):820–6.
3. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King Jr TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. ATS/ERS/JRS/ALAT committee on idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.
4. Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D. ATS/ERS committee on idiopathic interstitial pneumonias: an official American thoracic society/European respiratory society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733–48.
5. Wuyts WA, Cavazza A, Rossi G, Bonella F, Sverzellati N, Spagnolo P. Differential diagnosis of usual interstitial pneumonia: when is it truly idiopathic? Eur Respir Rev. 2014; 23(133):308–19.
6. Margaritopoulos GA, Harari S, Caminati A, Antoniou KM. Smoking-related idiopathic interstitial pneumonia: A review. Respirology. 2015;2. doi:10.1111/resp.12576.
7. Sverzellati N, Guerci L, Giorgia R, Calabrò E, La Vecchia C, Marchianò A, Pesci A, Zompatori M, Pastorino U. Interstitial lung diseases in a lung cancer screening trial. Eur Respir J. 2011;38(2):392–400.
8. Washko GR, Hunninghake GM, Fernandez IE, Nishino M, Okajima Y, Yamashiro T, Ross JC, Estépar RS, Lynch DA, Brehm JM, Andriole KP, Diaz AA, Khorasani R, D'Aco K, Sciurba FC, Silverman EK, Hatabu H, Rosas IO, COPDGene Investigators. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011; 364(10):897–906.
9. Jin GY, Lynch D, Chawla A, Garg K, Tammemagi MC, Sahin H, Misumi S, Kwon KS. Interstitial lung abnormalities in a CT lung cancer screening population: prevalence and progression rate. Radiology. 2013;268(2):563–71.
10. Lacasse Y, Selman M, Costabel U, Dalphin JC, Morell F, Erkinjuntti-Pekkanen R, Mueller NL, Colby TV, Schuyler M, Jomphe V, Cormier Y, HP Study Group. Classification of hypersensitivity pneumonitis: a hypothesis. Int Arch Allergy Immunol. 2009;149(2):161–6.
11. Morell F, Villar A, Montero MÁ, Muñoz X, Colby TV, Pipvath S, Cruz MJ, Raghu G. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study. Lancet Respir Med. 2013;1(9):685–94.
12. Plessner M. A disease of feather sorters: duck fever [Article in French]. Arch Mal Prof. 1960; 21:67–9.
13. Haitjema T, van Velzen-Blad H, van den Bosch JM. Extrinsic allergic alveolitis caused by goose feathers in a duvet. Thorax. 1992;47(11):990–1.

14. Inase N, Ohtani Y, Endo J, Miyake S, Yoshizawa Y. Feather duvet lung. Med Sci Monit. 2003; 9(5):CS37–40.
15. Morell F, Roger A, Reyes L, Cruz MJ, Murio C, Muñoz X. Bird fancier's lung: a series of 86 patients. Med (Baltimore). 2008;87(2):110–30.
16. Koschel D, Wittstruck H, Renck T, Müller-Wening D, Höffken G. Presenting features of feather duvet lung. Int Arch Allergy Immunol. 2010;152(3):264–70.
17. Akashi T, Takemura T, Ando N, Eishi Y, Kitagawa M, Takizawa T, Koike M, Ohtani Y, Miyazaki Y, Inase N, Yoshizawa Y. Histopathologic analysis of sixteen autopsy cases of chronic hypersensitivity pneumonitis and comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia. Am J Clin Pathol. 2009;131(3):405–15.
18. Takemura T, Akashi T, Kamiya H, Ikushima S, Ando T, Oritsu M, Sawahata M, Ogura T. Pathological differentiation of chronic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis/usual interstitial pneumonia. Histopathology. 2012;61(6):1026–35.
19. Silva CI, Müller NL, Lynch DA, Curran-Everett D, Brown KK, Lee KS, Chung MP, Churg A. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology. 2008;246(1):288–97.
20. Ohnishi H, Miyamoto S, Kawase S, Kubota T, Yokoyama A. Seasonal variation of serum KL-6 concentrations is greater in patients with hypersensitivity pneumonitis. BMC Pulm Med. 2014;7(14):129.
21. Koschel D, Lützkendorf L, Wiedemann B, Höffken G. Antigen-specific IgG antibodies in feather duvet lung. Eur J Clin Invest. 2010;40(9):797–802.
22. Inase N, Ohtani Y, Sumi Y, Umino T, Usui Y, Miyake S, Yoshizawa Y. A clinical study of hypersensitivity pneumonitis presumably caused by feather duvets. Ann Allergy Asthma Immunol. 2006;96(1):98–104.
23. Cordeiro CR, Alfaro TM, Freitas S. Clinical case: differential diagnosis of idiopathic pulmonary fibrosis. BMC Res Notes. 2013;6(Suppl 1):S1.
24. Mosca M, Tavoni A, Neri R, Bencivelli W, Bombardieri S. Undifferentiated connective tissue diseases: the clinical and serological profiles of 91 patients followed for at least 1 year. Lupus. 1998;7(2):95–100.
25. Kinder BW, Collard HR, Koth L, Daikh DI, Wolters PJ, Elicker B, Jones KD, King Jr TE. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med. 2007;176(7):691–7.
26. Corte TJ, Copley SJ, Desai SR, Zappala CJ, Hansell DM, Nicholson AG, Colby TV, Renzoni E, Maher TM, Wells AU. Significance of connective tissue disease features in idiopathic interstitial pneumonia. Eur Respir J. 2012;39(3):661–8.
27. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. Chest. 2010;138(2):251–6.
28. Alhamad EH, Al-Kassimi FA, Alboukai AA, Raddaoui E, Al-Hajjaj MS, Hajjar W, Shaik SA. Comparison of three groups of patients with usual interstitial pneumonia. Respir Med. 2012;106(11):1575–85.
29. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. Chest. 2011;140(5):1292–9.
30. Kono M, Nakamura Y, Enomoto N, Hashimoto D, Fujisawa T, Inui N, Maekawa M, Suda T, Colby TV, Chida K. Usual interstitial pneumonia preceding collagen vascular disease: a retrospective case control study of patients initially diagnosed with idiopathic pulmonary fibrosis. PLoS One. 2014;9(4), e94775.
31. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, Kitaichi M. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005; 127(6):2019–27.
32. Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. J Rheumatol. 2007;34(5):1151–4.

33. Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. Respir Med. 2009;103(5):661–9.
34. Chatterjee S. Severe interstitial pneumonitis associated with infliximab therapy. Scand J Rheumatol. 2004;33(4):276–7.
35. Kramer N, Chuzhin Y, Kaufman LD, Ritter JM, Rosenstein ED. Methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2002; 47(6):670–1.
36. Ando M, Okamoto I, Yamamoto N, Takeda K, Tamura K, Seto T, Ariyoshi Y, Fukuoka M. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol. 2006;24(16):2549–56.
37. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets. Oncologist. 2003;8(4):303–6.
38. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. Br J Clin Pharmacol. 2008;66(1):82–7.
39. Kang IS, Kim KJ, Kim Y, Park SH. The diagnostic utility of chest computed tomography scoring for the assessment of amiodarone-induced pulmonary toxicity. Korean J Intern Med. 2014;29(6):746–53.
40. Nakajima M, Kawahara Y, Yoshida K, Miyashita N, Niki Y, Matsushima T. Serum KL-6 as a possible marker for amiodarone-induced pulmonary toxicity. Intern Med. 2000;39(12): 1097–100.
41. Umetani K, Abe M, Kawabata K, Iida T, Kohno I, Sawanobori T, Kugiyama K. SP-D as a marker of amiodarone-induced pulmonary toxicity. Intern Med. 2002;41(9):709–12.
42. Naik PK, Moore BB. Viral infection and aging as cofactors for the development of pulmonary fibrosis. Expert Rev Respir Med. 2010;4(6):759–71.
43. Ueda T, Ohta K, Suzuki N, Yamaguchi M, Hirai K, Horiuchi T, Watanabe J, Miyamoto T, Ito K. Idiopathic pulmonary fibrosis and high prevalence of serum antibodies to hepatitis C virus. Am Rev Respir Dis. 1992;146(1):266–8.
44. Kuwano K, Nomoto Y, Kunitake R, Hagimoto N, Matsuba T, Nakanishi Y, Hara N. Detection of adenovirus E1A DNA in pulmonary fibrosis using nested polymerase chain reaction. Eur Respir J. 1997;10(7):1445–9.
45. Dworniczak S, Ziora D, Kapral M, Mazurek U, Niepsuj G, Rauer R, Wilczok T, Kozielski J. Human cytomegalovirus DNA level in patients with idiopathic pulmonary fibrosis. J Physiol Pharmacol. 2004;55 Suppl 3:67–75.
46. Tang YW, Johnson JE, Browning PJ, Cruz-Gervis RA, Davis A, Graham BS, Brigham KL, Oates Jr JA, Loyd JE, Stecenko AA. Herpesvirus DNA is consistently detected in lungs of patients with idiopathic pulmonary fibrosis. J Clin Microbiol. 2003;41(6):2633–40.
47. Thannickal VJ, Horowitz JC. Evolving concepts of apoptosis in idiopathic pulmonary fibrosis. Proc Am Thorac Soc. 2006;3(4):350–6.
48. Lawson WE, Crossno PF, Polosukhin VV, et al. Endoplasmic reticulum stress in alveolar epithelial cells is prominent in IPF: association with altered surfactant protein processing and herpesvirus infection. Am J Physiol Lung Cell Mol Physiol. 2008;294(6):L1119–26.
49. Tablan OC, Reyes MP. Chronic interstitial pulmonary fibrosis following Mycoplasma pneumoniae pneumonia. Am J Med. 1985;79(2):268–70.
50. Konishi K, Gibson KF, Lindell KO, et al. Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2009;180(2):167–75.
51. Zamo A, Poletti V, Reghellin D, et al. HHV-8 and EBV are not commonly found in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(2):123–8.

# Part III
# Management and Prognosis

# Chapter 9
# Pharmacotherapy of IPF Using Antifibrotic Compounds

## Can Antifibrotic Agents Rescue Patients with IPF?

**Tomohiro Handa and Arata Azuma**

**Abstract** Pirfenidone is an antifibrotic agent that has multiple functions, and three out of four phase III clinical trials proved its efficacy to suppress disease progression in patients with mild to moderate idiopathic pulmonary fibrosis (IPF). In addition, pooled data have shown its efficacy to improve survival of patients with IPF. Nintedanib is another drug whose efficacy in the treatment of IPF has been confirmed by clinical trials, and both these drugs have recently been approved by the FDA. However, the efficacy of both drugs in severe IPF and the optimal length of therapy remain unknown. Based on the balance of clinical efficacy, side effects, disease severity itself, and cost-effectiveness, neither of these drugs is strongly recommended in the international guidelines. Furthermore, inhaling NAC is a cost-effective therapy, and well-conducted RCT should be considered to assess its effectiveness in treating IPF. Because a substantial percentage of patients with IPF die from acute exacerbation or lung cancer, medical treatment for IPF should focus not only on slowing the disease progression, but also on reducing the risk of acute exacerbation and lung cancer. Further investigation regarding the efficacy of combination therapies is necessary.

**Keywords** Acute exacerbation • Lung cancer • N-acetylcysteine • Nintedanib • Pirfenidone

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## 9.1 Introduction

Recent studies have shown that the pathogenesis of idiopathic pulmonary fibrosis (IPF) is characterized by alveolar epithelial cell damage and death caused by repetitive injuries that is followed by aberrant wound healing and excessive fibrosis. It also appears that genetic susceptibility together with environmental factors confers predisposition to IPF development. Molecules involved in IPF pathogenesis are potential targets of drug treatment, and a number of large-scale clinical studies have been conducted since 2005 [1]. However, most of these studies have failed to show efficacy of the drugs being tested. To date, only pirfenidone and nintedanib (formerly known as BIBF 1120) have shown efficacy in slowing the progression of IPF. Pirfenidone is the first drug approved for the treatment of IPF in Japan and is now approved in more than 30 countries spanning the EU, Korea, and Canada [2]. Based on the positive results in multiple phase III clinical trials, including the ASCEND trial [3], it has also recently been approved by the Food and Drug Administration (FDA) in the United States. Nintedanib has demonstrated encouraging results in phase III studies [4] and has also been approved by the FDA. Emergence of multiple drugs is going to widen our choice of medical treatment for IPF. In this chapter, we focus on pirfenidone and nintedanib, which are expected to play a central role in the medical treatment for IPF, and review their mechanisms of action as well as results of their clinical trials, including their efficacy and side effects. The potential efficacy of inhalation therapy with N-acetylcysteine (NAC), which has been mainly used in Japan, will also be discussed.

## 9.2 Pathogenesis of IPF and Potential Therapeutic Targets

The precise disease pathogenesis of IPF still remains unclear, but it is considered to be a heterogeneous process that differs from patient to patient. Alveolar epithelial cell injury and death is a crucial step in IPF progression, which is caused by a variety of stimuli such as smoking, virus infection, and acid reflux. In response to the epithelial cell injury, an increase in vascular permeability, extravascular leak of inflammatory cells, and immune activation occurs. In addition, Th1/Th2 immune balance is shifted toward a Th2-dominant milieu and may contribute to the fibrotic process. In IPF, these responses hinder the complete wound healing and reepithelialization, but result in lung fibrosis and functional impairment (Fig. 9.1) [1]. The molecules involved in these disease processes are ideal potential targets for IPF therapy. It has been shown that genetic susceptibility may also be involved in the development of IPF. Telomere length is associated with cell life cycle, and telomere shortening may contribute to the epithelial cell injury observed in IPF [5]. Previous reports have shown that mutations of genes controlling telomere length, such as TERT and TREC, are associated with an increased risk of IPF development [6]. A recent genome-wide association study (GWAS) showed that a

common variant of the MUC5B gene is associated with the susceptibility to IPF [7], and this has been reproduced in a few other IPF cohorts. Furthermore, the susceptible allele of the MUC5B promoter gene is associated with better prognosis, suggesting that IPF patients who carry MUC5B-susceptible alleles may have different pathogenesis than other IPF patients [8]. Although the precise role of MUC5B remains unclear, this molecule may be involved in the host defense mechanisms present in IPF. Another recent study also showed association between lung microbiome and IPF progression [9], suggesting that host defense mechanism may play a key role in the pathogenesis of IPF. Further investigation of this mechanism may lead to the development of novel drugs for the treatment of IPF.

## 9.3 Pirfenidone

### *9.3.1 Mechanism of Action*

Animal studies have shown that pirfenidone suppresses accumulation of inflammatory cells within alveoli; production of inflammatory cytokines such as IL-1β, IL-6, and TNFα; and activation of growth factors, including transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Pirfenidone also suppresses the decrease of interferon (IFN)-γ production in bleomycin-administered animals, shifting the immune balance to a Th1-dominant milieu [10] (Fig. 9.1). Furthermore, pirfenidone has

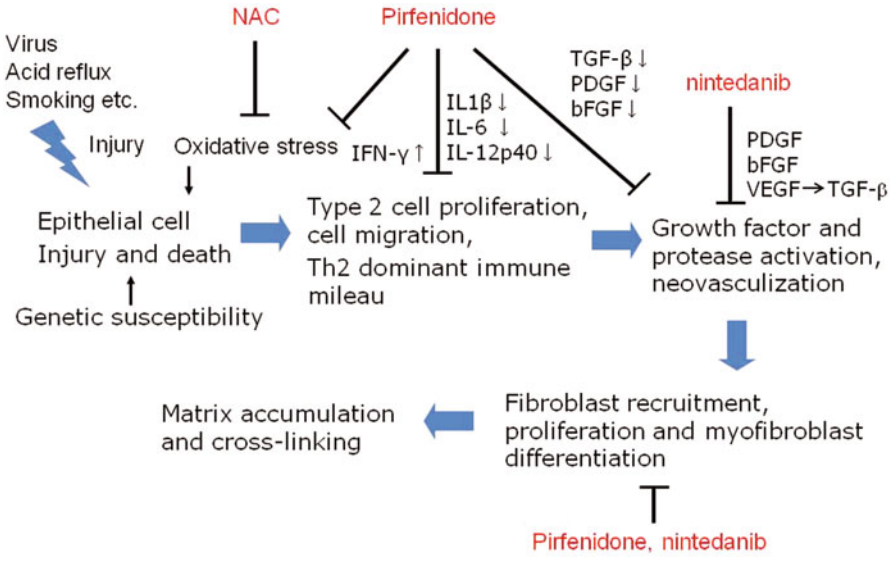


**Fig. 9.1** Pathogenesis of IPF and the mechanism of action of antifibrotic agents

antioxidant properties [11] and suppresses fibrocyte migration [12], which leads to its antifibrotic activity.

### 9.3.2 Results of RCT

According to the open-label studies conducted by Raghu et al. [13], a double-blind, phase II, placebo-controlled trial was conducted in Japan, which recruited 107 patients with IPF to evaluate the efficacy of pirfenidone (maximum 1800 mg/day) [14]. The patients recruited for this study were well-defined patients with IPF belonging to the age group of 20–75 years, with $PaO_2$ level ≧70 torr and the lowest $SpO_2$ level <90 % during the 6-min steady-state exercise walk test on the treadmill (6MET). The primary endpoint was a change in the lowest $SpO_2$ level during the 6MET. Based on trends in the decreased frequency of acute exacerbation in the pirfenidone group observed during the former 6 months of the trial, this study was terminated at the 9th month. There was no significant difference in the primary endpoint at the 9th month; however, significant improvement in the lowest $SpO_2$ level was observed in a subpopulation of 80 patients, who had the lowest $SpO_2$ level >80 % during 6MET ($p = 0.0069$ at the 6th month, $p = 0.0305$ at the 9th month). There was a significant difference in the decline of VC between the pirfenidone group (−0.03 L) and placebo group (−0.13 L) ($p = 0.0366$). In addition, there was a difference in the frequency of acute exacerbation during this 9-month study period between the pirfenidone group (no patients) and the placebo group [5/35 (14 %) patients] ($p = 0.0031$). In the pirfenidone group, photosensitivity was found in 43.8 % of the patients, and gastrointestinal symptoms were found in approximately 30 % of the patients, but these side effects were not associated with a significant difference in the frequency of patients who discontinued the medication.

In a subsequent phase III study in Japan, 267 patients with IPF were treated with pirfenidone for 52 weeks [15]. Eligible patients belonged to the age group of 20–75 years of age, with oxygen saturation of 5 % or more difference between the resting $SpO_2$ level and the lowest $SpO_2$ level during 6MET and the lowest $SpO_2$ level ≥85 % during the 6MET. Patients were allocated to high-dose (1800 mg/day), low-dose (1200 mg/day), and placebo groups in a 2:1:2 ratio. The primary endpoint was the change in VC at the 52nd week, and both the high-dose (−0.09 L) and the low-dose groups (−0.08 L) showed a significant difference when compared with the placebo group (−0.16 L) ($p < 0.05$). The secondary endpoints included progression-free survival (PFS) and minimal $SpO_2$ level during the 6MET. The high-dose group showed significant improvement in PFS ($p = 0.0280$), whereas the low-dose group showed marginal improvement ($p = 0.0655$). There was no significant difference in the minimal $SpO_2$ during 6MET or the frequency of acute exacerbation between the pirfenidone and placebo groups. Photosensitivity was observed in 51 % of the patients in the high-dose group and 53 % of the patients in the low-dose group; however, in most of the cases, it was mild in severity, and only 3 % of the patients discontinued the study due to photosensitivity.

The CAPACITY trial was a multicenter, randomized controlled trial consisting of two concurrent studies (study 004 and 006), which recruited patients with IPF from Australia, Europe, and North America and evaluated the efficacy of pirfenidone (2403 mg/day or 1197 mg/day) on FVC decline observed at the 72nd week [16]. In study 004, the group that received 2403 mg/day of pirfenidone showed a significantly lower decline in FVC each time from the 24th week to the 72nd week, and the groups that received 1197 mg/day of pirfenidone showed an intermediate outcome between the pirfenidone 2403 mg/day group and the placebo group. However, in study 006, there was no significant difference in FVC decline between the pirfenidone and placebo groups at 72 weeks, prompting US regulatory authorities to request an additional trial for its approval by the FDA.

The ASCEND trial was conducted at 127 sites in 9 countries, and 555 patients were allocated to either an oral pirfenidone (2403 mg/day) or placebo group. Patients recruited to the study had to meet all of the following criteria: %FVC, 50–90 %; %DLCO, 30–90 %; FEV1/FVC, >0.8; and 6MWD, >150 m [3]. These criteria were aimed at enrolling patients with more advanced progressive disease than the CAPACITY 006 trial, in which the negative result could be ascribed to the attenuated disease progression in the placebo group. These criteria also intended to exclude patients with an airflow limitation, as is seen in patients with comorbid emphysema. There was a significant difference between the groups pertaining to the primary endpoint, the change in the %FVC from baseline to the 52nd week ($p < 0.001$). The change in FVC was −428 mL in the placebo group and −235 mL in the pirfenidone group. In addition, regarding the secondary endpoint, pirfenidone treatment improved the 6MWD and PFS. Furthermore, in a pooled analysis of the three phase III studies (692 patients in the CAPACITY studies and 555 patients in the ASCEND trial), 1-year mortality was decreased by 48 % ($p = 0.01$), and IPF-associated mortality was decreased by 68 % ($p = 0.006$) in the pirfenidone group as compared with the placebo group. Skin-related events (pirfenidone group 28.1 %, placebo 8.7 %) and gastrointestinal events were more common in the pirfenidone group, but no patient in either group exhibited more than a grade 4 event.

RECAP is an open-label extension study that recruited patients who were previously randomized to the placebo groups in one of the two CAPACITY studies. Eligible patients received oral pirfenidone as 2403 mg/day, and their lung function and survival rates were evaluated. This study included 178 patients, who showed similar lung functioning and survival rates as compared with the patients treated using pirfenidone in the CAPACITY trials [17]. This study further confirmed the clinical efficacy of pirfenidone in the treatment of IPF.

### 9.3.3 Characteristics of Patients Who Benefit from Pirfenidone

In three out of four phase III studies, pirfenidone reduced the decrease in VC or FVC, and the pooled analysis of these studies showed that its administration improves survival of patients with IPF. However, it remains unclear what are the distinct characteristics of patients who benefit from pirfenidone. On an average, the study population in the phase II study in Japan [14] showed %VC as 80 % and % DLCO as 50–60 %. In the phase III study in Japan [15], the study population showed %VC as 75–80 % and %DLCO as 50–55 %, indicating that these studies were conducted in patients with mild to moderate levels of IPF. The participants in the ASCEND trial had relatively severe disease, showing %FVC as 65 to 70 % and %DLCO as 40–45 %, with 22 % of these patients having %DLCO $<35$ %. In the subanalyses of the phase III study in Japan [18], patients were stratified by baseline %VC, arterial oxygen partial pressure ($PaO_2$), and minimal $SpO_2$ during 6MET. The study showed that the effect of pirfenidone on VC was most prominent in a subgroup of patients having %VC $\geq 70$ and $SpO_2$ level during 6MET $<90$ % at baseline. However, in this study the number of patients stratified into the severe disease category was small and definite conclusions could not be made.

An open-label study by Nagai et al. [19], which comprised 8 patients with IPF and 2 patients with systemic sclerosis-associated UIP who had relatively severe disease with average %VC as 54.6 %, but some of these patients showed stabilization of the disease by pirfenidone. In another study, Okuda et al. evaluated the efficacy of pirfenidone in 76 patients with IPF including severe cases and found marginal significant effect of pirfenidone in 11 patients with %VC as $<60$ %, whose FVC changed from $-280$ mL before treatment to $-80$ mL after 6 months of treatment ($p = 0.074$) [20], and they also showed that a progressive FVC decline before treatment is associated with a good response to pirfenidone. These reports suggest that there may be some patients with severe disease who respond to pirfenidone. In contrast, Arai et al. showed that mild disease (Japanese severity grade I or II) and SLB diagnosis for IPF were associated with a favorable short-term response to pirfenidone [21]. As will be described later, some European guidelines recommend pirfenidone in mild to moderate disease based on CAPACITY data. Further investigation is necessary to elucidate the efficacy of this drug in severe IPF. As the ASCEND trial eliminated patient airflow limitations, the efficacy of pirfenidone in patients with comorbid emphysema should also be examined.

### 9.3.4 Side Effects of Pirfenidone and Its Management

As aforementioned, photosensitivity and gastrointestinal symptoms are two major side effects of pirfenidone. In post-marketing surveillance of 1370 Japanese patients who underwent pirfenidone treatment, the most common side effect was

loss of appetite (27.9 %), followed by photosensitivity (14.4 %) and nausea (7.9 %) (Inoue Y, Azuma A, Ogura T, et al. All-case post-marketing surveillance (PMS) of pirfenidone in Japan: clinical characteristics, efficacy and safety profile in >1300 patients with idiopathic pulmonary fibrosis (IPF). 2013 ERS Annual Meeting, P3369, Barcelona.). These data suggest that the frequency of photosensitivity can be reduced by educating patients to avoid ultraviolet exposure and encourage the use of sunscreen. In Japan, proton pump inhibitors (PPI), cisapride or rikkunshi-to (a herbal medicine) is used to prevent gastrointestinal symptoms, although their efficacy is often unsatisfactory. Arai et al. showed that PPI are efficacious in the management of gastrointestinal side effects caused by pirfenidone treatment [21], while others have shown a similar effect of rikkunshi-to [22]. Further investigation is necessary regarding the management of the side effects of pirfenidone to ensure its full effect.

### *9.3.5 Potential Role of Pirfenidone in Other Clinical Settings*

There are only limited data available regarding the efficacy of pirfenidone in interstitial lung diseases besides IPF. Miura et al. used pirfenidone in patients with untreated systemic sclerosis-associated interstitial pneumonia, and VC improved in all patients [23]. Vos et al. reported a case of restrictive allograft syndrome (RAS) following lung transplantation, in which pulmonary function and HRCT results were found to be improved during the treatment with pirfenidone [24]. In this patient, lung histology demonstrated a combination of diffuse PPFE, alveolar fibrosis, and bronchiolitis obliterans. Some physicians hesitate to use pirfenidone in patients with PPFE due to potential adverse effects on pneumothorax. However, due to the limited medical therapy available for this disease, further investigation is necessary regarding the effect of pirfenidone on PPFE.

Retrospective data in Japan showed that pirfenidone may be effective for the prevention of lung cancer in patients with idiopathic interstitial pneumonias, including IPF (Miura Y, Saito T, Tsunoda Y et al. Clinical effect on incidence of lung cancer of pirfenidone in idiopathic interstitial pneumonias. 2014 ERS Annual meeting, Munich), which requires further confirmation in prospective studies.

Pirfenidone is also used to prevent acute exacerbation after surgery. Iwata et al. retrospectively analyzed postoperative events in twelve patients with IPF and concomitant lung cancer that received perioperative pirfenidone and compared them with those of 16 patients with IPF who underwent lung cancer surgery without pirfenidone treatment. They showed that there were no IPF-related events in patients with perioperative pirfenidone treatment, whereas six control patients developed acute exacerbation of IPF ($P = 0.0167$) [25]. A prospective clinical study is currently ongoing in Japan examining whether pirfenidone has a prophylactic effect on acute exacerbation following lung cancer surgery in patients with IPF.

## 9.4 Nintedanib

### *9.4.1 Mechanism of Action*

Receptor tyrosine kinases play a crucial role in regulating cell proliferation, migration, metabolic changes, differentiation, and survival. Nintedanib (formerly known as BIBF 1120) is an intracellular tyrosine kinase inhibitor that suppresses multiple tyrosine kinase receptors, including those of VEGF, fibroblast growth factor (FGF), and platelet-derived growth factors (PDGF). Nintedanib is used in several malignant diseases, including lung cancer [26]. Chaudhary et al. showed that BIBF suppresses TGF-β2-induced αSMA expression in fibroblasts derived from patients with interstitial pneumonia, suggesting that VEGF, FGF, and PDGF are involved in the pathogenesis of pulmonary fibrosis [27]. Thus, this agent was expected to be a potential therapeutic drug for IPF. Nintedanib is believed to exert its antifibrotic effect by suppressing elevation of inflammatory cells within alveoli, fibroblast proliferation, and fibroblast to myofibroblast transformation [28]. In addition, PDGF and FGF are also involved in the pathogenesis of pulmonary arterial hypertension (PAH) [29]. Therefore, nintedanib may also have a beneficial effect on pulmonary hypertension in patients with IPF.

### *9.4.2 Results of RCT*

A phase II study was conducted in 432 patients with IPF to investigate the efficacy and optimal dosage of nintedanib in this disease [30]. The primary endpoint was the annual rate of decline in FVC. Patients were randomly assigned to one of the five groups, which included four groups that received different doses of nintedanib (50 mg once a day, 50 mg twice a day, 100 mg twice a day, or 150 mg twice a day) and a placebo group. After 12 months, FVC decreased by 0.19 L in the placebo group, whereas FVC decreased by only 0.06 L in the nintedanib 150 mg twice a day group ($p = 0.01$ with the hierarchical testing procedure, $p = 0.06$ for multiplicity correction). With this dose, nintedanib decreased the frequency of acute exacerbation ($p = 0.02$) and improved SGRQ ($p = 0.007$). However, the frequency of liver enzyme elevation and discontinuation of the treatment due to gastrointestinal symptoms were higher in the nintedanib 150 mg twice a day group as compared with placebo. Next two replicate phase III trials (INPULSIS-1 and INPULSIS-2) were conducted to evaluate the efficacy and safety of 150 mg of nintedanib twice a day [4]. In these trials, 1066 patients with IPF were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The primary endpoint, which was in the 52-week rate of FVC decline, was improved with nintedanib treatment in both INPULSIS-1 ($-114.7$ mL vs. $-239.9$ mL, $p < 0.001$) and INPULSIS-2 ($-113.6$ vs. $-207.3$ ml, $p < 0.001$). Nintedanib was also shown to prolong time to the first acute exacerbation ($p = 0.005$) in INPULSIS $-$ 2, but not in INPULSIS-1. Pooled analysis of

these three clinical trials showed no significant effect of nintedanib on mortality, but nintedanib had a significant benefit to prolong the time to the first acute exacerbation in IPF. Diarrhea was the most frequent adverse event and was observed at a rate of 61.5 % and 63.2 % in the nintedanib groups from these studies. However, less than 5 % of the events led to the discontinuation of the study.

## 9.5 NAC

It has been reported that an oxidant/antioxidant balance is involved in the pathogenesis of IPF [31, 32]. NAC is a precursor of the major antioxidant glutathione and is a potential drug for the treatment of IPF. A non-randomized trial showed that treatment with oral NAC increased alveolar glutathione levels and improved the lung functioning in IPF and connective tissue diseases [33]. Following this, a double-blind, placebo-controlled multicenter study (IFIGENIA study) was conducted to evaluate the efficacy of adding oral NAC at a dose of 1800 mg/day to prednisolone and azathioprine, which was a standard drug therapy for IPF at that time. VC and DLCO significantly improved after a 12-month treatment in the NAC group compared with the control group [34]. However, this study did not include a pure placebo arm. The PANTHER trial was conducted to evaluate the efficacy of NAC alone compared to the three-drug regimen (prednisolone, azathioprine, NAC). Mild to moderate IPF patients with %FVC as >50 % and %DLCO as >30 % were assigned to triple therapy, NAC alone, and placebo groups. However, the study was interrupted due to the increased frequency of death or disease progression in the three-drug regimen group [35], and a clinical alert was issued. After a period of interruption, the trial protocol was modified, and patients were recruited for NAC alone and placebo groups and were evaluated for 60 weeks. There was no significant difference in the primary endpoint (FVC change), although 6MWD and quality of life (QOL) tended to improve in the NAC group compared with placebo. However, cardiac disorders were significantly higher in the NAC group (6.8 %) as compared with the placebo group (1.5 %) [36].

In Japan, oral NAC is unavailable, but NAC inhalation therapy has been tried in some institutes. A multicenter, prospective, randomized controlled clinical trial which included 76 patients with mild to moderate IPF that experienced no desaturation following exercise was conducted in Japan [37]. Patients were assigned to a group that received 352.4 mg of NAC via inhalation twice daily or to a control group. There was no significant difference in the primary endpoint (FVC change) after 48 weeks. However, NAC therapy was associated with FVC stability in a subset of patients with initial %predicted FVC as <95 % ($n = 49$, $p = 0.02$) or initial %predicted DLCO as <55 % ($n = 21$, $p = 0.009$). Adverse events included mild to moderate bacterial pneumonia, cough, sore throat, and hypercholesterolemia. NAC inhalation therapy is reported to have an advantage in cost-effectiveness, but further investigation with a larger number of patients is required to determine the efficacy of inhaled NAC in patients with IPF.

## 9.6 Other Agents

Based on the disease pathogenesis of IPF (Fig. 9.1), several new drugs are under evaluation which target Th1/Th2 balance, cytokines, or chemokines. A number of clinical trials have been conducted to evaluate the efficacy of bosentan, macitentan, ambrisentan, interferon, sildenafil, TNF-α inhibitor, imatinib mesylate, Anti-CCL2 antibody, anti-IL-13 monoclonal antibody, and others. However, none of the trials with these drugs have shown significant efficacy in the treatment of IPF. Ongoing clinical trials include those with IL-13 monoclonal antibody, Integrin avβ6 monoclonal antibody, CTGF inhibitor, lysophosphatidic acid receptor antagonist, and LOXL2 monoclonal antibody [1]. It is hoped that these studies may lead to the discovery of novel drugs which widen our choice of treatment for IPF.

## 9.7 Guideline Recommendation

In the revised IPF guideline by ATS/ERS/JRS/ALAT published in 2011 [38], no medical therapy is positively recommended when taking the balance of clinical evidence, efficacy, cost, and potential harmful effects into account. "Strong against" recommendation was given to many of the drugs which had been used in clinical practice, including corticosteroids alone or in combination with immunomodulatory drugs. "Weak against" recommendation was given to pirfenidone, triple therapy (prednisone, azathioprine, NAC), and anticoagulation therapy, meaning that these drugs may not be appropriate for majority of the patients. However, it should be noted that majority of the committee members abstained from voting for pirfenidone because they were involved in the CAPACITY trials, and the panel felt that many would want the treatment [2, 38]. After the approval of pirfenidone in the European Union in 2011, guidelines for IPF have been updated in European countries, and many of them recommend that patients with mild to moderate IPF should be offered pirfenidone [2]. For instance, in the United Kingdom pirfenidone is recommended for patients with IPF with %FVC as 50–80 %, and in France pirfenidone is recommended for patients with %FVC as 50–80 % and %DLCO as $<$35 %. Now that triple therapy [35] and anticoagulation therapy [39] have been proved to be ineffective or even harmful, pirfenidone is the only drug to be recommended in these guidelines. Following the result of the ASCEND trial, pirfenidone has been approved by the FDA, and the ATS/ERS/JRS/ALAT evidence-based guideline is now under the process of being updated so that pirfenidone and nintedanib will be given conditional recommendation. However, whether the use of pirfenidone will be indicated in severe IPF cases or in those with emphysema still remains unclear.

## 9.8 Combination Therapy

Due to the emergence of many drugs with varying mechanisms of action, combination drug therapy for IPF is expected. It is of our particular interest whether combination therapy with pirfenidone and nintedanib is more effective than therapy with either drug alone. Despite the initial lack of efficacy of oral NAC combined with immunosuppressive drugs, further investigation is required to evaluate the efficacy of adding NAC to antifibrotic drugs. Sakamoto et al. retrospectively analyzed the effect of pirfenidone in 18 patients with progressive and advanced IPF and found that patients who had combination use of inhaled NAC showed a favorable response to pirfenidone, including better survival [40]. In the Spanish guideline for IPF, pirfenidone is recommended as the first-line therapy in patients with IPF with FVC as >50 %. In patients whose disease continues to progress, the possibility of designing pirfenidone combination regimens was described [41]. At present, limited data is available for combination drug therapy in IPF, and further investigation is required.

## 9.9 Conclusion

Based on clinical experience in Japan and other countries where pirfenidone is approved, pirfenidone is presently the most reliable drug for the treatment of mild to moderate IPF when considering both efficacy and safety. However, its effect on IPF is far from a "cure," and it remains unclear at what stage of disease and in which type of patients it should be used. In a mild case, an initial policy of observation may be appropriate. Nintedanib is another drug which should demonstrate clinical utility in the treatment of IPF; however, further information is necessary regarding its long-term efficacy and safety.

Although oral NAC did not show a significant effect in a clinical trial, further investigation is necessary on the effectiveness of NAC inhalation therapy in patients with mild disease. In Japan, acute exacerbation and lung cancer account for 40 % and 11 %, respectively, of the cause of death in IPF [42], and thus they are important prognostic factors. Unfortunately, the effect on acute exacerbation has not been consistently observed in clinical trials evaluating pirfenidone and nintedanib. Since acute exacerbation is not always diagnosed accurately, we need to standardize diagnostic process of this devastating disease that develops during chronic course of IPF. Further analysis of the benefit of antifibrotic agents on acute exacerbation and/or overall survival is needed for appropriate indication of these agents which were not clearly given in RCTs. In addition, pulmonary hypertension (PH) is another prognostic factor in IPF, and the effect of antifibrotic agents on PH should be investigated. Further investigation is required on the efficacy of combination therapy, or the possibility of therapy tailored based on disease severity, genetic background, and comorbidities, to establish a comprehensive strategy for the treatment of IPF.

## References


1. Ahluwalia N, Shea BS, Tager AM. New therapeutic targets in idiopathic pulmonary fibrosis: aiming to rein in runaway wound healing responses. Am J Respir Crit Care Med. 2014;190: 867–78.
2. Xaubet A, Behr J, Bendstrup E, et al. Review of IPF diagnosis and management recommendations in Europe. Sarcoidosis Vasc Diffuse Lung Dis. 2013;30:249–61.
3. King Jr TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
4. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
5. Cronkhite JT, Xing C, Raghu G, et al. Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med. 2008;178:729–37.
6. Mushiroda T, Wattanapokayakit S, Takahashi A, et al. A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. J Med Genet. 2008;45:654–6.
7. Fingerlin TE, Murphy E, Zhang W, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet. 2013;45:613–20.
8. Peljto AL, Zhang Y, Fingerlin TE, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA. 2013;309: 2232–9.
9. Molyneaux PL, Cox MJ, Willis-Owen SA, et al. The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;190:906–13.
10. Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol. 2008;590:400–8.
11. Misra HP, Rabideau C. Pirfenidone inhibits NADPH-dependent microsomal lipid peroxidation and scavenges hydroxyl radicals. Mol Cell Biochem. 2000;204:119–26.
12. Inomata M, Kamio K, Azuma A, et al. Pirfenidone inhibits fibrocyte accumulation in the lungs in bleomycin-induced murine pulmonary fibrosis. Respir Res. 2014;15:16.
13. Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. Am J Respir Crit Care Med. 1999;159:1061–9.
14. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–7.
15. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:821–9.
16. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760–9.
17. Costabel U, Albera C, Bradford WZ, et al. Analysis of lung function and survival in RECAP: an open-label extension study of pirfenidonein patients with idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31:198–205.
18. Azuma A, Taguchi Y, Ogura T, et al. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefiting from treatment. Respir Res. 2011;12:143.
19. Nagai S, Hamada K, Shigematsu M, et al. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med. 2002;41:1118–23.
20. Okuda R, Hagiwara E, Baba T, et al. Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice. Respir Med. 2013;107:1431–7.
21. Arai T, Inoue Y, Sasaki Y, et al. Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis. Respir Investig. 2014;52:136–43.

22. Shimizu Y, Shimoyama Y, Kawada A, et al. Gastrointestinal symptoms in idiopathic pulmonary fibrosis patients treated with pirfenidone and herbal medicine. J Biol Regul Homeost Agents. 2014;28:433–42.
23. Miura Y, Saito T, Fujita K, et al. Clinical experience with pirfenidone in five patients with scleroderma-related interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31: 235–8.
24. Vos R, Verleden SE, Ruttens D, et al. Pirfenidone: a potential new therapy for restrictive allograft syndrome? Am J Transplant. 2013;13:3035–40.
25. Iwata T, Yoshida S, Nagato K, et al. Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis. Surg Today. 2014. DOI:10.1007/s00595-014-1071-5
26. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15:143–55.
27. Chaudhary NI, Roth GJ, Hilberg F, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J. 2007;29:976–85.
28. Wollin L, Maillet I, Quesniaux V, et al. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther. 2014;349:209–20.
29. Montani D, Chaumais MC, Guignabert C, et al. Targeted therapies in pulmonary arterial hypertension. Pharmacol Ther. 2014;141:172–91.
30. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–87.
31. Cantin AM, North SL, Fells GA, et al. Oxidant-mediated epithelial cell injury in idiopathic pulmonary fibrosis. J Clin Invest. 1987;79:1665–73.
32. Liu RM, Liu Y, Forman HJ, et al. Glutathione regulates transforming growth factor-beta-stimulated collagen production in fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2004;286: L121–8.
33. Behr J, Maier K, Degenkolb B, et al. Antioxidative and clinical effects of high-dose N-acetylcysteine in fibrosing alveolitis. Adjunctive therapy to maintenance immunosuppression. Am J Respir Crit Care Med. 1997;156:1897–901.
34. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2005;353:2229–42.
35. Raghu G, Anstrom KJ, King Jr TE, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77.
36. Martinez FJ, de Andrade JA, Anstrom KJ, et al. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2093–101.
37. Homma S, Azuma A, Taniguchi H, et al. Efficacy of inhaled N-acetylcysteine monotherapy in patients with early stage idiopathic pulmonary fibrosis. Respirology. 2012;17:467–77.
38. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
39. Noth I, Anstrom KJ, Calvert SB, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186:88–95.
40. Sakamoto S, Itoh T, Muramatsu Y, et al. Efficacy of pirfenidone in patients with advanced-stage idiopathic pulmonary fibrosis. Intern Med. 2013;52:2495–501.
41. Xaubet A, Ancochea J, Bollo E, et al. Sociedad Española de Neumología y Cirugía Torácica (SEPAR) research group on diffuse pulmonary diseases. Arch Bronconeumol. 2013;49: 343–53. [Article in English, Spanish]
42. Natsuizaka M, Chiba H, Kuronuma K, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190:773–9.

# Chapter 10
# Pharmacotherapy of IPF (Corticosteroids, Immunosuppressants, Etc.)

## Are These Actually Effective? Ineffective? Harmful?

**Masashi Bando**

**Abstract** There was no evidence showing the usefulness of corticosteroid and immunosuppressant with anti-inflammatory effects for the treatment of idiopathic pulmonary fibrosis (IPF). This therapy may induce acute exacerbation associated with dose reduction and side effects such as a complicated infection. Therefore, the treatment with corticosteroid and immunosuppressant is not recommended in definite IPF patients in an official ATS/ERS/JRS/ALAT statement (evidence-based guidelines for diagnosis and management of IPF).

However, the usefulness of the combination therapy with a small amount of corticosteroid and immunosuppressant or antifibrotic agents is still unknown. It cannot be completely denied that this combination therapy becomes one of the therapies as conditional recommendation for the moment.

**Keywords** Idiopathic pulmonary fibrosis • Corticosteroid • Immunosuppressant

## 10.1 Introduction

Because it is thought to be important to control "lung injury caused by chronic inflammation of alveolar septa and the process of becoming fibrotic," historically, a corticosteroid and immunosuppressant with anti-inflammatory effects have been administered as the treatment strategy for idiopathic pulmonary fibrosis (IPF) [1–3].

However, in low-evidence studies performed before 2000 [4, 5], not all IPF patients were given combination treatment of a corticosteroid and immunosuppressant. In addition, patients with nonspecific interstitial pneumonia (NSIP) or secondary interstitial pneumonia might have been included in the studies showing that corticosteroid therapy was effective. In the ATS/ERS international consensus statement in 2000 [6], the combination of a relatively small amount of

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corticosteroid and immunosuppressant has been proposed as a therapy for IPF. Additionally, because combination therapy with immunosuppressant was effective compared with corticosteroid monotherapy which was shown to be less effective [7, 8], the combination of a corticosteroid and immunosuppressant is designated as a proposed therapy in guidelines on the diagnosis and therapy of idiopathic interstitial pneumonias (IIPs) published in Japan in 2004. The combination of an immunosuppressant with corticosteroid tapering or corticosteroid alternate-day therapy has been provided as a specific treatment for IPF until the revised second edition published in 2008 [9].

Moreover, in recent years, a major pathological condition of IPF that produces resistance to corticosteroid therapy is believed to be "repetitive alveolar epithelial cell injury and subsequent abnormal lesion repair, which induce proliferation of fibroblasts and deposition of extracellular matrix," by the development of molecular techniques used in studies of pathophysiological conditions, resulting that an antifibrotic therapy is playing a central role [10–12].

This chapter describes functions of treatment with a corticosteroid and immunosuppressant in the medical care of IPF patients in the stable phase based on the latest evidences.

## 10.2 Corticosteroid and Immunosuppressant for the Treatment of IPF from the Perspective of the Latest Guidelines

In the evidence-based guidelines for diagnosis and management of IPF [13] prepared by the ATS/ERS/JRS (the Japanese Respiratory Society)/ALAT (the Latin American Thoracic Association) in 2011, the treatment recommendations were determined based on the previous evidence-based studies. These guidelines recommended that patients with IPF should not be treated with corticosteroid monotherapy, cyclosporine A therapy, and the combination of corticosteroid with immunosuppressant (azathioprine or cyclophosphamide) (strong recommendation, very low-quality evidence). A three-drug combination therapy of corticosteroid, azathioprine, and oral N-acetylcysteine (NAC) was not recommended in the majority of IPF patients, but this therapy may be a reasonable choice in a minority (weak recommendation, low-quality evidence) (Table 10.1). However, according to an interim report of the clinical trial with three arms of steroid/azathioprine/oral NAC, NAC monotherapy, and placebo (PANTHER-IPF) [14], because elevations in the mortality rate, and hospitalization, and acute exacerbation had been reported, the previous recommendation was revised, and the recommendation against the use of the three-drug combination therapy with corticosteroid, azathioprine, and oral NAC for the treatment of IPF is strong in 2015 guidelines [15].

Taken together, there was no evidence showing the usefulness of the combination of corticosteroid and immunosuppressant for the treatment of IPF. Considering

**Table 10.1** Evidence-based treatment

| Treatment | Recommended | Strength of recommendation | Quality of evidence |
|---|---|---|---|
| Pharmacologic therapies | | | |
| Corticosteroid monotherapy | No | Strong | ⨁◯◯◯ |
| Colchicine | No | Strong | ⨁◯◯◯ |
| Cyclosporine A | No | Strong | ⨁◯◯◯ |
| Corticosteroid + immunomodulatory | No | Strong | ⨁◯◯◯ |
| Corticosteroid + azathioprine + acetylcysteine | Majority – no | Weak | ⨁⨁◯◯ |
| | Minority – may be a reasonable choice | | |
| 2015 Guidelines | No | Strong | |

2011 Guidelines for the diagnosis and management of IPF. An ATS Pocket Publication (modified)

the possibility that this therapy may induce acute exacerbation associated with dose reduction and side effects such as a complicated infection which occurs with long-term usage, the treatment with corticosteroid and immunosuppressant is not recommended in definite IPF patients.

## 10.3 Therapy for IPF in Our Clinical Practice

A study that aimed at elucidating the actual medical practice concerning IPF in Japan entitled "A prospective investigation research for diffuse pulmonary disease, Project on Measures for Intractable Diseases, Health and Labour Science Research Grant" was registered on the Internet, and a prospective epidemiological study was conducted [12]. Information obtained from a multicenter study including the therapeutic regimen, clinical findings, and the clinical course of patients with IIPs including IPF was actively entered in a database on the Internet. As a result, 321 IPF patients from 19 medical facilities were registered. Regarding the therapeutic regimen for IPF patients and a change in the regimen (see Fig. 10.1), the majority of IPF patients were untreated (78.7 %) by the end of fiscal year 2008 when pirfenidone was approved, but the untreated rate among IPF patients decreased by 44.6 % between 2009 and the end of fiscal year 2013. Pirfenidone has been used as a therapy for IPF patients (32.9 % between 2009 and the end of fiscal year 2013) including pirfenidone monotherapy (17.4 %), and therefore this medication plays a key role in the treatment of IPF in Japan. On the other hand, the use of corticosteroid monotherapy for IPF patients showed a slight increase from 6.2 to 7.5 %; likewise, the use of the combination of corticosteroid and immunosuppressant slightly increased from 11.2 to 13.1 %. These results show that the combination of a corticosteroid and immunosuppressant is used conditionally as symptomatic therapy for IPF in our medical practice with awareness of the side effects of each medication.

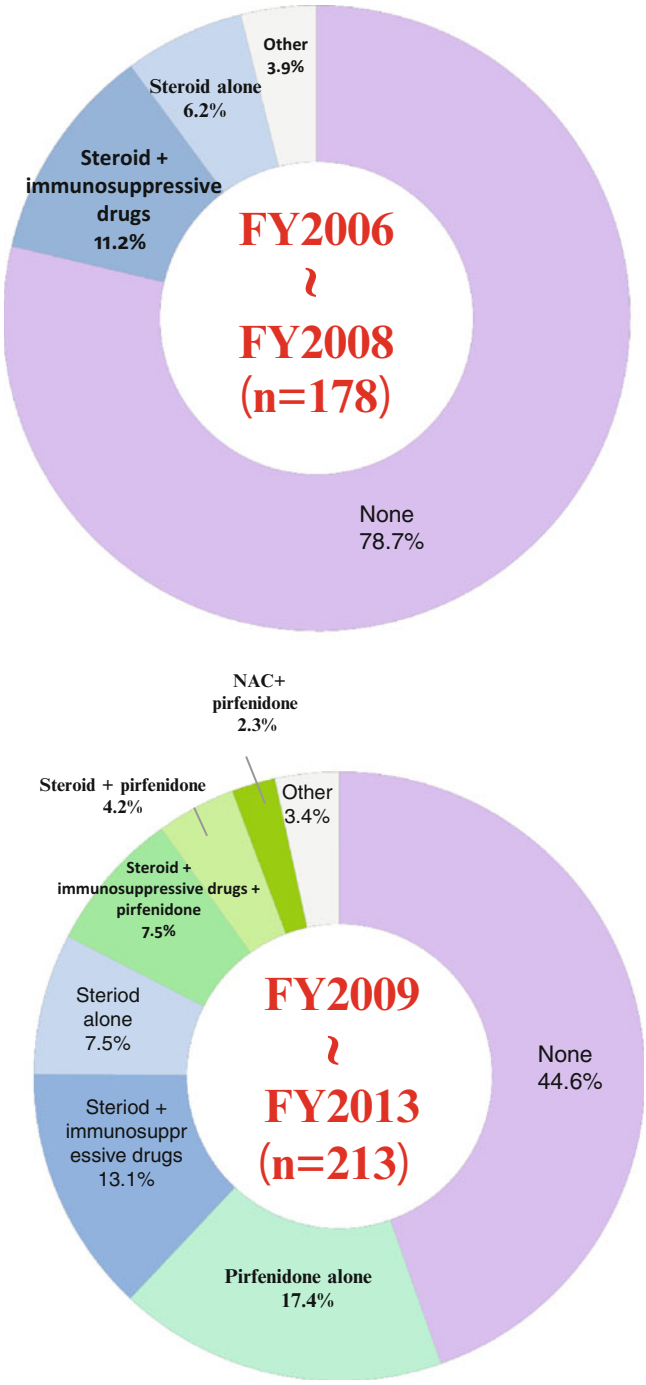


**Fig. 10.1** The treatments and their changes in IPF

## 10.4 Pharmacological Effects and Side Effects from the Use of Corticosteroid and Immunosuppressant

### *10.4.1 Corticosteroids*

The anti-inflammatory effects of corticosteroids are well known for their genomic mechanism producing biological actions. After the corticosteroids form complexes with glucocorticoid receptors (GCRs) inside the cytoplasm, the complexes translocate to the nucleus and bind to glucocorticoid-response elements on DNA. Once GCRs that had translocated into the nucleus bind to negative glucocorticoid-response element, the mRNA transcription of various cytokines involved in inflammation is inhibited. On the other hand, when GCRs translocate into the nucleus and bind to positive glucocorticoid-response element on DNA, the mRNA transcription of anti-inflammatory proteins is upregulated. The binding of transcription factors including nuclear factor-κB and AP-1 to DNA is inhibited, resulting in interference of cytokine production [16]. The amount of corticosteroid that would saturate corticosteroid receptors in an adult human is approximately 60 mg of prednisolone, although there are individual differences. In contrast, high-dose corticosteroid therapy is thought to act through a non-corticosteroid receptor-mediated mechanism, so-called non-genomic mechanism [17], which is entirely different from the genomic mechanism and has an onset of effect between a few seconds and a few minutes. Although the details are unknown at this time, there are two kinds of non-genomic mechanisms: nonspecific effects that directly act on cell membrane fluidity and specific effects that act on a specific receptor. Corticosteroid pulse therapy can be expected to have stronger genomic and non-genomic effects and have an impact on inflammatory cells, alveolar epithelial cells, T lymphocytes, vascular endothelial cells, etc. [18, 19]. Meanwhile, because corticosteroids do not inhibit the production of basic fibroblast growth factor and transforming growth factor-β (TGF-β) in bleomycin-induced murine pulmonary fibrosis [20], they have no antifibrotic actions. The following side effects of corticosteroids are important: diseases induced by infectious diseases (particularly tuberculosis, fungus, cytomegalovirus, Pneumocystis pneumonia, etc.), peptic ulcer, diabetes, mental deterioration, hypertension, secondary adrenocortical insufficiency, osteoporosis, aseptic necrosis of the femur and others, myopathy, glaucoma, cataract, thrombosis, endocrine abnormality, and so on. Because the above major side effects influence disease prognosis, whether the therapeutic effect is beneficial to the patient or not needs to be carefully pondered when such a side effect occurs. In addition, a decision must be made as to whether patients will continue the therapy with corticosteroid, reduce the dose, or discontinue this therapy. When a corticosteroid is administered for a long period of time, the combined treatment of sulfamethoxazole and trimethoprim is necessary to prevent Pneumocystis pneumonia. Because postmenopausal women and elderly people are vulnerable to the development of osteoporosis and compressed fracture, a medication such as bisphosphonate is also required. In contrast, minor side effects of corticosteroid administration include

hirsutism, acne, moon-shaped face, extravasation of blood into the skin, purpura, and so on, but these side effects are sometimes not severe, and the physician may not recommend reducing the dose or discontinuing the drug.

## *10.4.2 Immunosuppressants*

Generally, an immunosuppressant is used for the treatment of various interstitial pneumonias other than IPF in the following cases: patients who have no response to corticosteroids, those who experienced severe side effects of corticosteroid, and those who are at high risk of developing side effects with corticosteroid. In the United States and Europe, cyclophosphamide and azathioprine are often used for treatment, but cyclosporine A is also used in Japan.

### 10.4.2.1 Cyclophosphamide

Cyclophosphamide is classified as an alkylating compound that is activated by hepatic microsomal enzymes and exhibits pharmacological action. The inhibitory effects of cyclophosphamide on DNA synthesis act on the cell cycle in a nonspecific manner. Cyclophosphamide shows a stronger inhibitory action against B lymphocytes than T lymphocytes. The general dosage required for cyclophosphamide is 1.0–2.0 mg/kg/day (ideal body weight, highest dose: 150 mg/day). The medication is initiated at 50 mg/day and increased by 25 mg every 7–14 days as needed. Because the onset of the therapeutic effect is usually more than 3 months after starting this medication, the medication needs to be continued for at least 6 months or longer as long as there are no severe side effects. Some side effects of cyclophosphamide are bone marrow suppression, hemorrhagic cystitis, second primary cancer, hair loss, a feeling of sickness, stomatitis, diarrhea, and hepatic impairment associated with cholestasis. Pulmonary fibrosis has also been reported although it is rare. The medication is suspended or the dose is reduced by half when the white blood cell count falls below 4,000/$mm^3$ or platelet count falls below 100,000/$mm^3$. Patients drink adequate fluids to prevent hemorrhagic cystitis, establish urine flow, and take a urine test monthly. When hemorrhagic cystitis occurs, the medication is discontinued.

### 10.4.2.2 Azathioprine

Azathioprine, which is classified as an antimetabolic drug, is transformed into 6-mercaptopurine in the liver and is later physiologically activated. Azathioprine is a medication that acts specifically on the cell cycle and inhibits purine synthesis by acting on the DNA synthetic phase. Its immunosuppressive effect is mainly caused by suppression of the proliferation of T lymphocytes. The general dosage

required for azathioprine is 2.0–3.0 mg/kg/day (ideal body weight, highest dose: 150 mg/day). The medication is initiated at 50 mg/day and the dose is increased by 25 mg every 7–14 days as needed. Side effects are bone marrow suppression, a feeling of sickness, vomiting, gastrointestinal symptoms such as diarrhea, and hepatic impairment. The medication is suspended or its dose is reduced by half when the white blood cell count falls below 4,000/mm$^3$ and the platelet count falls below 100,000/mm$^3$. Patients undergo a hepatic function test monthly, and the medication is later suspended, or its dose is reduced when the measured value of AST and ALT reaches more than three times the upper limit of a normal hepatic function.

#### 10.4.2.3 Cyclosporine A

Cyclosporine A binds with cyclophilin in the cytoplasm and exerts an effect by suppressing the proliferation and activation of T lymphocytes [21, 22]. Additionally, cyclosporine A improves corticosteroid resistance through inhibition of p-glycoprotein involved in drug resistance. There is a report that cyclosporine inhibits late-onset hypersensitive reaction, transplant rejection, and T-lymphocyte-dependent antigen-antibody reaction. On the other hand, another study reported that cyclosporine induces TGF-β [23]. However, further analysis is needed because there is a new study indicating that cyclosporine inhibits TGF-β secretion and has antifibrotic actions against muscle fibroblasts [24, 25]. Because the difference between the critical region and blood level that can exert an immunosuppressive effect is small in cyclosporine, the dose is determined by monitoring its blood level in whole blood. The medication is initiated at 3.0 mg/kg/day twice daily, and the level 12 h after administration is approximately 100–150 ng/mL. There are two issues that should receive special attention: one is that oral absorption varies considerably among individuals, and the other is that it interacts with many drugs (calcium antagonist, macrolide antimicrobial drug, and antifungal drug increase blood levels). Side effects are kidney failure (dosage dependent), hypertension, gingival hypertrophy, neurological symptoms (headache, tremulousness, and dysesthesia), hirsutism, and so on. Periodic observation of renal function is needed during treatment with cyclosporine. In addition, although the onset is relatively less frequent, special attention needs to be paid to infection by viruses (cytomegalovirus, herpes simplex virus, chicken pox, herpes zoster virus, and Epstein-Barr virus), protozoa, fungus, and so on.

## 10.5 The Remaining Challenges

As described earlier, there is no evidence that shows the usefulness of corticosteroid or immunosuppressant as a therapy for definite IPF [13, 26, 27]. However, it's sometimes difficult to make the diagnosis of IPF among many differential

diagnoses including chronic hypersensitivity pneumonitis, connective tissue disease-associated interstitial lung disease, and so on in medical practice. Concretely speaking, therapy with a corticosteroid and immunosuppressant can be considered in the following cases (Table 10.2) [9]: a case in which image findings and subjective symptoms worsen compared with a few months prior, a case in which a honeycomb lung is not visibly found by high-resolution computed tomography, a case in which the number of lymphocytes in bronchoalveolar lavage fluid is increasing, and a case in which a diagnosis on the basis of pathological findings in other IIPs such as NSIP and cryptogenic organizing pneumonia is confusable. There are also many unsolved issues in the usage and rate of reduction of the dose of corticosteroid and immunosuppressant.

Because the dosage regimen for corticosteroid therapy conducted in the PANTHER trial [14], which differs from what we have experientially determined in Japan, is a regimen that reduces the dosage rapidly, it is too soon to decide a total ban on medication based on only the result from this clinical trial. In Japan, as a prospective multicenter therapeutic study of a clinical trial of revolutionary therapy, a comparative trial between the groups of combination therapy with cyclosporine and corticosteroid (10–20 mg) and that with cyclophosphamide and corticosteroid (10–20 mg) for IPF has been conducted since 2005 [28]. According to this study, the amount of decrease in forced vital capacity for 48 weeks was 78 mL (cyclosporine and corticosteroid) and 87 mL (cyclophosphamide and corticosteroid) in each of the combination therapy groups, which showed no significant difference; therefore, the combination therapy with cyclosporine is non-inferior. In addition, in the recent clinical trial for a new inhibitor of fibrosis, nintedanib [29], a small amount of corticosteroid is concurrently administered to approximately 20 % of patients in each group.

In conclusion, at present, the usefulness of the combination therapy with a small amount of corticosteroid and immunosuppressant or antifibrotic drugs is still unknown. Therefore, it cannot be completely denied that this combination therapy becomes one of the options as conditional recommendation.

**Table 10.2** Cases of IPF in which the use of corticosteroid and immunosuppressant can be considered

| | |
|---|---|
| 1. | Image findings and subjective symptoms worsen compared with a few months ago |
| 2. | Honeycomb lung is not visibly found by high-resolution computed tomography |
| 3. | The number of lymphocytes in bronchoalveolar lavage fluid is increasing |
| 4. | A diagnosis on the basis of pathological findings in other IIPs such as NSIP and cryptogenic organizing pneumonia is confusable |

## References


1. Mapel DW, Samet JM, Coultas DB. Corticosteroids and the treatment of idiopathic pulmonary fibrosis. Past, present, and future. Chest. 1996;110:1058–67.
2. Mason RJ, Schwartz MI, Hunninghake GW, et al. Pharmacological therapy for idiopathic pulmonary fibrosis: past, present, and future. Am J Respir Crit Care Med. 1999;160:1771–7.
3. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med. 2001;345:517–25.
4. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. Thorax. 1980;35:593–9.
5. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med. 1998;157:1063–72.
6. American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med. 2000;161:646–64.
7. Johnson MA, Kwan S, Snell NJ, et al. Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. Thorax. 1989;44:280–8.
8. Raghu G, Depaso WJ, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis. 1991;144:291–6.
9. Japanese Respiratory Society diffuse lung diseases diagnosis and treatment guidelines committee. Guidelines for diagnosis and treatment of idiopathic interstitial pneumonias. Revised 2nd ed. Tokyo: Nankodo; 2011.
10. Selman M, King Jr TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypothesis about its pathogenesis and implications for therapy. Ann Intern Med. 2001;134:136–51.
11. King Jr TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378:1949.
12. Bando M, Sugiyama Y, Azuma A, et al. A prospective survey of idiopathic interstitial pneumonias in a web registry in Japan. Respir Investig. 2015;53:51–9.
13. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
14. Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King Jr TE, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77.
15. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALST clinical practice guideline: treatment of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2015;192:e3–e19.
16. Jonat C, Rahmsdorf HJ, Park KK, et al. Antitumor promotion and antiinflammation: down-modulation of AP-1 (Fos/Jun) activity by glucocorticoid hormone. Cell. 1990;62:1189–204.
17. Falkenstein E, Tillmann HC, Christ M, et al. Multiple actions of steroid hormones-a focus on rapid, nongenomic effects. Pharmacol Rev. 2000;52:513–56.
18. Buttgereit F, Brand MD, Burmester GR. Equivalent doses and relative drug potencies for non-genomic glucocorticoid effects: a novel glucocorticoid hierarchy. Biochem Pharmacol. 1999;58:363–8.
19. Lipworth BJ. Therapeutic implications of non-genomic glucocorticoid activity. Lancet. 2000;356:87–9.
20. Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur J Pharmacol. 2008;590:400–8.
21. Ho S, Clipstone N, Timmermann L, et al. The mechanism of action of cyclosporine A and FK506. Clin Immunol Immunopathol. 1996;80:S40–5.

22. Ruhlmann A, Nordheim A. Effects of the immunosuppressive drugs CsA and FK506 on intracellular signaling and gene regulation. Immunobiology. 1997;198:192–206.
23. AKool e-S, Doller A, Babelova A, et al. Molecular mechanisms of TGF beta receptor-triggered signaling cascades rapidly induced by the calcineurin inhibitors cyclosporine A and FK506. J Immunol. 2008;181:2831–45.
24. Eickelberg O, Pansky A, Koehler E, et al. Molecular mechanisms of TGF-(beta) antagonism by interferon (gamma) and cyclosporine A in lung fibroblasts. FASEB J. 2001;15:797–806.
25. Nagano J, Iyonaga K, Kawamura K, et al. Use of tacrolimus, a potent antifibrotic agent, in bleomycin-induced lung fibrosis. Eur Respir J. 2006;27:460–9.
26. Richeldi L, Davies HR, Ferrara G, et al. Corticosteroids for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev. 2003;3:CD002880.
27. Davies HR, Richeldi L, Walters EH. Immunomodulatory agents for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev. 2003;3:CD003134.
28. Miyazaki A, Azuma N, Inase T, et al. A randomized, double-blind, multi-centered controlled trial of cyclosporine A vs. cyclophosphamide with corticosteroid in patients with idiopathic pulmonary fibrosis in Japan. Am Thorac Soc Int Conf 2011. In Denver, USA; 2011.
29. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.

# Chapter 11
# Non-pharmacological Therapy for IPF

## Is Respiratory Care Actually Effective?

**Yukihiro Umeda, Tamotsu Ishizuka, and Takeshi Ishizaki**

**Abstract** Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterized by a poor prognosis and the lack of proven effective treatments. The symptoms and complications of IPF such as dyspnea, exercise intolerance, and depression severely impair patients' quality of life (QOL) and decrease social participation. Although evidence for the benefit of pulmonary rehabilitation (PR) in IPF is limited, it has recently been reported that PR can improve dyspnea and exercise tolerance. Furthermore, exercise training and educational programs may also be effective means of addressing low mood and depression in selected patients with IPF. Long-term oxygen therapy (LTOT) is also considered to improve QOL in patients with IPF. Although LTOT may have no survival benefit, patients with resting hypoxemia, pulmonary hypertension, exercise-induced hypoxemia, or nocturnal hypoxemia should be treated with LTOT to improve QOL. Noninvasive ventilation and nasal high-flow oxygen therapy have been recently used to manage acute respiratory failure complicating IPF. Early use of these techniques might afford the opportunity to avoid tracheal intubation and reduce the high incidence of mortality associated with acute deterioration of respiratory function in IPF. In conclusion, the evidence base informing management strategies for IPF has been growing gradually. It appears that PR may have an important role to play in improving the QOL of patients with IPF, although further research is still needed.

**Keywords** Idiopathic pulmonary fibrosis • Non-pharmacological therapy • Pulmonary rehabilitation • Long-term oxygen therapy • Noninvasive ventilation

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## 11.1 Introduction

Patients with IPF suffer from relentlessly progressive shortness of breath and cough and have a median survival of less than 3 years after diagnosis. Recent studies have shown that some pharmacological strategies may bring about a short-term interruption in the decline in forced vital capacity, but no specific pharmacological therapy has proved consistently to reverse the changes seen in IPF, and improvements are rarely observed. Given the lack of pharmaceutical therapeutic options in IPF, it is important to find other means of improving quality of life (QOL), by reducing the symptoms of dyspnea, improving exercise tolerance, and addressing low mood. Dyspnea, cough, and depression severely impair QOL in IPF and also decrease social participation. Respiratory care aims to improve exercise tolerance, mood, and QOL.

The non-pharmacological treatment of IPF includes pulmonary rehabilitation (PR), long-term oxygen therapy (LTOT), noninvasive ventilation (NIV), end-of-life care, and lung transplantation. In this chapter, we will discuss the pathophysiology of IPF and the evidence that PR, LTOT, and NIV improve QOL in patients affected by the disease.

## 11.2 Exercise Pathophysiology in Idiopathic Pulmonary Fibrosis

In chronic obstructive lung disease (COPD), exercise limitation results from ventilatory constraints, gas exchange abnormalities, peripheral muscle dysfunction, and cardiac dysfunction. Exercise limitation in patients with IPF is a consequence of reduced lung volume, gas exchange abnormalities due to impaired diffusion and ventilation–perfusion (V/Q) inequality, ventilatory muscle weakness, general musculoskeletal deconditioning, and cardiovascular impairment.

In patients with IPF, lung recoil is increased over the entire range of a reduced inspiratory capacity. A diminished tidal volume contributes to elevated physiologic dead space (dead space volume/tidal volume). In normal subjects, physiologic dead space declines during exercise as a result of increased tidal volumes as effort increases. In IPF, however, physiologic dead space does not decline, and breathing frequency must increase to achieve the minute ventilation required to meet increased oxygen demand. As a result, when patients with IPF exercise, the breathing pattern becomes more rapid and shallow.

Hypoxemia typically worsens during exercise in IPF. Factors that may contribute to exercise-induced hypoxemia in IPF include poor recruitment of alveolar capillaries during exercise resulting in an increased red blood cell transit time across the gas exchange surface of the lung and reduced mixed venous partial pressure of oxygen ($P_VO_2$) in the setting of low V/Q ratios and shunt [1]. As pulmonary blood flow increases with exercise, the normal contact time between

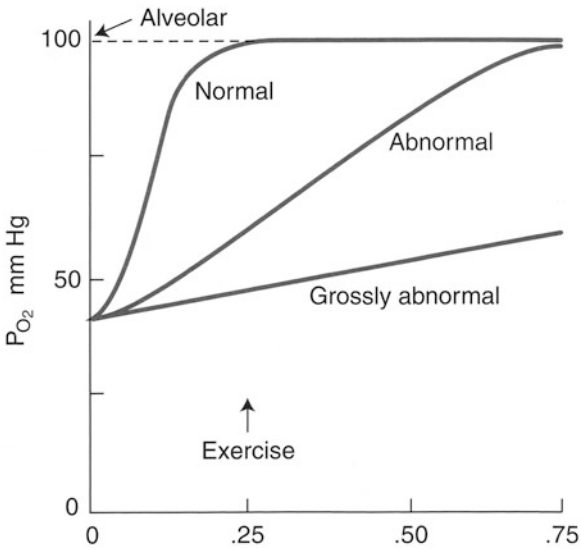


**Fig. 11.1** Oxygen time courses in pulmonary capillary when diffusion is normal and abnormal (e.g., because of thickening of the blood–gas barrier by disease) (Reprinted with permission of Wolters Kluwer Health/Lippincott Williams & Wilkins, West [2])

alveolar gas and capillary erythrocytes, about 0.75 s at rest, is reduced to approximately 0.25 s. The arterial partial pressure of oxygen ($PaO_2$) may not reach the partial pressure of oxygen in alveolar gas before red blood cells leave the pulmonary capillary if oxygen diffusion is impaired (Fig. 11.1) [2]. Consequently, the alveolar–arterial oxygen gradient ($A–aDO_2$) is increased in patients with IPF during exercise. In the majority of those with IPF, although the $P_VO_2$ may be normal at rest, it will likely fall during exercise because of reduced oxygen delivery to the muscles: this reduced $P_VO_2$ results in further elevation of $A–aDO_2$ and causes hypoxemia during exercise.

## 11.3 Symptoms and Complications of IPF

### *11.3.1 Dyspnea*

Dyspnea is common in IPF and is a major contributor to impaired QOL and symptoms of depression [3–5]. The extent of dyspnea is closely related to pulmonary function, peripheral muscle weakness, and activities of daily living (ADL) score [6]. Exercise-induced hypoxemia contributes to dyspnea more in IPF than COPD: oxygen desaturation during the 6-min walk test (6MWT nadir $SpO_2$) independently predicts dyspnea during the test and is reportedly more severe in patients with IPF than COPD [7]. As a result, patients are deterred from engaging in physical activity, need to take frequent rests, and take longer to recover after exertion. Managing dyspnea is therefore an important means of improving QOL in patients with IPF.

### 11.3.2 Exercise Intolerance

Reduced lung volumes and gas exchange abnormalities contribute to exercise intolerance as a result of dyspnea and leg fatigue in patients with IPF. Furthermore, decreased capillary blood volume and hypoxic pulmonary vasoconstriction may also contribute to exercise intolerance as a result of pulmonary hypertension and right heart failure.

In COPD, it has been shown that peripheral muscle dysfunction is also a factor determining exercise intolerance. Similarly, quadriceps force is reduced in patients with IPF and correlates with dyspnea at end-exercise and exercise capacity [8]. Although recent evidence-based guidelines for IPF did not recommend corticosteroid therapy, treatment with corticosteroid and/or immunosuppressants is nonetheless often used to manage refractory cough and rapidly progressive cases. Because steroid-induced myopathy has been reported to impair peripheral muscle function in these patients, corticosteroid therapy may in fact cause a further deterioration in exercise tolerance [9]. Many PR programs include peripheral muscle training, especially in the legs, with the aim of improving exercise tolerance.

### 11.3.3 Mood Disturbance and Depression

Idiopathic pulmonary fibrosis is a lifelong disorder that causes substantial morbidity and mortality. Dyspnea limits mobility and impairs the ability to engage in physical activity, and more than 40 % of patients with an above average dyspnea score have clinically meaningful symptoms of depression [10]. The prevalence of symptoms of depression in patients with interstitial lung disease (ILD) is higher than that in normal older subjects (23–27 % *versus* 9.8 %) [3, 10, 11]. Patients with IPF should be screened routinely for depression, and treatment of depression and management of dyspnea may need to be progressed in parallel to improve QOL.

## 11.4 Pulmonary Rehabilitation

The American Thoracic Society–European Respiratory Society consensus statement defines PR as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors" [12]. Pulmonary rehabilitation is an established therapeutic intervention in COPD, improving exercise tolerance and QOL and reducing hospital admission. Although the

mechanisms of respiratory limitation in IPF differ from COPD, similarities between the clinical consequences (dyspnea, exercise intolerance, fatigue, and depression) suggest that PR may also benefit patients with IPF.

Although evidence for the benefit of PR in IPF is limited compared with COPD, it has recently been reported that PR may result in meaningful short-term benefits in patients with ILD [12]. The recently revised American Thoracic Society–European Respiratory Society–Japanese Respiratory Society–Latin American Thoracic Association evidence-based guidelines for IPF recommend PR for the majority of patients (weak recommendation, low-quality evidence) [13]. Nevertheless, PR is becoming an increasingly important part of the non-pharmacological therapy of IPF.

### *11.4.1 Benefits of Pulmonary Rehabilitation on Exercise Capacity*

Pulmonary rehabilitation programs generally comprise a 5–12-week outpatient program followed by home-based rehabilitation. The main component is exercise training that aims to improve strength and endurance. Endurance training can be achieved simply by walking, or a treadmill or stationary cycle ergometer can be used. Strength training regimens vary substantially between institutions, in terms of the exercise techniques, duration, and intensity.

There have been several reports that exercise tolerance evaluated by the 6-min walk test (6MWT) or endurance time was improved after 6–12-week PR programs [9, 14–20] (Table 11.1). A recent meta-analysis showed that the common effect for change in 6MWT distance was 35.63 m in favor of the PR group in patients with IPF [21], more than 28 m above the expected minimal important difference (MID) [22].

In IPF, exercise-induced hypoxemia is a major cause of exercise intolerance and limits improvements in strength and endurance during PR. Oxygen supplementation can lead to significant improvements in exercise capacity by increasing cardiac output and arterial oxygen content in chronic hypoxemic lung disease [23]. Hallstrand and colleagues reported that the timed walk test distance increased from 271.2 m to 345.6 m when oxygen was administered during the test in patients with IPF and resting peripheral oxygen saturation $>88$ % [24]. Although a recent guideline suggested that the quality of the evidence for the benefit of LTOT in IPF was very low, the benefit of oxygen supplementation during PR appears to be indisputable.

Exercise-induced hypoxemia may also contribute to metabolic acidosis in peripheral muscles. Pulmonary rehabilitation improves sustained submaximal exercise capacity and anaerobic threshold in patients with IPF, and it has been reported that PR reduces exercise-induced lactic acidosis and increases oxidative enzyme activity in peripheral muscles [15].

**Table 11.1** Characteristics and outcomes of studies examining the role of pulmonary rehabilitation in idiopathic pulmonary fibrosis

| Study | Study design | Sample size | Pulmonary function | Duration of PR, number of sessions | Outcomes |
|---|---|---|---|---|---|
| Vainshelboim et al. [14] | RCT, PR *versus* control | $n = 32$ | FVC 66.1 ± 14.8 % pred | 12 weeks, 24 sessions | *PR group* |
| | | | $DL_{CO}$ 48.6 ± 17.2 % pred | | 6MWT distance: 70.4 ± 77.0 m (+14.9 %)† |
| | | | | | $VO_2$ peak: 2.1 ± 2.3 ml/kg/min (+15.4 %)† |
| | | | | | Anaerobic threshold: 2.4 ± 2.4 ml/kg/min† |
| | | | | | mMRC: −0.73 ± 0.8† |
| | | | | | SGRQ total score: −6.9 ± 6.5 points |
| | | | | | *Control group* |
| | | | | | 6MWT distance: −10.6 ± 35.4 m |
| | | | | | $VO_2$ peak: −0.5 ± 2 ml/kg/min |
| | | | | | Anaerobic threshold: −0.72 ± 1.8 ml/kg/min |
| | | | | | mMRC: 0.35 ± 0.7 |
| | | | | | SGRQ total score: 2.8 ± 3.6 points |
| Arizono et al. [15] | Prospective non-randomized, observational study: patients declining to participate were the control group | $n = 53$ | VC 70.8 ± 18.1 % pred | 10 weeks, 20 sessions | *PR group* |
| | | | $DL_{CO}$ 49.7 ± 15.9 % pred | | 6MWT distance: 26.7 m (+6 %)** |
| | | | | | Peak work rate: 5.9 W (+10 %)** |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Anaerobic threshold: 105.7 ml/min (+22 %)** |
| | | | | | Quadriceps force: 8.9 N (+10.7 %)** |
| | | | | | Endurance time: 9.3 min (+163 %)** |
| | | | | | *Control group* |
| | | | | | 6MWT distance: −20.6 m (−4.1 %) |
| | | | | | Peak work rate: −3.5 W (−5.3 %) |
| | | | | | Anaerobic threshold: −93.3 ml/min (−15.2 %) |
| | | | | | Quadriceps force: 3.3 N (+4.0 %) |
| | | | | | Endurance time: −1.1 min (−16.9 %) |
| Jackson et al. [16] | RCT, PR *versus* control | $n = 21$ | FVC 60 ± 11 % pred | 12 weeks, 24 sessions | *PR group* |
| | | | $DL_{CO}$ 44 ± 11 % pred | | 6MWT distance: −6.2 m (−1.7 %) |
| | | | | | Exercise time on cycle ergometer: 118 s (+64.1 %)* |
| | | | | | *Control group* |
| | | | | | 6MWT distance: −15.3 m (−4.5 %) |
| | | | | | Exercise time on cycle ergometer: 4 s (+2.8 %) |

(continued)

**Table 11.1** (continued)

| Study | Study design | Sample size | Pulmonary function | Duration of PR, number of sessions | Outcomes |
|---|---|---|---|---|---|
| Holland et al. [17] | Prospective, non-randomized, controlled study: patients with non-IPF ILD as the control group | $n = 25$ IPF patients | FVC 76.4 ± 20.3 % pred | 8 weeks, 16 sessions | 6MWT distance: 21 ± 58 m (+5.7 %)* |
| | | | $DL_{CO}$ 48.5 ± 19.1 % pred | | CRDQ dyspnea score: 2.7 ± 5.6 points (+17.6 %)* |
| Kozu et al. [18] | Prospective, non-randomized, uncontrolled study: no control group | $n = 65$ | *FVC* (% pred) | 8 weeks, 16 sessions | *6MWT distance* |
| | | | MRC grade 2: 83 ± 11 | | MRC grade 2: 31 m (+7 %)** |
| | | | MRC grade 3: 67 ± 13 | | MRC grade 3: 19 m (+5 %)* |
| | | | MRC grade 4: 60 ± 16 | | MRC grade 4: 9 m (+3 %) |
| | | | MRC grade 5: 51 ± 11 | | MRC grade 5: 0 m (−1 %) |
| | | | *$DL_{CO}$* (% pred) | | *Mental health score of SF-36* |
| | | | MRC grade 2: 58 ± 20 | | MRC grade 2: 6.9 points (+11.0 %)** |
| | | | MRC grade 3: 35 ± 10 | | MRC grade 3: 8.5 points (+19.8 %) |
| | | | MRC grade 4: 28 ± 12 | | MRC grade 4: 2.4 points (+5.7 %) |
| | | | MRC grade 5: 21 ± 8 | | MRC grade 5: −2.7 points (−7.7 %) |

| | | | | | |
|---|---|---|---|---|---|
| Kozu et al. [9] | RCT, PR in IPF *versus* MRC grade-matched COPD | $n = 45$ IPF patients | FVC 68.6 ± 16 % pred | 8 weeks, 16 sessions | 6MWT distance: 16.2 (7.1 to 25.4) m (+5.0 %)** |
| | | | $DL_{CO}$ 38.8 ± 20 % pred | | Quadriceps force: 2.0 (0.9 to 3.1) kg (+9.8 %)** |
| | | | | | ADL score: 1.1 (0.8 to 1.3) (+29.7 %)** |
| | | | | | MRC grade: −0.4 (−0.6 to −0.3) (−13.3 %)** |
| Swigris et al. [19] | Prospective, non-randomized, controlled study: patients with COPD in previous study as control group | $n = 21$ IPF patients | FVC 73 ± 2 % pred | 6–8 weeks, 18 sessions | 6MWT distance: 61.6 ± 41.1 m (+22.3 %)* |
| | | | $DL_{CO}$ 38 ± 13 % pred | | Fatigue severity scale: −1.5 ± 0.5 (−35.7 %)* |
| Nishiyama et al. [20] | RCT, PR *versus* control | $n = 30$ | FVC 66.1 ± 13.2 % pred | 10 weeks, 20 sessions | *PR group* |
| | | | | | 6MWT distance: 42 m (+10.9 %)* |
| | | | $DL_{CO}$ 59.4 ± 16.7 % pred | | SGRQ total score: −2.9 points (−5.8 %)* |
| | | | | | *Control group* |
| | | | | | 6MWT distance: −4 m (−0.8 %) |
| | | | | | SGRQ total score: 3.1 points (+8.2 %) |

Abbreviations: *PR* pulmonary rehabilitation, *RCT* randomized controlled trial, *FVC* forced vital capacity, *pred* predicted, *6MWT distance* 6-min walk test distance, $VO_2$ oxygen consumption, *SGRQ* St. George's Respiratory Questionnaire, $DL_{CO}$ diffusing capacity of the lung for carbon monoxide, *IPF* idiopathic pulmonary fibrosis, *ILD* interstitial lung disease, *mMRC* modified Medical Research Council, *CRDQ* Chronic Respiratory Disease Questionnaire, *COPD* chronic obstructive pulmonary disease, *ADL* activities of daily living

*$P < 0.05$ *versus* baseline, **$P < 0.01$ *versus* baseline, †$P < 0.05$ *versus* control, ††$P < 0.01$ *versus* control

Quadriceps force, a predictor of exercise capacity, is also reduced in patients with IPF [8]. The training of peripheral muscles, especially in the lower extremities, as part of PR is reported to improve exercise tolerance significantly (by a mean of 10 %) [15], although substantially greater improvements are seen in COPD (23 %) [9]. Exercise training as part of PR is also reported to reduce heart rate at maximum iso workload, suggesting that a cardiovascular adaptation to training can be achieved [25], but it is not clear whether exercise training improves peak oxygen consumption in IPF [14, 25]. As exercise tolerance is limited by dyspnea and exercise-induced hypoxemia in many cases of IPF, exercise strength might not reach the peak oxygen consumption in moderate or severe cases.

Pulmonary rehabilitation in IPF appears to have beneficial effects on exercise tolerance immediately after the program, yielding improvements in muscle strength, the extent of exercise-induced lactic acidosis in peripheral muscle, and cardiovascular adaptation.

### *11.4.2 Benefits of Pulmonary Rehabilitation on Dyspnea*

Dyspnea is common in IPF and one of the most disabling symptoms of the disease. Most of the research that has examined the influence of PR on dyspnea in IPF has been questionnaire based, using the Medical Research Council (MRC) dyspnea grade, Chronic Respiratory Disease Questionnaire (CRDQ), or Mahler's transition dyspnea index.

Several studies have reported that dyspnea improved after 6–12 weeks of PR [9, 14, 17, 26], although one randomized trial found that PR did not improve dyspnea [20]. Holland and colleagues reported that dyspnea, assessed by the CRDQ, improved immediately after an 8-week PR program [17], and the extent of the improvement (2.7 points) exceeded that of the expected MID (2.5 points) [27]. A recent meta-analysis found that the common effect (standard mean difference) for change in dyspnea was −0.68 in favor of the PR group in IPF (95 % confidence interval [CI] −1.12 to −0.25) [21]. Based on these findings, it appears that PR may indeed have the potential to alleviate dyspnea in patients with IPF.

### *11.4.3 Benefits of Pulmonary Rehabilitation on Quality of Life*

One randomized controlled trial has examined the influence of PR on QOL in patients with IPF: QOL measured using the St. George's Respiratory Questionnaire was improved in those who underwent PR [20]. A recent meta-analysis has also provided moderately strong evidence that PR improves QOL in patients with IPF (standard mean difference 0.59, 95 % CI 0.14–1.03) [21].

### 11.4.4 Benefits of Pulmonary Rehabilitation on Anxiety and Depression

In patients with COPD, the improvements in respiratory symptoms achieved after PR are generally accompanied by reduced symptoms of anxiety and depression and improved patient perceptions of the positive consequences of illness. In contrast, little is known about the benefit of PR on depression in patients with IPF. Swigris and colleagues proposed that PR benefits patients with IPF by interrupting several pathways that lead to undesirable sequelae or comorbidities (Fig. 11.2). Various emotional health issues including fear, anxiety, and impaired QOL are likely consequences of having to live with an incurable disease. Thus, any improvements in walking distance and dyspnea after PR may also benefit patients with IPF by reducing tachypnea, anxiety, and fear [28]. Patient education, including breathing techniques, coping strategies, and pacing and managing the activities of daily living, is also an important component of PR [29]. These strategies may achieve perception of self-efficacy, social persuasion, and positive mood. Two studies have reported that depression score or mental health score improved after a PR program that included educational sessions in patients with ILD [30, 31]. In contrast, Kozu and colleagues reported that PR only improved mental health – assessed by SF-36 – in patients with IPF and MRC grade 2 symptoms of dyspnea [18]. It appears that the exercise and educational components of PR programs effectively alleviate low-mood disturbance and depression in selected patients with IPF.

### 11.4.5 Predicting Positive Response to Pulmonary Rehabilitation

There are no guidelines recommending when PR should be offered. Although several studies have examined the relationship between baseline disease severity in IPF and improvement in exercise capacity after PR, findings have been inconsistent. Patients with less severe disease might be expected to achieve greater benefits from PR, because severe dyspnea, cough, and exercise-induced hypoxemia may prevent patients from engaging sufficiently in physical training. Moreover, a higher proportion of subjects with severe dyspnea would likely be taking corticosteroid therapy [18], and it is possible that the effects of the training regimen were diminished by corticosteroid-induced muscle dysfunction. Kozu and colleagues reported that patients with MRC grade 2 or 3 dyspnea at enrollment showed significant improvements in 6MWT distance and health status (measured by SF-36) after PR, but those with MRC dyspnea grade 4 or 5 showed little or no improvement [18]. Furthermore, Holland and colleagues have reported that greater improvements in 6MWT distance after PR were associated with larger baseline forced vital capacity, less exercise-induced desaturation, and lower right ventricular systolic pressure in patients with IPF [17].

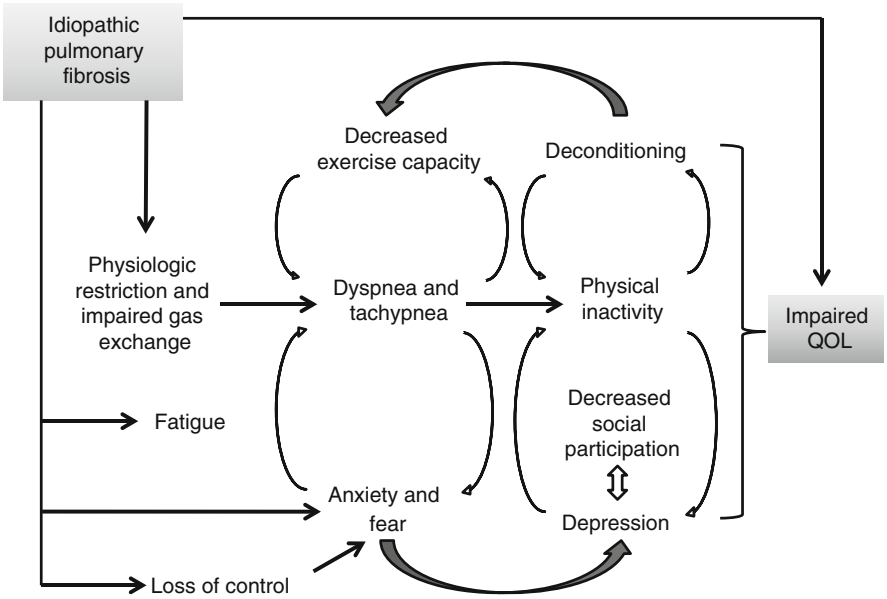


**Fig. 11.2** Pathways to sequelae or comorbidities in idiopathic pulmonary fibrosis (Reprinted with permission of Elsevier, Swigris et al. [28])

Three studies have reported that the greatest improvements in 6MWT distance after PR were achieved in those who could cover the shortest distance at baseline [26, 30, 31], suggesting that the patients with the most severe respiratory impairment could be expected to benefit more from PR. These studies, however, had some limitations. First, the subjects were diagnosed with a variety of ILDs, although the findings of one study were not influenced by ILD subtype (IPF or non-IPF) [30]. Second, two were retrospective cohort studies [26, 31], and enrollment shortly after acute exacerbation might have influenced the extent of the improvements detected in patients with more severe respiratory impairment. Intention-to-treat analysis was used in the one prospective study, so the findings may be insufficiently generalizable to patients with more severe respiratory impairment [30].

Taken together, the findings of these studies suggest that early referral to a PR program is necessary to maximize the benefits for patients with IPF, and an intensive supervised PR program is likely more appropriate for patients with severely impaired physical function.

### *11.4.6 Long-Term Benefits of Pulmonary Rehabilitation*

Functional improvements after PR are maintained for over 6 months in patients with COPD [9]. In contrast, little is known about the long-term benefits of PR in

patients with IPF: as respiratory failure is relentlessly progressive in IPF, it may not be possible for these patients to achieve long-term benefits [9, 25]. Kozu and colleagues reported that although significant improvements in dyspnea, muscle force, exercise capacity, and ADL score were observed in patients with IPF immediately after PR, only the benefits on ADL were evident 6 months later [9]. However, there has been a more recent report that long-term improvements in 6MWT distance, physical activity, QOL, and depression could still be observed 6 months after PR in patients with IPF or non-IPF ILD, although 28 % of the patients were lost to follow-up [30]. A controlled study is required to fully examine this issue.

To maintain long-term improvements in IPF, healthcare providers should tailor PR to each patient. For example, the duration of the PR program likely plays an important role, although there is no consensus on how long a PR program should be [12]. Salhi and colleagues reported that 29 patients with restrictive lung diseases, including 11 with ILD, who completed a 24-week PR program had significant improvements in 6MWT distance and dyspnea 12 and 24 weeks later (6MWT distance was $321 \pm 155$ m at inclusion, $400 \pm 184$ m at 12 weeks, and $428 \pm 211$ m at 24 weeks) [32]. As longer programs might produce greater gains and longer maintenance of benefits, the optimal duration of PR for an individual could be considered the longest possible [12]. In addition, better adherence and social support, and control of underlying disease and comorbidities, may also be important factors in the maintenance of benefits.

## 11.5 Long-Term Oxygen Therapy

There is little evidence that LTOT has a survival benefit in patients with IPF. One retrospective cohort study of IPF patients showed that LTOT had no survival benefit after adjusting for age, sex, diffusing capacity of the lung for carbon monoxide, alveolar volume, and evidence of disease progression [33]. However, because a survival benefit has been demonstrated in patients with COPD [34, 35], recent guidelines for IPF recommend that "patients with IPF and clinically significant resting hypoxemia should be treated with LTOT (strong recommendation, very low quality of evidence)" based on the indirect evidence from patients with COPD [13].

Exercise-induced hypoxemia is a major factor limiting exercise tolerance in IPF, and oxygen supplementation can lead to significant improvements in exercise capacity even in patients without hypoxemia at rest [24]. In addition, nocturnal hypoxemia is reportedly common in patients with IPF and impairs daytime QOL [36]. In the latter study, participants' mean daytime capillary oxygen concentration was 69.8 mmHg, and none were receiving overnight oxygen therapy at inclusion. Overnight oxygen therapy may be the best way of addressing nocturnal hypoxemia in patients without daytime hypoxemia.

The prevalence of pulmonary hypertension (PH) ranges from 32 to 84 % in patients with IPF. It arises as a consequence of vascular obstruction, destruction from parenchymal fibrosis, pulmonary hypoxic vasoconstriction, and vascular remodeling due to overexpression of cytokines and growth factors [37]. As it is thought that hypoxic vasoconstriction is one of the most important contributors to PH in IPF, correction of hypoxemia is the only recommended strategy [38]; however, there is no evidence that LTOT has a survival benefit in patients with IPF and PH. It should be noted that even if the pulmonary hemodynamic status of a patient with IPF is normal at rest, significant PH may arise during exercise [39, 40]. It has been reported that oxygen supplementation does not influence exercise-induced PH in IPF, suggesting that hypoxic vasoconstriction may not be the main cause of any acute increase in pulmonary arterial pressure during exercise after all [40]. Poor recruitment of alveolar capillaries during exercise may also contribute to severe hypoxemia as well as PH.

In summary, patients with IPF and resting hypoxemia or PH should be treated with LTOT to improve symptoms and QOL, even though it may not have a survival benefit. Furthermore, physicians should assess the extent of exercise-induced hypoxemia and nocturnal hypoxemia, to assess the need for intermittent or overnight oxygen therapy.

## 11.6 Noninvasive Ventilation and Nasal High-Flow Oxygen Therapy

Patients with IPF admitted to the intensive care unit for invasive mechanical ventilation as a result of acute respiratory failure have a very poor prognosis; the mortality rate is reportedly approximately more than 80 % under these circumstances [41]. The guidelines for IPF recommend that "the majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, but mechanical ventilation may be a reasonable intervention in a minority (weak recommendation, low-quality evidence)" [13].

Nonetheless, NIV (including noninvasive positive-pressure ventilation and continuous positive airway pressure [CPAP]) was recently recognized as a potentially effective means of avoiding intubation and reducing mortality in selected patients with acute respiratory failure and IPF. Vianello and colleagues, however, reported that the mortality rate of patients with IPF treated with NIV for acute respiratory failure was 85 %, consistent with that of patients who were invasively ventilated [41, 42]. Yokoyama and colleagues reported that in a cohort of 11 patients treated with NIV for an acute exacerbation of IPF, 90-day mortality was superior to patients in a different report of invasive mechanical ventilation (54.5 % compared with 81.8 %) and that six of 11 patients who failed NIV died of progressive respiratory failure within 3 months [43, 44]. Although these two retrospective studies examined small cohorts, early NIV may nonetheless be a more favorable

option than invasive ventilation for acute respiratory failure in IPF, as NIV may reduce the risk of ventilator-associated pneumonia, particularly as these patients are also generally treated with corticosteroids or other immunosuppressants.

Nasal high-flow oxygen therapy (NHF) is a relatively new technique developed to treat type 1 acute respiratory failure. Adults reportedly find NHF more comfortable than NIV, even though NHF may not improve oxygenation to such an extent [45]. NHF can provide humidified gas flow at a rate of up to 70 L/min and control the fraction of inspired oxygen up to 1.0. Nevertheless, as NHF washes out the upper respiratory tract dead space, the technique could be particularly suitable for IPF due to the large physiologic dead space (dead space volume/tidal volume). A recent study reported that NHF led to an increase in airway pressure amplitude and reductions in breathing rate, minute volume, and the arterial partial pressure of $CO_2$ in patients with IPF [46]. This emerging evidence base may mean that NHF becomes an increasingly popular option for the management of early-phase acute respiratory failure in IPF.

In patients with COPD, it is reported that NIV techniques such as CPAP, pressure support ventilation, and proportional-assist ventilation improve exercise performance [47–49]. However, it is not known whether NIV improves exercise performance in IPF. In one small study, proportional-assist ventilation improved exercise tolerance, breathlessness, and cardiac effort in ten patients with IPF [50]. As physiologic dead space does not decline during exercise in patients with IPF, the breathing pattern during exercise becomes more rapid and shallow. It is thought that NIV improves exercise tolerance by increasing tidal volume and reducing physiologic dead space: NIV might therefore be a means of augmenting PR in selected patients.

## 11.7 Conclusions

Respiratory care for IPF is an effective means of improving symptoms, comorbidities, and QOL, although there are no survival benefits. The attending physician should understand the pathophysiology of IPF to allow balanced judgments to be made about the indication for each therapeutic option. As the evidence base for the benefits of non-pharmacological therapies for IPF is limited, large, prospective, and preferably randomized studies are urgently needed.

## References

1. Schwarz MI, King Jr TE. Physiology of interstitial lung disease. In: Interstitial lung disease. 4th ed. London: BC Decker Inc; 2003. p. 54–74.
2. West JB. Diffusion. In: Respiratory physiology: the essentials. 9th ed. Baltimore: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. p. 24–35.

3. De Vries J, Kessels BL, Drent M. Quality of life of idiopathic pulmonary fibrosis patients. Eur Respir J. 2001;17:954–61.
4. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax. 2005;60:588–94.
5. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? Respir Med. 2005;99:408–14.
6. Kozu R, Jenkins S, Senjyu H. Evaluation of activity limitation in patients with idiopathic pulmonary fibrosis grouped according to Medical Research Council dyspnea grade. Arch Phys Ned Rehabil. 2014;95:950–5.
7. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Ogawa T, et al. Dyspnoea at 6-min walk test in idiopathic pulmonary fibrosis: comparison with COPD. Respir Med. 2007;101:833–8.
8. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Ogawa T, Watanabe F, et al. Quadriceps weakness is related to exercise capacity in idiopathic pulmonary fibrosis. Chest. 2005;127:2028–33.
9. Kozu R, Senjyu H, Jenkins SC, Mukae H, Sakamoto N, Kohno S. Differences in response to pulmonary rehabilitation in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Respiration. 2011;81:196–205.
10. Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, Collard HR. Depression and functional status are strongly associated with dyspnea in interstitial lung disease. Chest. 2011;139:609–16.
11. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. Br J Psychiatry. 1999;174:307–11.
12. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188:e13–64.
13. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
14. Vainshelboim B, Oliveira J, Yehoshua L, Weiss I, Fox BD, Fruchter O, et al. Exercise training-based pulmonary rehabilitation program is clinically beneficial for idiopathic pulmonary fibrosis. Respiration. 2014;88:378–88.
15. Arizono S, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, et al. Endurance time is the most responsive exercise measurement in idiopathic pulmonary fibrosis. Respir Care. 2014;59:1108–15.
16. Jackson RM, Gómez-Marín OW, Ramos CF, Sol CM, Cohen MI, Gaunaurd IA, et al. Exercise limitation in IPF patients: a randomized trial of pulmonary rehabilitation. Lung. 2014;192:367–76.
17. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. Respir Med. 2012;106:429–35.
18. Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16:1196–202.
19. Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, et al. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. Respir Care. 2011;56:783–9.
20. Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008;13:394–9.
21. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2014;10:CD006322.
22. Swigris JJ, Wamboldt FS, Behr J, du Bois RM, King TE, Raghu G, et al. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax. 2010;65:173–7.

23. Morrison DA, Stovall JR. Increased exercise capacity in hypoxemic patients after long-term oxygen therapy. Chest. 1992;102:542–50.
24. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J. 2005;25:96–103.
25. Holland AE, Hill CJ, Conron M, Munro P, McDonald CF. Short term improvement in exercise capacity and symptoms following exercise training in interstitial lung disease. Thorax. 2008;63:549–54.
26. Ferreira A, Garvey C, Connors GL, Hilling L, Rigler J, Farrell S, et al. Pulmonary rehabilitation in interstitial lung disease: benefits and predictors of response. Chest. 2009;135:442–7.
27. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10:407–15.
28. Swigris JJ, Brown KK, Make BJ, Wamboldt FS. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. Respir Med. 2008;102:1675–80.
29. Kenn K, Gloeckl R, Behr J. Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis–a review. Respiration. 2013;86:89–99.
30. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med. 2014;108:203–10.
31. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schönheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. Eur Respir J. 2013;42:444–53.
32. Salhi B, Troosters T, Behaegel M, Joos G, Derom E. Effects of pulmonary rehabilitation in patients with restrictive lung diseases. Chest. 2010;137:273–9.
33. William W, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med. 2000;161:1172–8.
34. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med. 1980;93:391–8.
35. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet. 1981;1:681–6.
36. Clark M, Cooper B, Singh S, Cooper M, Carr A, Hubbard R. A survey of nocturnal hypoxaemia and health related quality of life in patients with cryptogenic fibrosing alveolitis. Thorax. 2001;56:482–6.
37. Pitsiou G, Papakosta D, Bouros D. Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. Respiration. 2011;82:294–304.
38. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53:1573–619.
39. Weitzenblum E, Ehrhart M, Rasaholinjanahary J, Hirth C. Pulmonary hemodynamics in idiopathic pulmonary fibrosis and other interstitial pulmonary diseases. Respiration. 1983;44:118–27.
40. Pouwels-Fry S, Pouwels S, Fournier C, Duchemin A, Tillie-Leblond I, Le Tourneau T, et al. Effects of oxygen on exercise-induced increase of pulmonary arterial pressure in idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25:133–9.
41. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. Respir Med. 2008;102:1355–9.

42. Vianello A, Arcaro G, Battistella L, Pipitone E, Vio S, Concas A, et al. Noninvasive ventilation in the event of acute respiratory failure in patients with idiopathic pulmonary fibrosis. J Crit Care. 2014;29:562–7.
43. Yokoyama T, Kondoh Y, Taniguchi H, Kataoka K, Kato K, Nishiyama O, et al. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2010;49:1509–14.
44. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J. 2006;27:143–50.
45. Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). BMC Anesthesiol. 2014;14:66.
46. Bräunlich J, Beyer D, Mai D, Hammerschmidt S, Seyfarth HJ, Wirtz H. Effects of nasal high flow on ventilation in volunteers, COPD and idiopathic pulmonary fibrosis patients. Respiration. 2013;85:319–25.
47. O'Donnell DE, Sanii R, Younes M. Improvement in exercise endurance in patients with chronic airflow limitation using continuous positive airway pressure. Am Rev Respir Dis. 1988;138:1510–14.
48. Keilty SEJ, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. Thorax. 1994;49:990–4.
49. Van't Hul A, Kwakkel G, Gosselink R. The acute effects of noninvasive ventilatory support during exercise on exercise endurance and dyspnea in patients with chronic obstructive pulmonary disease: a systematic review. J Cardiopulm Rehabil. 2002;22:290–7.
50. Moderno EV, Yamaguti WP, Schettino GP, Kairalla RA, Martins MA, Carvalho CR, et al. Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients. Respir Med. 2010;104:134–41.

# Chapter 12
# Pharmacotherapy of Acute Exacerbation of IPF (Corticosteroids, Immunosuppressants, and Direct Hemoperfusion with Polymyxin)

## Are High-Dose Steroid Therapy, Other Immunosuppressant Therapy, and PMX Therapy (Often Used in Japan) Really Effective?

**Masayuki Itoh**

**Abstract** Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) carries a rather poor prognosis. The condition has been treated using high-dose steroids, immunosuppressants (cyclosporine A, tacrolimus, cyclophosphamide, azathioprine), anticoagulants (heparin, recombinant human soluble thrombomodulin), neutrophil elastase inhibitors (sivelestat), etc. Recently, direct hemoperfusion using a polymyxin B-immobilized fiber column (PMX-DHP) has been used increasingly in combination with these medications. However, most reports on the efficacy of these treatment methods are based on small-scale retrospective studies, and there is no report of randomized controlled trials (RCTs) demonstrating their efficacy. Thus, there is little scientific evidence of the efficacy of these treatment methods, and no AE-IPF treatment method of high evidence level is included in the guidelines available at present. It would be desirable to facilitate clarification of the pathophysiology of AE-IPF and to carry out RCTs with the cooperation of multiple facilities.

**Keywords** Acute exacerbation of idiopathic pulmonary fibrosis • Steroid pulse therapy • Immunosuppressive therapy • Direct hemoperfusion using a polymyxin B-immobilized fiber column • Anticoagulation therapy

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## 12.1 Introduction

Acute exacerbation of IPF (idiopathic pulmonary fibrosis) (AE-IPF) is a condition that carries a rather poor prognosis, with a 1-month mortality rate of 60 % and 3-month mortality rate of 67 % [1]. AE-IPF was first reported from Japan [2], with numerous reports also published subsequently from this country. Because the incidence of AE-IPF is higher in the Japanese population than in Western populations, it is considered that the Japanese might be genetically predisposed to the development of AE-IPF [3, 4]. Many of the past reports on the treatment of AE-IPF are from Japan; however, the exact pathophysiology of AE-IPF remains unclarified. Furthermore, most published reports on the treatment of this disease are based on empirical treatments, with no evidence of the effectiveness of any treatment based on randomized controlled trials (RCT). Meanwhile, since organizing diffuse alveolar damage (DAD) is known as a pathological feature common to both AE-IPF and acute respiratory distress syndrome (ARDS), drug therapy regimens employed for the treatment of ARDS are sometimes applied to patients with AE-IPF. However, postmortem examination of patients with AE-IPF often reveals not only DAD but also pulmonary thromboembolism, alveolar bleeding, etc. [5]. Thus, AE-IPF may be considered as a mixture of diverse pathologic conditions. Furthermore, because modification of the clinical condition by opportunistic infection, diabetes mellitus, pneumothorax, etc., arising from high-dose steroid and immunosuppressant treatment, can occur additionally, treatment of AE-IPF tends to become complex enough to require the use of many drugs. This chapter will summarize past reports on the treatment of AE-IPF and discuss its treatment, focusing on current drug therapies.

## 12.2 Steroid Therapy

High-dose steroid therapy (steroid pulse therapy) was developed originally for the control of host rejection to organ transplants and the treatment of collagen disease [6]. Subsequently, it began to be used also for the treatment of AE-IPF. Global guidelines (official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis) justify high-dose steroid therapy for AE-IPF, although the evidence level is low [7]. Japanese guidelines recommend 3-day treatment with 1 g methylprednisolone daily.

According to the paper published by Kondoh et al., the first report on this therapy, treatment of 3 AE-IPF patients with methylprednisolone 1 g for 3 days followed by tapering of the steroid dose led to alleviation of the clinical symptoms and improvement of the $PaO_2/FiO_2$ (P/F) ratio [2]. However, Song et al. reported that following administration of high-dose steroid therapy to 13 of 90 patients with AR-IPF, only 7 survived, and there was no remarkable improvement of the survival rate [8]. In the patient series reported by Al-Hameed et al., of the 25 patients with AE-IPF to whom

high-dose steroid therapy was applied (in combination with cyclophosphamide in 8 patients), 24 died [9]. Usui et al. conducted a retrospective survey of 52 patients with acute exacerbation of interstitial pneumonia (including cases of IPF) and concluded that high-dose steroid therapy did not improve the survival rate [10]. On the other hand, according to the report by Takahashi et al., who analyzed 17 cases of AE-IPF receiving high-dose steroid therapy, the mean survival time (MST) was 1.2 months in patients showing no improvement of the alveolar-arterial oxygen difference (A-a$DO_2$), while the MST was prolonged to 4.5 months in patients showing transient improvement of the A-a$DO_2$ and to 24.4 months in patients showing sustained improvement of the A-a$DO_2$ for 3 months, thus concluding that improvement of the A-a$DO_2$ may be a useful predictor of the responses to high-dose steroid therapy [11]. Thus, all previous reports on the outcome of high-dose steroid therapy for AE-IPF are based on retrospective surveys, and no RCT has been carried out. Furthermore, high-dose steroid therapy is associated with a high risk for adverse reactions and complications, and there is no consensus on whether it should be applied definitely [12–14].

AE-IPF is characterized by organizing DAD as a pathologic feature resembling that in ARDS. Therefore, an RCT of steroid therapy for ARDS may provide information useful for the treatment of AE-IPF [15–17]. However, even though a similarity of the pathologic changes is noted, ARDS without preexisting lung lesions and ARDS attributable to extrapulmonary factors should be considered as conditions differing from AE-IPF in terms of the mechanism of onset.

In the RCT reported by Bernard et al., treatment with methylprednisolone (30 mg/kg) every 6 h during the acute period after the onset of ARDS resulted in no difference in the death rate from that in the placebo group and no improvement of the clinical indicators [18]. In the RCT reported by Annane et al., hydrocortisone 50 mg was administered every 6 h and 9-α-fludrocortisone 50 μg was administered once daily, both for 7 days soon after the onset of ARDS [19]. The length of time until weaning from respiratory support was longer in the steroid therapy group than that in the placebo group; however, there was no difference in the death rate between the two groups. In the RCT conducted by ARDSnet, treatment with medium-dose methylprednisolone (dose level reduced gradually from 2 mg/kg/day) from Day 7 to Day 28 after the onset of ARDS resulted in no difference in the death rate from that in the placebo group. Weaning from respiratory support was achieved earlier in the methylprednisolone treatment group, although auxiliary ventilation was often needed after weaning. The death rates at 60 days and 180 days were higher in the group that had begun to receive methylprednisolone on Day 14 after onset than that in the placebo group [20].

In contrast to these reports, Meduri et al. reported that treatment with methylprednisolone soon after the onset of ARDS at a medium initial dose level (1 mg/kg/day, gradually reduced over time) resulted in shortening of the duration of mechanical ventilation and length of stay in the ICU as compared to the placebo group, associated with a reduction of the death rate [21]. The same investigators reported that treatment with methylprednisolone from Day 7 onward after the onset of ARDS at gradually reducing dose levels from 2 mg/kg/day resulted in improvement

of the lung injury score (LIS), P/F ratio, and multiple organ dysfunction score (MODS) and reduction of the death rate as compared to the placebo group [22]. A systematic review summarizing these reports concluded that treatment of ARDS with methylprednisolone at low to medium dose levels (0.5–2.5 mg/kg) initiated within 14 days after the onset can lower the death rate without increasing the incidence of adverse reactions [15, 16].

At present, high-dose steroid therapy (methylprednisolone 1 g/day, 3 days) is often used for the treatment of AE-IPF. However, if data from RCTs on ARDS are taken into account, it would seem rational to administer methylprednisolone at low to medium dose levels (0.5–2.5 mg/kg) in the acute stage or within 14 days after the onset of ARDS as another alternative of treatment.

## 12.3 Immunosuppressants

Immunosuppressants such as cyclosporine A, tacrolimus, cyclophosphamide, and azathioprine are often used in combination with steroids for the treatment of AE-IPF. Cyclosporine A is a cyclic polypeptide antibiotic produced by fungi and has been shown to exert immunosuppressive activity through inhibition of interleukin-2 (IL-2) production by helper T cells and other mechanisms. According to a retrospective study conducted by Inase et al., 4 of 7 patients with AE-IPF survived following combined therapy with high-dose steroid (methylprednisolone 1 g/day, 3 days) + cyclosporine A (1.0–2.0 mg/kg, trough 100–150 ng/ml), while all of the patients treated with high-dose steroid therapy alone without concomitant cyclosporine A treatment died [23]. In a retrospective study conducted by Homma et al., the MST was 1.7 months in the prednisolone-alone treatment group ($n = 35$), shorter than the 9.9 months recorded in the combined prednisolone + cyclosporine A (50–200 mg) treatment group ($n = 9$) [24]. In a retrospective study reported by Sakamoto et al., comparison of the prognosis between 11 AE-IPF patients treated with high-dose steroid therapy alone and 11 AE-IPF patients treated with high-dose steroid + cyclosporine A (1–2 mg/kg) therapy revealed a longer MST in the combined treatment group (502 days) than in the uncombined treatment group (60 days) [25]. However, a retrospective study by Okamoto et al. revealed no difference in the MST between the 8 AE-IPF patients treated with steroid + cyclosporine A therapy and 9 AE-IPF patients treated with a steroid alone [26].

Cyclophosphamide is an immunosuppressant agent that is used for the control of host rejection of organ transplant and treatment of collagen vascular diseases. According to Japanese guidelines, repetition of treatment with cyclophosphamide (500 mg/day) in combination with a steroid at intervals of 1–2 weeks is recommended in the treatment of AE-IPF, although the evidence level is low. As an example of cyclophosphamide therapy for AE-IPF, there is one report of a patient with AE-IPF developing after influenza vaccination, whose life was successfully saved by treatment with a combination of a high-dose steroid (methylprednisolone 1 g/day, 3 days), cyclophosphamide (500 mg/day), sivelestat, and

polymyxin B-immobilized fiber column hemoperfusion [27]. However, according to the report by Ambrosini et al., 4 of the 5 AE-IPF patients who received treatment with high-dose steroids in combination with cyclophosphamide or azathioprine died 13 days after the start of treatment, on average [28]. Also according to the report by Parambil et al., all of the 7 AE-IPF patients (including 2 patients receiving treatment with steroids + cyclophosphamide) died [29].

Tacrolimus is a drug that suppresses the proliferation and differentiation of cytotoxic T lymphocytes through inhibition of IL-2 formation. Horita et al. reported a retrospective study in which combined administration of steroids with tacrolimus served as an effective strategy for treating AE-IPF [30]. In their study, all patients received high-dose steroid therapy (methylprednisolone 1 g/day, 3 days), with some additionally receiving serial intravenous infusion of tacrolimus for 5–14 days (target blood level 20 ng/ml), followed by oral tacrolimus treatment (target blood level 2 ng/ml). The P/F ratio and blood lactate dehydrogenase (LDH) level improved, and the MST was prolonged in the combined treatment group ($n = 5$) as compared to the uncombined treatment group ($n = 10$) (more than 92 days vs. 38 days, $p < 0.05$).

## 12.4 Anticoagulant Therapy

IPF is characterized by enhanced blood coagulability due to vascular endothelial disorders [31–34]. Kubo et al. reported the results of an RCT of anticoagulant therapy using warfarin in IPF patients receiving oral steroid therapy ($n = 56$) [35]. During the observation period, 60 % of the patients were hospitalized because of exacerbation of respiratory failure, which was often attributable to AE-IPF. During the hospital stay, the anticoagulant therapy group received low-molecular-weight heparin in place of warfarin. The death rate due to AE-IPF was lower in the anticoagulation treatment group than in the anticoagulant drug-untreated group (18 % vs. 71 %, $P = 0.008$), and elevation of the blood D-dimer level was associated with the death rate. However, Simon-Blancal et al. reported that the prognosis of patients with AE-IPF was not improved by combined steroid + low-molecular-weight heparin treatment [36]. Furthermore, Noth et al. reported, based on an RCT in patients with IPF, a higher death rate in the warfarin treatment group as compared to that in the placebo group [37].

Thrombomodulin is known to have high mobility group box-1 (HMGB1)-inhibitory activity in addition to anticoagulant activity [38, 39]. In recent years, a number of reports have been published from Japan on the results of treatment with AE-IPF with recombinant human soluble thrombomodulin (rhTM) [40–42]. Taniguchi et al. reported that when 40 patients with AE-IPF were treated with a high-dose steroid (methylprednisolone 1 g/day, 3 days) + cyclosporine, accompanied by 6-day rhTM treatment (0.06 mg/kg/day) in 20 of these patients, the death rate at 3 months was lower in the rhTM-treated group than that in the rhTM-untreated group ($HR = 0.17$, $P = 0.015$) [40]. Isshiki et al. treated 42 AE-IPF patients with a high-

dose steroid (methylprednisolone 1 g/day, 3 days), accompanied by 6-day rhTM treatment (0.06 mg/kg/day) in 16 of these patients [41]. The blood HMGB1 protein level on Day 7 of treatment was lower, and the survival rate at 3 months was higher in the rhTM-treated group than that in the rhTM-untreated group (69 % vs. 38 %, $P = 0.03$). Tsushima et al. reported that patients with AE-IPF had abnormalities of the clotting system, such as increased plasma levels of fibrinogen degradation products (FDP), thrombin-antithrombin complex (TAT), plasma-alpha2 plasmin inhibitor complex (PIC), and D-dimers, and that the death rate at 28 days was lower in the group treated with a steroid + rhTM ($n = 20$) than that in the group treated with a steroid alone ($n = 6$) (35 % vs. 45 %, $p < 0.05$) [42].

## 12.5 Neutrophil Elastase Inhibitors

Sivelestat is a neutrophil elastase inhibitor that was developed in Japan. Although a meta-analysis failed to demonstrate the effect of sivelestat in lowering the death rate due to ARDS [43], an animal study revealed its effect in suppressing the progression of bleomycin-induced pulmonary fibrosis [44]. Because patients with AE-IPF have been shown to have high blood neutrophil elastase levels, sivelestat is expected to be useful in the treatment of AE-IPF. In a phase 3 study of AE-IPF carried out in Japan, treatment with sivelestat was shown to alleviate or improve the shortness of breath and P/F ratio [45].

## 12.6 Pirfenidone

Pirfenidone is an antifibrotic drug that was developed in Japan. In an RCT carried out in 107 patients with IPF, the incidence of acute exacerbation during the 9-month observation period was 14 % in the pirfenidone-untreated group but 0 % in the pirfenidone treatment group ($P = 0.003$) [46]. Pirfenidone has also been reported to additionally suppress acute exacerbations of IPF after lung cancer surgery [47].

## 12.7 Nintedanib

Nintedanib is an intracellular signal inhibitor targeting multiple tyrosine kinases. Of the phase III trials conducted in patients with IPF, INPULSIS-1 did not reveal any difference in the time until onset of acute exacerbation after the start of treatment between the nintedanib treatment group and the placebo group (AE-IPF hazard ratio, 1.15; 95 % CI, 0.54–2.42; $p = 0.67$). However, INPULSIS-2 revealed a longer period of time until onset of acute exacerbation in the nintedanib group (AE-IPF hazard ratio, 0.38; 95 % CI, 0.19–0.77; $p = 0.005$). Analysis of the combined data

from both trials revealed that the incidence of AE-IPF was 36 % lower in the nintedanib group than that in the placebo group, although this difference was not statistically significant (HR, 0.64; 95 % CI, 0.39–1.05; $p = 0.08$) [48]. However, some investigators pointed out problems with the statistical analysis method in these trials, stating that the effect of nintedanib in suppressing AE-IPF could be deemed as statistically significant [49].

## 12.8 Macrolides

The antibiotic macrolide has been reported to suppress acute lung injury [50]. In a study in which AE-IPF patients receiving high-dose steroid + azithromycin treatment ($n = 20$) were compared with those receiving high-dose steroid + fluoroquinolone treatment ($n = 56$), the number of patients who died was 39 (70 %) in the fluoroquinolone-treated group but only 4 (20 %) in the azithromycin-treated group ($p < 0.001$) [51]. In regard to the reasons for the suppression of death among the AE-IPF patients treated with azithromycin, the immunosuppressive and/or anti-inflammatory activity of azithromycin has been suggested.

## 12.9 Direct Hemoperfusion Using a Polymyxin B-Immobilized Fiber Column (PMX-DHP)

PMX-DHP therapy was developed as a means of treating sepsis through adsorption of blood endotoxins [52]. It has also been shown to be useful in the treatment of ARDS caused by sepsis, with the mechanism of action involving adsorption and removal of not only endotoxins but also of some other harmful substances [53–55]. For example, it has been reported that there are no differences in the blood levels of tumor necrosis factor-alpha (TNF-alpha), IL-6, IL-8, and IL-10 before and after PMX-DHP therapy [54] and that PMX-DHP therapy lowered the blood levels of matrix metalloproteinase (MMP)-9, tissue inhibitor of metalloproteinase (TIMP)-1 and HMGB-1, and the urinary levels of 8-hydroxy-2′-deoxyguanosine (8-OHDG) level [55, 56].

Recently, reports on PMX-DHP therapy for AE-IPF have been published primarily from Japanese facilities. Noma et al. reported that of 2 patients with AE-IPF administered high-dose steroid + PMX-DHP therapy, both showed reduction of the blood levels of HMGB1, monocyte chemoattractant protein-1 (MCP-1), IL-8, and IL-6, but only one of the two patients could be saved [57]. Tachibana et al. reported that of the 19 AE-IPF patients administered high-dose steroid + PMX-DHP therapy, 9 survived, allowing reduction of the blood IL-7 level to be identified as a prognostic factor [58]. Oishi et al. applied high-dose steroid + PMX-DHP therapy to

9 patients with AE-IPF, reporting that the therapy resulted in a reduction of the blood levels of IL-9, IL-12, IL-17, platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) and that the extent of improvement of the P/F ratio was correlated with the quantity of VEGF adsorbed on the column [59]. Abe et al. observed the column used for PMX-DHP therapy in AE-IPF patients and found adsorption of numerous activated neutrophils [60]. The same investigators additionally reported that PMX-DHP therapy of AE-IPF patients resulted in HMGB-1 adsorption on the column and reduction of the blood HMGB-1 level [61]. Enomoto et al. reported no changes in the blood levels of IL-6, IL-8, IL-10, neutrophil elastase, or HMGB-1 after PMX-DHP therapy as compared to the levels recorded prior to the therapy; however, the peripheral white blood cell count decreased markedly after the therapy [62].

Seo et al. evaluated the clinical efficacy of PMX-DHP therapy, reporting that 4 of the 6 AE-IPF patients who received high-dose steroid + PMX-DHP therapy showed improvement of the A-a$DO_2$ and blood levels of Krebs von den lungen-6 (KL-6) and LDH, allowing them to be weaned from mechanical ventilation, but the remaining 2 patients died [63]. According to the abovementioned report by Enomoto et al., PMX-DHP therapy improved the P/F ratio and the chest X-ray findings, but PMX-DHP for 12 h or longer was needed to improve the survival rate [62]. Kono et al. compared the outcome of PMX-DHP therapy for acute exacerbation of interstitial pneumonia, such as IPF, between a short-daily-duration treatment group (PMX-DHP for 6 h or less per day, $n = 5$) and long-daily-duration treatment group (12 h per day, $n = 12$), reporting a greater improvement of the P/F ratio and higher 30-day survival rate in the long-daily-duration treatment group [64]. Abe et al. summarized the results of PMX-DHP therapy administered to 160 cases with acute exacerbation of interstitial pneumonia (AE-IPF in 73 cases) at multiple facilities [65]. They reported that a high-dose steroid was used concomitantly in all cases and that the survival rate was 70 % at 1 month and 35 % at 3 months after the start of PMX-DHP therapy. Takada et al. compared the prognosis of a group of patients with acute exacerbation of interstitial pneumonia (including AE-IPF) which was administered high-dose steroid/immunosuppressant + PMX-DHP therapy ($n = 13$) and another group which was administered high-dose steroid/immunosuppressant treatment alone ($n = 13$) [66]. The survival period tended to be longer in the group that received PMX-DHP therapy ($p = 0.067$), and the survival period was statistically significantly prolonged in the patients who began to receive PMX-DHP therapy and steroid treatment simultaneously ($p < 0.01$). These reports suggest that if PMX-DHP therapy is started simultaneously with high-dose steroid treatment, with a long duration set for each session of therapy (12 h or more per day), the prognosis of patients with AE-IPF may be improved.

## 12.10 Conclusion

Methods attempted to date for the treatment of AE-IPF include drug therapy using high-dose steroids, immunosuppressants (cyclosporine A, cyclophosphamide, azathioprine), anticoagulants (heparin, rhTM), neutrophil elastase inhibitors (sivelestat), etc. and PMX-DHP therapy. However, none of these methods have been demonstrated to be effective by RCTs. In regard to the most common treatment method of "high-dose steroid therapy (methylprednisolone 1 g/day, 3 days)," while some retrospective analyses of the efficacy have been carried out, there has been no report of any prospective study to confirm its efficacy. In clinical practice at present, however, attempts are being made to save the lives of patients with AE-IPF (a condition with quite a high mortality) by means of high-dose steroid therapy administered in combination with other drugs such as immunosuppressants (cyclosporine A, tacrolimus, cyclophosphamide, azathioprine), anticoagulants, and neutrophil elastase inhibitors or with PMX-DHP therapy.

## References

1. Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. Eur J Intern Med. 2008;19:227–35.
2. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest. 1993;103:1808–12.
3. Azuma A, Hagiwara K, Kudoh S. Basis of acute exacerbation of idiopathic pulmonary fibrosis in Japanese patients. Am J Respir Crit Care Med. 2008;177:1397–8.
4. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190:773–9.
5. Oda K, Ishimoto H, Yamada S, Kushima H, Ishii H, Imanaga T, et al. Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis. Respir Res. 2014;15:109.
6. Bacigalupo A, van Lint MT, Frassoni F, Podesta' M, Veneziano G, Avanzi G, et al. High dose bolus methylprednisolone for the treatment of acute graft versus host disease. Blut. 1983;46:125–32.
7. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
8. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J. 2011;37:356–63.
9. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. Can Respir J. 2004;11:117–22.
10. Usui Y, Kaga A, Sakai F, Shiono A, Komiyama K, Hagiwara K, et al. A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia. BMJ Open. 2013;3. pii: e002971. doi:10.1136/bmjopen-2013-002971.
11. Takahashi T, Munakata M, Ohtsuka Y, Nasuhara Y, Kamachi A, Satoh R, et al. Effects of corticosteroid pulse treatment on outcomes in acute exacerbations of idiopathic interstitial pneumonia. Nihon Kyobu Shikkan Gakkai Zasshi. 1997;35:9–15. Japanese.

12. Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Triantafillidou C, Tsangaris I, et al. Clinical review: idiopathic pulmonary fibrosis acute exacerbations–unravelling Ariadne's thread. Crit Care. 2010;14:246. doi:10.1186/cc9241.
13. Papiris SA, Manali ED, Kolilekas L, Triantafillidou C, Tsangaris I, Kagouridis K. Steroids in idiopathic pulmonary fibrosis acute exacerbation: defenders or killers? Am J Respir Crit Care Med. 2012;185:587–8.
14. Papiris SA, Kagouridis K, Kolilekas L, Bouros D, Manali ED. Idiopathic pulmonary fibrosis acute exacerbations: where are we now? Expert Rev Respir Med. 2014;8:271–3.
15. Meduri GU, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med. 2008;34:61–9.
16. Tang BM, Craig JC, Eslick GD, Seppelt I, McLean AS. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. Crit Care Med. 2009;37:1594–603.
17. Khilnani GC, Hadda V. Corticosteroids and ARDS: a review of treatment and prevention evidence. Lung India. 2011;28:114–19.
18. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med. 1987; 317:1565–70.
19. Annane D, Sébille V, Bellissant E, Ger-Inf-05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med. 2006;34:22–30.
20. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354:1671–84.
21. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest. 2007;131: 954–63.
22. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1998;280:159–65.
23. Inase N, Sawada M, Ohtani Y, Miyake S, Isogai S, Sakashita H, et al. Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis with corticosteroid. Intern Med. 2003;42:565–70.
24. Homma S, Sakamoto S, Kawabata M, Kishi K, Tsuboi E, Motoi N, et al. Cyclosporin treatment in steroid-resistant and acutely exacerbated interstitial pneumonia. Intern Med. 2005;44: 1144–50.
25. Sakamoto S, Homma S, Miyamoto A, Kurosaki A, Fujii T, Yoshimura K. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2010;49:109–15.
26. Okamoto T, Ichiyasu H, Ichikado K, Muranaka H, Sato K, Okamoto S, et al. Clinical analysis of the acute exacerbation in patients with idiopathic pulmonary fibrosis. Nihon Kokyuki Gakkai Zasshi. 2006;44:359–67. Japanese.
27. Umeda Y, Morikawa M, Anzai M, Sumida Y, Kadowaki M, Ameshima S, et al. Acute exacerbation of idiopathic pulmonary fibrosis after pandemic influenza A (H1N1) vaccination. Intern Med. 2010;49:2333–6.
28. Ambrosini V, Cancellieri A, Chilosi M, Zompatori M, Trisolini R, Saragoni L, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. Eur Respir J. 2003;22:821–6.
29. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest. 2005; 128:3310–15.

30. Horita N, Akahane M, Okada Y, Kobayashi Y, Arai T, Amano I, et al. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2011;50: 189–95.
31. Ward PA, Hunninghake GW. Lung inflammation and fibrosis. Am J Respir Crit Care Med. 1998;157:S123–9.
32. Kamp DW. Idiopathic pulmonary fibrosis: the inflammation hypothesis revisited. Chest. 2003; 124:1187–90.
33. Magro CM, Allen J, Pope-Harman A, Waldman WJ, Moh P, Rothrauff S, et al. The role of microvascular injury in the evolution of idiopathic pulmonary fibrosis. Am J Clin Pathol. 2003; 119:556–67.
34. Panos RJ, Mortenson RL, Niccoli SA, King Jr TE. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med. 1990;88:396–404.
35. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest. 2005;128:1475–82.
36. Simon-Blancal V, Freynet O, Nunes H, Bouvry D, Naggara N, Brillet PY, et al. Acute exacerbation of idiopathic pulmonary fibrosis: outcome and prognostic factors. Respiration. 2012;83:28–35. doi:10.1159/000329891.
37. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, et al. Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186: 88–95. doi:10.1164/rccm.201202-0314OC.
38. Abeyama K, Stern DM, Ito Y, Kawahara K, Yoshimoto Y, Tanaka M, et al. The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel antiinflammatory mechanism. J Clin Invest. 2005;115:1267–74.
39. Ito T, Kawahara K, Okamoto K, Yamada S, Yasuda M, Imaizumi H, et al. Proteolytic cleavage of high mobility group box 1 protein by thrombin-thrombomodulin complexes. Arterioscler Thromb Vasc Biol. 2008;28:1825–30. doi:10.1161/ATVBAHA.107.150631.
40. Taniguchi H, Kondoh Y, Kimura T, Kataoka K. Recombinant thrombomodulin improves survival in acute exacerbation of idiopathic pulmonary fibrosis. ERJ. 2012;40 Suppl 56:2823.
41. Isshiki T, Sakamoto S, Kinoshita A, Gocho K, Sugino K, Homma S. Efficacy of recombinant human soluble thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2014;189:A1413.
42. Tsushima K, Yamaguchi K, Kono Y, Yokoyama T, Kubo K, Matsumura T, et al. Thrombomodulin for acute exacerbations of idiopathic pulmonary fibrosis: a proof of concept study. Pulm Pharmacol Ther. 2014;29:233–40. doi:10.1016/j.pupt.2014.04.008.
43. Iwata K, Doi A, Ohji G, Oka H, Oba Y, Takimoto K, et al. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. Intern Med. 2010;49: 2423–32.
44. Taooka Y, Maeda A, Hiyama K, Ishioka S, Yamakido M. Effects of neutrophil elastase inhibitor on bleomycin-induced pulmonary fibrosis in mice. Am J Respir Crit Care Med. 1997;156:260–5.
45. Ishii Y, Kitamura S, Ando M. A Phase III clinical study of a neutrophil elastase inhibitor; ONO-50460 Na on acute exacerbation in IIP patients. Rinsho iyaku. 1998;14:421–46. Japanese.
46. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2005;171:1040–7.
47. Iwata T, Yoshida S, Nagato K, Nakajima T, Suzuki H, Tagawa T, et al. Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis. Surg Today. 2014. doi:10.1007/s00595-014-1071-5.

48. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82. doi:10.1056/NEJMoa1402584.
49. Suissa S, Ernst P. The INPULSIS enigma: exacerbations in idiopathic pulmonary fibrosis. Thorax. 2014. pii: thoraxjnl-2014-206598. doi:10.1136/thoraxjnl-2014-206598.
50. Walkey AJ, Wiener RS. Macrolide antibiotics and survival in patients with acute lung injury. Chest. 2012;141:1153–9. doi:10.1378/chest.11-1908.
51. Kawamura K, Ichikado K, Suga M, Yoshioka M. Efficacy of azithromycin for treatment of acute exacerbation of chronic fibrosing interstitial pneumonia: a prospective, open-label study with historical controls. Respiration. 2014;87:478–84. doi:10.1159/000358443.
52. Aoki H, Kodama M, Tani T, Hanasawa K. Treatment of sepsis by extracorporeal elimination of endotoxin using polymyxin B-immobilized fiber. Am J Surg. 1994;167:412–17.
53. Tsushima K, Kubo K, Koizumi T, Yamamoto H, Fujimoto K, Hora K. Direct hemoperfusion using a polymyxin B immobilized column improves acute respiratory distress syndrome. J Clin Apher. 2002;17:97–102.
54. Tsushima K, Kubo K, Yoshikawa S, Koizumi T, Yasuo M, Furuya S, et al. Effects of PMX-DHP treatment for patients with directly induced acute respiratory distress syndrome. Ther Apher Dial. 2007;11:138–45.
55. Nakamura T, Kawagoe Y, Matsuda T, Shoji H, Ueda Y, Tamura N, et al. Effect of polymyxin B-immobilized fiber on blood metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 levels in acute respiratory distress syndrome patients. Blood Purif. 2004;22:256–60.
56. Nakamura T, Fujiwara N, Sato E, Kawagoe Y, Ueda Y, Yamada S, et al. Effect of polymyxin B-immobilized fiber hemoperfusion on serum high mobility group box-1 protein levels and oxidative stress in patients with acute respiratory distress syndrome. ASAIO J. 2009;55:395–9.
57. Noma S, Matsuyama W, Mitsuyama H, Suetsugu T, Koreeda Y, Mizuno K, et al. Two cases of acute exacerbation of interstitial pneumonia treated with polymyxin B-immobilized fiber column hemoperfusion treatment. Intern Med. 2007;46:1447–54.
58. Tachibana K, Inoue Y, Nishiyama A, Sugimoto C, Matsumuro A, Hirose M, et al. Polymyxin-B hemoperfusion for acute exacerbation of idiopathic pulmonary fibrosis: serum IL-7 as a prognostic marker. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28:113–22.
59. Oishi K, Mimura-Kimura Y, Miyasho T, Aoe K, Ogata Y, Katayama H, et al. Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. Cytokine. 2013;61:84–9. doi:10.1016/j.cyto.2012.08.032.
60. Abe S, Seo Y, Hayashi H, Matsuda K, Usuki J, Azuma A, et al. Neutrophil adsorption by polymyxin B-immobilized fiber column for acute exacerbation in patients with interstitial pneumonia: a pilot study. Blood Purif. 2010;29:321–6. doi:10.1159/000287232.
61. Abe S, Hayashi H, Seo Y, Matsuda K, Kamio K, Saito Y. Reduction in serum high mobility group box-1 level by polymyxin B-immobilized fiber column in patients with idiopathic pulmonary fibrosis with acute exacerbation. Blood Purif. 2011;32:310–16. doi:10.1159/000330325.
62. Enomoto N, Suda T, Uto T, Kato M, Kaida Y, Ozawa Y, et al. Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia. Respirology. 2008;13:452–60. doi:10.1111/j.1440-1843.2008.01290.x.
63. Seo Y, Abe S, Kurahara M, Okada D, Saito Y, Usuki J, et al. Beneficial effect of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment on acute exacerbation of idiopathic pulmonary fibrosis. Intern Med. 2006;45:1033–8.
64. Kono M, Suda T, Enomoto N, Nakamura Y, Kaida Y, Hashimoto D, et al. Evaluation of different perfusion durations in direct hemoperfusion with polymyxin B-immobilized fiber column therapy for acute exacerbation of interstitial pneumonias. Blood Purif. 2011;32:75–81. doi:10.1159/000320128.

65. Abe S, Azuma A, Mukae H, Ogura T, Taniguchi H, Bando M, et al. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. Intern Med. 2012;51:1487–91.
66. Takada T, Asakawa K, Sakagami T, Moriyama H, Kazama J, Suzuki E, et al. Effects of direct hemoperfusion with polymyxin B-immobilized fiber on rapidly progressive interstitial lung diseases. Intern Med. 2014;53:1921–6.

# Part IV
# Topics

# Chapter 13
# Combined Pulmonary Fibrosis and Emphysema (CPFE)

## Is It an Independent Disease Entity?

**Yoshiteru Morio and Kazuhisa Takahashi**

**Abstract** Combined pulmonary fibrosis and emphysema (CPFE) is a common but under-recognized syndrome characterized with distinct profiles of clinical, functional and radiological features from both pulmonary fibrosis and emphysema. Tobacco smoking may be situated at a major cause and differentiate prognosis of CPFE associated with PH and lung cancer from that of pulmonary fibrosis or emphysema alone. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of CPFE. The establishments of definition, classification and staging of CPFE, including delineation of boundaries between IPF and CPFE, also are required. Better understanding of CPFE will be able to develop future therapeutic strategies.

**Keywords** Combined pulmonary fibrosis and emphysema • Idiopathic pulmonary fibrosis • Emphysema • Pulmonary hypertension • Lung cancer

## 13.1 Introduction

Pulmonary emphysema and idiopathic interstitial pneumonia (IIP) are entities defined by distinct clinical, functional, radiological and pathological characteristics. Emphysema is defined as an enlargement of the distal air spaces from terminal bronchioles to alveoli due to the destruction of alveolar walls [1]. Idiopathic pulmonary fibrosis (IPF) is the most common IIP and characterized generally by not only a progressive and fatal disease but also a histopathological and/or radiological pattern of usual interstitial pneumonia (UIP) [2]. Despite traditionally considered as separate disease states, several studies have described series of combined pulmonary fibrosis and emphysema (CPFE). The combination of both disorders was described over 40 years ago by Auerbach et al. who examined a

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pathological study of 1824 autopsy lungs [3]. Since Cottin et al. described that CPFE exhibited emphysema at upper lobes and fibrosis at lower lobes on chest high-resolution computed tomography (HRCT) in 2005 [4], CPFE has been proposed as a distinct syndrome [5–7].

## 13.2 Epidemiology

The prevalence of CPFE in IIP has been estimated approximately from 8 to 50 % [8–17]. The variety of CPFE prevalence may be influenced by referral bias, recruit strategy and criteria definition. Nevertheless, the combination of emphysema and pulmonary fibrosis is considered as a relatively common finding on HRCT scanning (Table 13.1). Although a pattern of UIP/IPF appears to be the most common finding at lower lobes in CPFE, other patterns of fibrotic IP have been reported in the setting of CPFE [4, 9, 18, 19]. In addition, Cottin et al. described the heterogeneity of pulmonary fibrosis in CPFE associated with connective tissue diseases (CTDs) [20]. On the other hand, several patterns of emphysematous change, including paraseptal, centrilobular and bullous change, also have been reported in the setting of CPFE [4, 12, 17, 19, 20].

Most of cohort studies have demonstrated that CPFE is often observed in males over 65 years of age who are current smokers or ex-smoker of >40 pack-years [6, 7] (Table 13.2). However, despite demonstrating a similar smoking history and pulmonary function profile, CPFE associated with CTDs was observed more female dominantly and younger than "classic CPFE" [20].

**Table 13.1** Prevalence of CPFE in IIPs

| Study | Number of patients with CPFE/with IIPs | Prevalence (%) |
|---|---|---|
| Akira et al. [8] | 15/80 | 18.8 |
| Choi et al. [9] | 66/254 | 26.0 |
| Copley et al. [10] | 76/212 | 35.8 |
| Doherty et al. [11] | 9/23 | 39.1 |
| Jankowich et al. [12] | 20/44 | 45.5 |
| Kurashima et al. [13] | 221/660 | 33.5 |
| Mejía et al. [14] | 31/110 | 28.2 |
| Ryerson et al. [15] | 29/365 | 8.0 |
| Schmidt et al. [16] | 86/169 | 50.9 |
| Sugino et al. [17] | 46/108 | 42.6 |

**Table 13.2** Clinical characteristics of CPFE

| Study | No. | Age (y) | Male/female | Ever smokers/ total patients | $FEV_1/FVC$ | FVC (%) | TLC (%) | DLco (%) |
|---|---|---|---|---|---|---|---|---|
| Akagi et al. [33] | 26 | 65 ± 9 | 23/3 | 24/26 | 0.77 ± 0.09 | 86.6 ± 24.0 | 78.2 ± 17.4 | 45.3 ± 15.0 |
| Cottin et al. [4] | 61 | 65 ± 10 | 60/1 | 61/61 | 0.69 ± 0.13 | 90 ± 18 | 88 ± 17 | 37 ± 16 |
| Cottin et al. [20] | 34 | 57 ± 11 | 23/11 | 30/34 | 0.73 ± 0.15 | 85 ± 24 | 82 ± 17 | 46 ± 16 |
| Jankowich et al. [12] | 20 | 69 ± 10 | 20/0 | 20/20 | 0.67 ± 0.12 | 77 ± 14 | 76 ± 11 | 29 ± 11 |
| Kitaguchi et al. [19] | 47 | 70 ± 1 | 46/1 | 46/47 | 0.72 ± 0.02 | 94.7 ± 3.5 | NA | 39.6 ± 2.5 |
| Kurashima et al. [13] | 221 | 71 ± 8 | 209/12 | 221/221 | 0.70 ± 0.12 | 87.1 ± 17.0 | 93.9 ± 17.2 | 65.2 ± 20.9 |
| Mejía et al. [14] | 31 | 67 ± 7 | 30/1 | 24/31 | 0.91 ± 0.09 | 62.1 ± 15.6 | NA | NA |
| Ryerson et al. [15] | 29 | 70 ± 9 | 20/9 | 29/29 | 0.74 ± 0.06 | 79.8 ± 15.7 | 78.9 ± 14.4 | 37.1 ± 14.0 |
| Sugino et al. [17] | 46 | 71 ± 7 | 43/3 | 45/46 | 0.78 ± 0.12 | 93.9 ± 22.4 | 90.0 ± 16.4 | 49.8 ± 14.1 |

Data are presented as mean ± SD

*No.* number of patients, *$FEV_1$* forced expiratory volume in the first second, *FVC* forced vital capacity, *TLC* total lung capacity, *DLco* diffusing capacity of the lung for carbon monoxide, *NA* not available

## 13.3 Physical Findings

Exertional dyspnoea (functional class III or IV of the New York Heart Association) is the most common symptom despite of relatively normal spirometric values among CPFE patients [4]. Physical examination often reveals bibasilar inspiratory crackles and finger clubbing. Other signs and symptoms reported are cough, sputum production and asthenia among CPFE patients [4].

## 13.4 Radiological Features

Radiological findings of CPFE are considered to be characterized by emphysema at upper lobes and fibrosis at lower lobes. On chest X-ray findings of CPFE, an interstitial pattern or reticulonodular infiltration is present at basal periphery of bilateral lungs, while a hyperlucency with thinning or reduction in pulmonary vessels is observed at bilateral apices. However, HRCT scanning is the most appropriate tool for the diagnosis of CPFE, because the estimation by chest X-ray alone does not necessarily confirm the diagnosis of this entity (Fig. 13.1).

Cottin et al. described the radiological criteria to determine CPFE as follows: firstly, the presence of emphysema on HRCT, defined as well-demarcated areas of decreased attenuation in comparison with contiguous normal lung and marginated by a very thin ($<1$ mm) wall or no wall, and/or multiple bullae ($>1$ cm) with upper zone predominance, and, secondly, the presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT, defined as reticular opacities with peripheral and basal predominance, honeycombing, architectural distortion and/or traction bronchiectasis or bronchiolectasis; focal ground-glass opacities and/or areas of alveolar condensation may be associated but should not be prominent [4].

UIP is the most common pattern [4, 9, 18, 19], as reporting the most frequent presence of honeycombing in the wide variety of HRCT findings of CPFE. Other patterns reported in pulmonary fibrosis include reticular opacities, ground-glass opacities, traction bronchiectasis and architectural distortion, which are compatible with non-UIP, smoking-related interstitial pneumonia (IP) or unclassifiable interstitial lung diseases (ILDs) (Table 13.3).

The various findings of emphysema also are present at upper lobes, including centrilobular, paraseptal and bullous change [4, 12, 17, 19, 20]. Centrilobular and paraseptal emphysema appear to be typical features of CPFE (Table 13.3). In the various findings of emphysema, Sugino et al. indicated a paraseptal emphysema as a predictor of poor prognosis among 46 CPFE patients [17].

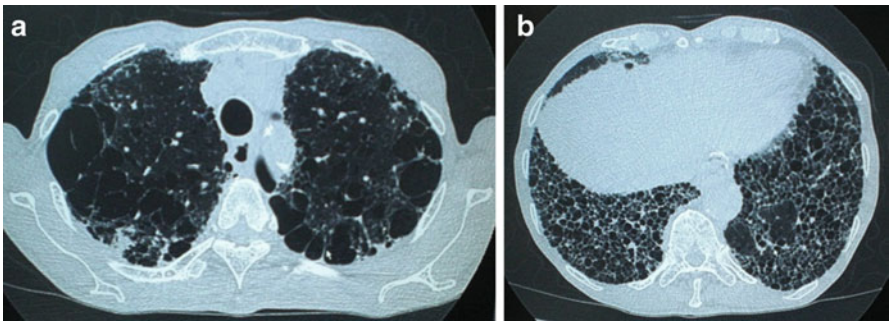


**Fig. 13.1** High-resolution computed tomography (HRCT) of a male smoker aged 77 years with combined pulmonary fibrosis and emphysema. (**a**) Presence of paraseptal emphysema and subpleural bullae in bilateral upper lobes. (**b**) Images of subpleural honeycombing and traction bronchiectasis in bilateral lower lobes

**Table 13.3** Various HRCT findings in CPFE

| | Study | |
|---|---|---|
| CT findings | Cottin et al. [4] | Kitaguchi et al. [19] |
| Fibrosis | | |
| Honeycombing | 95 % | 75.6 % |
| Reticular opacities | 87 % | 84.4 % |
| Ground-glass opacities | 66 % | 62.2 % |
| Traction bronchiectasis | 69 % | 40.0 % |
| Architectural distortion | 39 % | 15.6 % |
| Consolidation | 15 % | 13.3 % |
| Emphysema | | |
| Centrilobular | 97 % | |
| Centriacinar | | 24.4 % |
| Centriacinar + panacinar | | 15.6 % |
| Paraseptal | 93 % | 33.3 % |
| Paraseptal + centriacinar | | 26.7 % |
| Bullae | 54 % | |

## 13.5 Pathological Features

As the wide variety of radiological findings correlate closely with histopathological data, UIP is the most common pattern of pathological findings in accordance with the most frequent presence of honeycombing in HRCT findings of CPFE [4, 9]. Other patterns reported in pathological findings include nonspecific IP, desquamative IP, respiratory bronchiolitis-related ILD and unclassifiable ILD [4, 9, 18, 19]. Because of the pathological heterogeneity, a pathological criterion for diagnosis of CPFE is not mapped out [12].

## 13.6 Pulmonary Function and Gas Exchange

Pulmonary function tests show normal or subnormal findings of respiratory volume and flow, despite of severe dyspnoea on exertion and extensive radiographic findings among CPFE patients [4]. The coexistence of emphysema and fibrosis leads to an influence of pulmonary function that profiles each other in CPFE. Forced vital capacity (FVC), forced expiratory volume in the first second ($FEV_1$) and total lung capacity (TLC) are usually within normal or subnormal range (Table 13.2). The unexpected subnormal spirometric findings in CPFE may be explained by counterbalancing effects of the restrictive disorder in pulmonary fibrosis and the propensity to hyperinflation in emphysema [5, 6]. The hyperinflation and increased pulmonary compliance in emphysema probably compensate for the loss of volume in fibrosis, resulting in the preservation of spirometric findings.

Additionally to the spurious preservation of spirometric findings, a marked impairment of gas exchange manifested as a reduction in diffusing capacity of the lung for carbon monoxide (DLco) is common [4] (Table 13.2). The severe impairment of gas exchange is likely due to not only reduction in pulmonary vascular surface and capillary blood flow but also thickness of alveolar wall.

Resting and exertional hypoxaemia also are common among CPFE patients. In the series reported by Cottin et al., CPFE patients exhibited $63 \pm 14$ mmHg of partial pressure of oxygen in arterial blood ($PaO_2$) at rest on room air with $41 \pm 16$ mmHg of alveolar-arterial oxygen gradient and exertional decrease by $8.9 \pm 5.7$ % of arterial oxygen saturation ($SpO_2$) during a 6-min walk test (6MWT) [4]. Hypercapnia does not appear to be as frequent as hypoxaemia in CPFE [4, 19]. In a consequence of exertional hypoxaemia, Jankowich M.D. et al. reported that 80 % required oxygen therapy over a 5-year period among 20 CPFE patients [12].

## 13.7 Pathogenesis

Tobacco smoking has been suggested as a major cause, as a history of smoking is a constant factor in all the cohort studies [6, 7]. In addition, possible factors also have been identified, such as exposure to agrochemical compounds or asbestos [19]. While underlying mechanisms resulted from smoking exposure have been considered, the precise and exact pathogenesis of CPFE is unclear. Although potential roles for tumour necrosis factor-α [21] and platelet-derived growth factor-β [22] have been suggested in various animal models of CPFE, it is unclear whether any of these models represent typical CPFE in human smokers.

Rogliani et al. reported an augmented expression of metalloproteinases (MMPs) in fibroblasts of lungs from CPFE patients compared with emphysema patients, suggesting the roles for MMPs in acceleration of pulmonary fibrotic process in CPFE [23]. Tasaka et al. reported an increased CXC chemokine levels in

bronchoalveolar lavage fluid from CPFE patients compared with IPF patients, suggesting a relationship between the increased CXC chemokines and emphysematous change in CPFE [24]. Tzouvelekis et al. reported an elevated serum antinuclear antibodies and CD20-positive B-cell infiltration into the lungs from CPFE patients compared with IPF patients, suggesting a presence of underlying autoimmune disorders in CPFE [25]. Collectively, several mechanisms as mentioned above resulted from smoking exposure appear to underlie the pathogenesis of CPFE.

Recently, individual genetic backgrounds have been considered as a predisposal in the development of CPFE. Cottin et al. reported a heterozygous mutation in *SFTPC* (the gene encoding surfactant protein C) in a nonsmoking young female with CPFE [26]. In addition, telomeropathy also may be on the verge of becoming a predisposal in the development of CPFE, since shorter telomeres appear to be associated with pulmonary fibrosis, emphysema and smoking exposure [27]. However, the underlying genetic predisposition in CPFE remains to be elucidated because of the limited reports.

## 13.8 Complication

### *13.8.1 Pulmonary Hypertension*

Pulmonary hypertension (PH) is particularly prone to develop and a common complication during the clinical course of CPFE. Cottin et al. reported 47 % prevalence of PH (definition as an estimated systolic pulmonary arterial pressure (eSPAP) $\geq$ 45 mmHg by echocardiography system) among 61 CPFE patients [4]. In the study, 5-year survival rates were 25 % and 75 %, respectively, among CPFE patients with and without PH, indicating a presence of PH as a clinical determinant of prognosis in CPFE. Mejía et al. reported a complication of PH that was more frequent and severe in CPFE patients than in IPF patients [14]. The study also demonstrated a lower survival rate in CPFE patients than in IPF patients, indicating a complication of severe PH (eSPAP $>$ 75 mmHg by echocardiography system) as a predictor of mortality in CPFE.

Cottin et al. also reported 1-year survival rate of 60 % among 40 patients with CPFE and PH, with a mean PAP of $40 \pm 9$ mmHg by examination of right heart catheterization (RHC), and indicated both a reduced cardiac index ($<$2.4 L/min/m$^2$) and elevated pulmonary vascular resistance ($>$485 dyne/s/cm$^5$) as predictors of poor prognosis [28]. In the study, while the diagnosis of PH was established at mean of 16 months after the initial diagnosis of CPFE, no significant benefit of medical therapy, including pulmonary vasodilators, corticosteroids, immunomodulators and bronchodilators, was observed.

Therefore, as no data currently supports treatment of PH in CPFE with pulmonary vasodilators, oxygen therapy and referral for lung transplantation, if

appropriate, appear to be the most reasonable option for the management [29]. Randomized controlled trials are urgently required for the establishment of therapeutic strategy of PH in CPFE.

### *13.8.2 Lung Cancer*

CPFE patients may be at a high risk of developing lung cancer, as both pulmonary fibrosis and emphysema possess a possibility to predispose lung cancer. Despite several limited evidence in retrospective studies, an increased prevalence of lung cancer among CPFE patients has been reported.

Kitaguchi et al. reported 46.8 % and 7.3 % prevalence of lung cancer, respectively, in 47 CPFE patients and 82 emphysema patients [19], whereas Kurashima et al. reported 33.3 % and 12.1 % prevalence, respectively, in 129 CPFE patients and 233 IPF patients [13]. The more prevalence of lung cancer among CPFE patients may be influenced by referral bias and recruit strategy. Nevertheless, it is noteworthy that CPFE appears to be prone to cause lung cancer. Smoking-related lung cancers such as squamous cell lung cancer and small cell lung cancer (SCLC) appear to predominate in pathological features of lung cancer in CPFE [19, 30, 31].

Usui et al. described clinical characteristics of 101 CPFE subjects in 1143 patients with lung cancer [30]. In the study, CPFE subjects demonstrated the worst median overall survival (10.8 months) compared with normal subjects (i.e. without lung disease) ($n = 623$, 53.0 months) and emphysema subjects ($n = 404$, 21.9 months). The poor prognosis of lung cancer may be explained by not only earlier and more frequent recurrence of lung cancer but also less tolerance to chemotherapy and performance status in association with acute exacerbation of ILD among CPFE patients than among others [30, 32].

Collectively, as the more prevalence and worse clinical course of lung cancer have been demonstrated, CPFE patients may be at a high risk of developing lung cancer. However, it remains uncertain whether CPFE is an independent risk factor of lung cancer.

## 13.9 Treatment

Therapeutic options for CPFE patients are limited and may require treatment for both IPF and emphysema [5–7]. Smoking cessation, of course, is an obvious objective and should be encouraged and supported. Oxygen therapy is appropriate for the management of hypoxaemia. Inhaled bronchodilators are more often prescribed among CPFE patients than among patients with pulmonary fibrosis alone [12, 15]. Treatment for CPFE patients with systemic corticosteroids and immunomodulator therapy (e.g. azathioprine, *N*-acetylcysteine or pirfenidone) have been considered similar to that for IPF, but without beneficial results in the published series.

A possibility of using pulmonary vasodilators (e.g. endothelin-1 receptor antagonist, prostanoids or phosphodiesterase type 5 inhibitors) has been raised for therapeutic strategy of PH in CPFE, but no studies have been published to date on the issue. Both hypoxic pulmonary vasoconstriction (HPV), a phenomenon to avoid worsening arterial oxygenation, and imbalance in ventilation/perfusion ratio ($V_A$/Q) due to abnormal changes in pulmonary vascular bed and airway in CPFE may predispose PH. Pulmonary vasodilators have a possibility to worsen arterial oxygenation due to inhibition of HPV and potentiation of $V_A$/Q mismatch by nonselective vasodilation of pulmonary vessels. Therefore, as no data currently supports treatment of PH in CPFE with pulmonary vasodilators, a referral for lung transplantation, if appropriate, appears to be the most reasonable option for the management [29].

## 13.10 Survival

The median survival of CPFE in reported series has been ranged from 1.8 to 8.5 years (Table 13.4). The various survival of CPFE may be influenced by a presence of either complication or acute exacerbation. However, it remains controversial whether CPFE patients have worse survival than patients with pulmonary fibrosis or emphysema alone.

Mejía et al. reported a worse survival in association with severe and more frequent PH in CPFE patients than in IPF patients [14]. Sugino et al. also indicated both a paraseptal emphysema and PH as predictors of worse survival in CPFE patients than in IPF patients [17]. In addition, despite the spurious preservation of spirometric findings, Schmidt et al. indicated a longitudinal decline in $FEV_1$ as a more superior predictor of mortality than other pulmonary function parameters in CPFE patients [16]. In contrast, other studies demonstrated comparable or better survival in CPFE patients than in patients with pulmonary fibrosis or emphysema alone [11–13, 15, 24, 33]. The basis for these discrepant results is unclear and may be influenced by referral bias, recruit strategy and criteria definition.

**Table 13.4** Survival of CPFE

| Study | Number of patients with CPFE | Median survival (y) |
|---|---|---|
| Akagi et al. [33] | 26 | 5.0 |
| Choi et al. [9] | 66 | 6.0 |
| Cottin et al. [4] | 61 | 6.1 |
| Jankowich et al. [12] | 20 | 4.0 |
| Kurashima et al. [13] | 129 | 8.5 |
| Mejía et al. [14] | 31 | 2.2 |
| Ryerson et al. [15] | 29 | 2.8 |
| Sugino et al. [17] | 46 | 1.8 |

## 13.11 Conclusion

A number of published series have demonstrated that CPFE is a common syndrome characterized with distinct profiles of clinical, functional and radiological features from both pulmonary fibrosis and emphysema. Tobacco smoking may be situated at a major cause and differentiate prognosis of CPFE associated with PH and lung cancer from that of pulmonary fibrosis or emphysema alone. Is CPFE an independent entity? CPFE is a distinct but under-recognized and common syndrome with the characteristic presentation as mentioned above [7]. However, it is clear that many aspects remain to be explored for better recognition of CPFE. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of CPFE, with or without PH. The establishments of definition, classification and staging of CPFE, including delineation of boundaries between IPF and CPFE, also are required. Better understanding of CPFE will be able to develop future therapeutic strategies.

## References

1. Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932–46.
2. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
3. Auerbach O, Garfinkel L, Hammond EC. Relation of smoking and age to findings in lung parenchyma: a microscopic study. Chest. 1974;65:29–35.
4. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26:586–93.
5. Portillo K, Morera J. Combined pulmonary fibrosis and emphysema syndrome: a new phenotype within the spectrum of smoking-related interstitial lung disease. Pulm Med. 2012;2012:867870.
6. Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest. 2012;141:222–31.
7. Cottin V. The impact of emphysema in pulmonary fibrosis. Eur Respir Rev. 2013;22:153–7.
8. Akira M, Yamamoto S, Inoue Y, et al. High-resolution CT of asbestosis and idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 2003;181:163–9.
9. Choi SH, Lee HY, Lee KS, et al. The value of CT for disease detection and prognosis determination in combined pulmonary fibrosis and emphysema (CPFE). PLoS One. 2014;9:e107476.
10. Copley SJ, Wells AU, Sivakumaran P, et al. Asbestosis and idiopathic pulmonary fibrosis: comparison of thin-section CT features. Radiology. 2003;229:731–6.
11. Doherty MJ, Pearson MG, O'Grady EA, et al. Cryptogenic fibrosing alveolitis with preserved lung volumes. Thorax. 1997;52:998–1002.
12. Jankowich MD, Rounds S. Combined pulmonary fibrosis and emphysema alters physiology but has similar mortality to pulmonary fibrosis without emphysema. Lung. 2010;188:365–73.
13. Kurashima K, Takayanagi N, Tsuchiya N, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology. 2010;15:843–8.

14. Mejía M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest. 2009;136:10–5.
15. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest. 2013;144:234–40.
16. Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011;38:176–83.
17. Sugino K, Ishida F, Kikuchi N, et al. Comparison of clinical characteristics and prognostic factors of combined pulmonary fibrosis and emphysema versus idiopathic pulmonary fibrosis alone. Respirology. 2014;19:239–45.
18. Jankowich MD, Polsky M, Klein M, et al. Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration. 2008;75:411–17.
19. Kitaguchi Y, Fujimoto K, Hanaoka M, et al. Clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology. 2010;15:265–71.
20. Cottin V, Nunes H, Mouthon L, et al. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum. 2011;63:295–304.
21. Lundblad LK, Thompson-Figueroa J, Leclair T, et al. Tumor necrosis factor-alpha overexpression in lung disease: a single cause behind a complex phenotype. Am J Respir Crit Care Med. 2005;171:1363–70.
22. Hoyle GW, Li J, Finkelstein JB, et al. Emphysematous lesions, inflammation, and fibrosis in the lungs of transgenic mice overexpressing platelet-derived growth factor. Am J Pathol. 1999;154:1763–75.
23. Rogliani P, Mura M, Mattia P, Ferlosio A, et al. HRCT and histopathological evaluation of fibrosis and tissue destruction in IPF associated with pulmonary emphysema. Respir Med. 2008;102:1753–61.
24. Tasaka S, Mizoguchi K, Funatsu Y, et al. Cytokine profile of bronchoalveolar lavage fluid in patients with combined pulmonary fibrosis and emphysema. Respirology. 2012;17:814–20.
25. Tzouvelekis A, Zacharis G, Oikonomou A, et al. Increased incidence of autoimmune markers in patients with combined pulmonary fibrosis and emphysema. BMC Pulm Med. 2013;13:31.
26. Cottin V, Reix P, Khouatra C, et al. Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPC mutation. Thorax. 2011;66:918–19.
27. Nunes H, Monnet I, Kannengiesser C, et al. Is telomeropathy the explanation for combined pulmonary fibrosis and emphysema syndrome?: report of a family with TERT mutation. Am J Respir Crit Care Med. 2014;189:753–4.
28. Cottin V, Le Pavec J, Prévot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J. 2010;35:105–11.
29. Seeger W, Adir Y, Barberà JA, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013;62:D109–16.
30. Usui K, Tanai C, Tanaka Y, et al. The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology. 2011;16:326–31.
31. Girard N, Marchand-Adam S, Naccache JM, et al. Lung cancer in combined pulmonary fibrosis and emphysema: a series of 47 Western patients. J Thorac Oncol. 2014;9:1162–70.
32. Kumagai S, Marumo S, Yamanashi K, et al. Prognostic significance of combined pulmonary fibrosis and emphysema in patients with resected non-small-cell lung cancer: a retrospective cohort study. Eur J Cardiothorac Surg. 2014;46:e113–19.
33. Akagi T, Matsumoto T, Harada T, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. Respir Med. 2009;103:1209–15.

# Chapter 14
# Common Pathways in IPF and Lung Cancer

## Why Is Lung Cancer Highly Associated with IPF at a High Frequency?

**Nobuyuki Koyama**

**Abstract** Lung cancer which is the leading cause of cancer death worldwide leads to poor clinical outcome, similar to idiopathic pulmonary fibrosis (IPF). Lung cancer and IPF are often characterized by high comorbidity, and IPF is therefore considered to be a risk factor for the incidence of lung cancer. On the other hand, its high comorbidity recalls the existence of a common pathway in the pathogenesis and progression of both diseases. However, lung cancer and IPF have distinct phenotypes in the clinicopathological characteristics and therapeutic strategies. Rather, the standard of care for lung cancer with IPF has not yet been established, as treatments for lung cancer are sometimes harmful for comorbid IPF and induce its exacerbation that results in death. In order to pursue the answer to the question, "Why is lung cancer highly associated with IPF at a high frequency?" this chapter focused on the common pathogenesis of IPF and lung cancer and reviewed possible common pathways that are associated with both diseases. Besides common causative factors such as physical changes and environmental exposure, genetic modifications, epigenetic aberrations, and dysregulation in signaling pathways have indeed been reported as possible biological mechanisms that commonly underlie both diseases. Diverse common pathways as described in this chapter may account for the high frequency of lung cancer with IPF. The approach to a better understanding of these pathways will invite a novel perspective on therapeutics for this comorbidity, leading to an improved prognosis.

**Keywords** Lung cancer • Common pathogenesis • Gene mutation • Epigenetics • Signaling pathway

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## 14.1 Introduction

Lung cancer is the leading cause of cancer death worldwide. Approximately 80 % of lung cancer consists of non-small cell lung cancer (NSCLC), more than three-quarters of which is diagnosed at an advanced stage, leading to a low 5-year survival rate of approximately 20 %. Thus, lung cancer, along with idiopathic pulmonary fibrosis (IPF), is associated with poor clinical outcome. Both diseases are often characterized by high comorbidity as it is reported that IPF concurred in 7.5 % of surgically resected lung cancer patients [1]. Furthermore, high rates of comorbidity have been reported; lung cancer occurred in 4.4–38 % of patients with interstitial pneumonia. Therefore, IPF is considered to be a risk factor for the incidence of lung cancer. Along with these epidemiologic data, IPF and lung cancer have possible common causative factors such as aging, environmental exposure, and infection from an etiological perspective. Indeed, squamous cell carcinoma, which is highly related to smoking, is the predominant histological type of lung cancer that is comorbid with IPF. On the other hand, gene mutations, epigenetic aberrations, activation of signaling pathways, dysregulation of apoptosis, and impaired expression of microRNA (miRNA) have been reported as possible biological mechanisms that commonly underlie lung cancer and IPF, particularly fibrosis that is considered as aberrant "wound healing" similar to cancer. These findings suggest the existence of a common pathway in the pathogenesis and progression of IPF and lung cancer. However, IPF that consists of a heterogeneous population is estimated to have numerous pathogenesis and courses. Its radiological severity has no correlation with the prevalence of lung cancer, which is not always developed in fibrotic lesions of IPF. Additionally, IPF demonstrates no increased risk of malignancies other than lung cancer. Lung cancer and IPF have distinct phenotypes in terms of the distribution of lesions and metastatic potential.

Aside from these pathogenetic implications, IPF is one of the morbidities that require the most careful attention when treated with lung cancer, because treatments for lung cancer such as antitumor drugs, thoracic radiation, and surgical resection sometimes lead to acute exacerbation of IPF. Given the limited number of clinical trials, the optimal treatment modality for lung cancer with IPF has not yet been established. A novel therapeutic strategy for lung cancer or IPF that differs from the conventional treatment modalities is being developed. This process is currently focusing on "molecular targeted drugs" such as nintedanib that selectively inhibit pathways that underlie the pathogenesis of these diseases.

In this chapter, possible common pathways of IPF and lung cancer are pleiotropically searched and reviewed to determine the reason for the high rates of comorbidity of both diseases. This approach for elucidation of the common pathogenesis of both diseases may consequently shed light on efficient and effective treatment for these comorbid refractory diseases with poor prognosis.

## 14.2 Gene Mutation, Amplification, and Deletion

Previous reports have suggested the association of many gene mutations with lung cancer, which generally contribute to the development and progression of the cancer. On the other hand, some cases of interstitial pneumonia are known to be inherited. Recent reports suggest that familial inherited interstitial pneumonia accounts for approximately 20 % of IPF [2]. To date, mutations in the genes encoding telomerase reverse transcriptase (TERT); the RNA component of the telomerase complex (TERC) [3]; surfactant protein A, SP-A (SFTPA); surfactant protein C, SP-C (SFTPC); and ATP-binding cassette transporter A3 (ABCA3) have been reported as genes responsible for familial interstitial pneumonia. Of these genes, *TERT* mutations, gene deletions of *SFTPA* and *SFTPC*, and gene amplification of *TERC* are also found in NSCLC.

There is very little information regarding single nucleotide polymorphisms (SNPs) as a common pathogenesis of lung cancer and IPF, although some gene mutations are often identified in sporadic IPF cases with lung cancer, suggesting that they may be associated with the development of lung cancer in IPF. This section focuses on common gene mutations in IPF and lung cancer.

### *14.2.1 Telomerase Reverse Transcriptase and the RNA Component of the Telomerase Complex*

Telomerase is the enzyme complex that maintains telomeres, protecting chromosomes from degradation, end-to-end fusion, and atypical recombination. Once telomeres reach a critical length, RB and p53 signaling pathways initiate irreversible arrest of cell growth, cellular senescence, or apoptosis. Telomere dysfunction is associated with disease development. Telomeres require the telomerase enzyme complex to generate and maintain their structure and function. The telomerase complex has an enzyme and an RNA template component that are encoded by the *TERT* and *TERC* genes, respectively. The review by Gansner et al. indicated that *TERT* and *TERC* mutations were identified in both patients with familial interstitial pneumonia (8–15 %) and sporadic IPF (1–3 %) [4]. IPF caused by *TERT* and *TERC* mutations is inherited as an autosomal dominant pattern with haploinsufficiency, while these mutations associated with telomere shortening are also found in lung cancer, especially in small cell carcinomas [5]. Genome-wide association studies (GWAS) have identified the *TERT* locus on chromosome 5p15.33 as a lung cancer susceptibility marker [6], and recurrent TERT promoter mutation was found in 2.57 % of NSCLC patients [7]. In terms of *TERT* function, one of the targets of *TERT* regulation is the Wnt/β-catenin signaling pathway, whose activation via transforming growth factor-β (TGFβ) signaling promotes epithelial-mesenchymal transition (EMT) as well as myofibroblast differentiation [8]. Aberrant Wnt/β-catenin pathway signaling is tightly associated with carcinogenesis.

### 14.2.2 Surfactant Proteins

Of the surfactant proteins, germline mutations of the *surfactant protein A2* (*SFTPA2*) gene that interfere with protein trafficking have been identified in both IPF and lung cancer [9]. *Surfactant protein C* (*SFTPC*) gene mutations were also found in IPF [10], whereas deletion of its gene was identified in lung cancer [11].

### 14.2.3 p53

The *p53* gene is widely known to function as a tumor suppressor by modulating DNA repair, cell division, and apoptosis induction, and its mutation alters the conformation of the p53 protein, which accumulates in the nucleus, resulting in carcinogenesis. *p53* mutation is found in many types of cancer as an early event of multistep carcinogenesis. *p53* mutations, which are mostly attributed to smoking, are implicated in 40–60 % of lung cancer, and transversion of GC to TA in *p53* was observed in 40 % of patients with smoking-associated cancer. On the other hand, TGFβ that is activated in IPF upregulates *p21*, which is highly expressed in IPF and is also upregulated by p53 and fibroblast-regulating cytokines. Intriguingly, *p53* mutations were detected in peripheral type squamous cell carcinoma within fibrotic areas of IPF. Smoking exposure that can cause *p53* mutations is commonly associated with squamous cell carcinoma and pulmonary fibrosis.

### 14.2.4 RAS

The *RAS* oncogene family includes *HRAS*, *KRAS*, and *NRAS*, which code for 21-kDa guanosine triphosphate (GTP)-binding proteins called p21. RAS proteins that are activated by binding with GTP elicit cellular proliferation via the RAS-dependent kinase cascade. Point mutations and overexpression of *RAS* lead to a loss of the intrinsic GTPase activity that inactivates RAS proteins, and consequently they activate RAS signaling. KRAS regulates cellular proliferation through signal transduction across cellular membranes. *KRAS* mutations are found in 12–57 % of adenocarcinoma and 2–9 % of squamous cell carcinoma of the lung and are furthermore associated with poor overall survival of lung cancer patients. Approximately 80 % of *KRAS* mutations in NSCLC involve codon 12 [12], and its point mutation, $KRAS^{G12D}$, was detected in lung tissue with interstitial pneumonia comorbid with lung cancer [13].

### 14.2.5 Fragile Histidine Triad

*Fragile histidine triad* (*FHIT*), a member of the histidine triad gene family, is a tumor suppressor gene that spans the FRAB3B common fragile site at chromosome 3p14.2. Homozygous deletions and loss of heterozygosity (LOH) at the *FHIT* locus leading to inactivation of the *FHIT* gene have been frequently reported in lung cancer cell lines and primary tumors. Aberrant *FHIT* mRNA transcripts have been identified in 40–80 % of tumor samples, and loss of FHIT protein expression is observed in approximately 70 % of primary tumors, mainly in smokers. Hypermethylation of the *FHIT* promoter region containing CpG islands was found in 36.7 % of tumor and 32.7 % of normal lungs, whereas LOH was detected in 61.9 % of tumors. Lost or reduced *FHIT* expression was found in 36.7 and 75.7 % of the tumor samples, respectively [14]. Consequently, the combination of methylation and LOH is considered to result in the loss of *FHIT*, and this phenomenon has been frequently identified in smokers with squamous cell carcinoma. In contrast, *FHIT* mutations have been rarely reported in lung cancer cells. However, *FHIT* gene mutations and protein reduction have been demonstrated in IPF, particularly in peripheral honeycomb areas. Accordingly, *FHIT* mutations may contribute to oncogenesis in some squamous cell carcinoma patients with a smoking history, although LOH of the *FHIT* locus and reduced FHIT protein were frequently found in metaplastic lesions in IPF.

These findings suggest that gene mutations may be at least partly associated with a common pathway of IPF and lung cancer, functioning as a trigger.

## 14.3 DNA Methylation by DNA Methyltransferase in Epigenetic Changes

Gene expression profiles are at least partly dependent on epigenetic changes, including DNA methylation, histone modifications, and regulation of noncoding RNA. Epigenetic changes can lead to changes in the expression of target genes without any changes in DNA sequence and are therefore potentially reversible. In this chapter, epigenetic changes are classified into three types of changes, DNA methylation, histone modifications, and noncoding RNA (microRNA).

Hypermethylation and hypomethylation of genes play an important role in epigenetic changes in gene expression. Modulation of gene transcription through DNA methylation is carried out directly by DNA methyltransferases (DNMTs) and is indirectly mediated through histone modifications. These epigenetic alterations are often caused by environmental exposure, tobacco smoke, diets, or aging. Hypermethylation of tumor suppressor genes and hypomethylation of oncogenes have been widely investigated, particularly in oncogenesis. Moreover, Rabinovich et al. have shown that the global methylation pattern in IPF is partly similar to that

in lung cancer, suggesting similar pathogenic mechanisms underlying the development of both diseases [15].

### *14.3.1 Phosphatase and Tensin Homolog*

Phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a dual-specificity protein and lipid phosphatase, inhibits cellular migration and proliferation, promotes cellular apoptosis, and is considered as an antifibrotic mediator, through inhibition of myofibroblast differentiation, as well as a tumor suppressor gene. PTEN dephosphorylates PI-3,4,5-trisphosphate, thereby inhibiting PI3K/AKT/mTOR signals. Inactivation of PTEN induced by rare gene mutations (5 %) and reduced PTEN protein expression (75 %) in NSCLC results in ligand-independent AKT/protein kinase B activation [16]. On the other hand, inhibition of PTEN that is negatively regulated by TGFβ promotes α-smooth muscle actin (αSMA) and collagen production, leading to induction of myofibroblast differentiation and development of pulmonary fibrosis [17].

### *14.3.2 Caveolin-1*

Caveolin-1 (CAV1) is a 22-kDa scaffold protein that is one of three essential constituents of the flask-shaped (50–100 nm) invaginated membranes termed caveolae. CAV1 is considered to be associated with the development of various diseases, especially tumorigenesis, because it regulates diverse pathways of integrin, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGF), MAPK, and PI3K/AKT/mTOR signaling. Wang et al. reported that CAV1 expression is reduced in lung tissues and in primary pulmonary fibroblasts from IPF patients and that TGFβ decreases CAV1 expression in pulmonary fibroblasts, whereas CAV1 can suppress TGFβ-induced ECM production in cultured fibroblasts through regulation of the c-JUN N-terminal kinase (JNK) pathway [18]. On the other hand, the role of CAV1 in cancers remains controversial. CAV1 expression was reportedly decreased in lung cancer [19], and exogenous CAV1 expression in cancer cell lines inhibited cellular growth and tumorigenesis [20]. In contrast, in other studies CAV1 expression was found to be upregulated in lung cancer, and its upregulation was associated with tumor metastasis and poor outcome [21, 22]. Li et al. reported that CAV1 maintains activated AKT, although this effect was observed in prostatic cancer cells [23]. Sunaga et al. reported that CAV1 reciprocally exerts oncogenic function in NSCLC and tumor suppressive function in SCLC [24].

### 14.3.3 Claudin-5

Hypermethylation and decreased expression of the *claudin-5* (*CLDN5*) gene encoding a transmembrane protein are found in IPF lung tissues [25]. The decrease in *CLDN5* expression found in bleomycin-induced pulmonary fibrosis may promote EMT [26]. Decreased or no expression of *CLDN5* is also observed in pulmonary squamous cell carcinoma [27], which is the most frequent histological type identified in lung cancer with IPF [28].

### 14.3.4 $p14^{ARF}$

$p14^{ARF}$, a tumor suppressor gene, induces cell cycle arrest in both the G1 and G2 phases of the cell cycle and induces apoptosis in a p53-dependent and p53-independent manner. $p14^{ARF}$ silencing via DNA methylation has been reported in some tumor types. Nitric oxide (NO) upregulates $p14^{ARF}$ and, in turn, enhances p53 activity, resulting in apoptosis [29], whereas NO that is downregulated by TGFβ attenuates EMT in alveolar type II (ATII) cells, whose apoptosis can lead to pulmonary fibrosis [30].

### 14.3.5 $p15^{INK4B}$, Caspase Recruit Domain 10, and O-6-Methylguanine-DNA Methyltransferase

Huang et al. reported hypermethylation and reduced expression of the *cyclin-dependent kinase inhibitor 2B* (*CDKN2B*, $p15^{INK4B}$) gene and the *caspase recruitment domain 10* (*CARD10*) gene in IPF [31]. In particular, $p15^{INK4B}$, a tumor suppressor gene, is a member of the INK4 family, which includes the $p16^{INK4A}$ and $p14^{ARF}$ genes. This gene is induced by TGFβ through SMAD proteins, and aberrant methylation at the 5′ end of the $p15^{INK4B}$ gene was observed in 15 % of the neuroendocrine type of lung cancer [32], which includes small cell lung cancer that is frequently detected in IPF. Another report showed that *CARD10*, also known as *CARMA3*, was overexpressed in NSCLC [33]. The reason for the different *CARD10* expression profiles between IPF and lung cancer remains unknown and requires further investigation. Furthermore, the same group also reported that O-6-methylguanine-DNA methyltransferase (MGMT) was hypomethylated and overexpressed in IPF, whereas many articles have reported loss or decrease of *MGMT* expression through promoter methylation of this gene in lung cancer [34]. MGMT is a DNA repair enzyme that protects against DNA adduct formation of carcinogenesis, leading to a stabilized chromatin structure and prevention of apoptosis induction.

### 14.3.6 Prostaglandin E2 (PGE2)

Prostaglandin E2 (PGE2), a metabolite of cyclooxygenase-2 (COX2), is a lipid mediator derived from the COX pathway of arachidonic acid metabolism. COX2/PGE2 stimulates PI3K/AKT and extracellular signal-regulated kinase 1/2 (ERK1/2) signaling to induce tumor angiogenesis and invasiveness. COX2 expression and PGE2 production are increased in many tumor types including lung cancer [35]. On the other hand, PGE2 mediates many inhibitory signals in cells, thereby attenuating myofibroblast differentiation and potentially suppressing pulmonary fibrogenesis [36]. Lower levels of PGE2 in bronchoalveolar lavage fluid (BALF), and diminished PGE2 synthesis in fibroblasts, are found in IPF patients, suggesting its antifibrotic function [37]. PGE2 exerts its biological effects through the E-prostanoid 2 (EP2) receptor, the major G protein-coupled receptor for PGE2, and could thereby inhibit TGFβ-induced myofibroblast differentiation [38]. Decreased expression of the EP2 receptor confers PGE2 resistance on fibroblasts from mice with experimental fibrosis and from some patients with IPF. On the other hand, multiple signaling pathways can be associated with EP2-mediated oncogenesis: (1) activation of inducible nitric oxide synthase (iNOS)/guanylate cyclase (GC) and ERK1/2 via transactivation of the EGFR; (2) phosphorylation of the tyrosine-protein kinase SRC by β-arrestin 1 signaling, activation of the EGFR, and activation of PI3K/AKT and RAS/ERK pathways; (3) phosphorylation of JNK by β-arrestin 1 signaling and upregulation of profilin-1 (PFN1) to increase F-actin; (4) regulation of the cAMP/PKA/CREB pathway; or (5) increased expression of β-catenin-mediated cMYC and vascular endothelial growth factor (VEGF) [39]. Aberrant methylation of the promoter region of the *PTGER2* gene encoding the EP2 receptor is proposed as one plausible explanation for these phenomena. Hypermethylation of this region, which contains numerous CpG islands, was frequently observed in both IPF and lung cancer and is reported to be driven by PTEN suppression/AKT activation in fibroblast of IPF.

### 14.3.7 Thy1

Thy1 (CD90), a 25–37-kDa glycosylphosphatidylinositol (GPI)-anchored glycoprotein that is expressed mainly in leukocytes, is involved in cell-cell and cell-matrix interactions and may be a marker for lung cancer stem cells (CSCs) in NSCLC cell lines [40]. In IPF, hypermethylation of the promoter region of the *Thy1* gene causes loss or reduction of *Thy1* expression in fibroblasts [41]. Loss of this gene expression leads to myofibroblast differentiation within fibroblastic foci in IPF, whereas this alteration is associated with invasiveness in lung cancer.

### *14.3.8 Tumor Protein p53-Induced Nuclear Protein 1*

In addition to evidence for hypermethylation, Sanders et al. have reported increased gene expression due to hypomethylation in IPF [25]. Tumor protein p53-induced nuclear protein 1 (TP53INP1), a major mediator of p53 antioxidant function that is localized on chromosome 8q22, is upregulated in IPF. Exposure to diverse stress agents enhances expression of *TP53INP1*, which encodes two nuclear isoforms, TP53INP1a and TP53INP1b. TP53INP1 transcriptionally activates p53-target genes such as *p21* and *p53-inducible gene 3* (*PIG3*), consequently leading to cell cycle arrest and apoptosis upon DNA damage stress in different cell types [42]. TP53INP1 in particular is considered as a tumor suppressor gene, because its expression is decreased in different tumor types.

These findings suggest that aberrant epigenetic alteration may be a potent candidate for a common pathogenesis of IPF and lung cancer through modification of corresponding gene expression.

## 14.4 Histone Modification in Epigenetic Changes

Histone modification that posttranscriptionally regulates gene expression is another epigenetic change. Histones are mainly modified by acetylation, methylation, phosphorylation, and ubiquitination. Of these changes, aberrant acetylation status that has been identified in many types of diseases is governed by histone acetyltransferase (HAT)-mediated acetylation and histone deacetylase (HDAC)-mediated deacetylation, which modulates the chromatin condensation status, thereby altering gene expression. HAT acetylates lysine residues of histones, which generally induces gene expression, whereas HDAC deacetylates these residues, resulting in chromatin condensation and consequently reducing gene transcription. Di- and trimethylated histone H3 lysine 9 (H3K9me2/3) and trimethylated histone H3 lysine 27 (H3K27me3) that repress gene transcription, and trimethylated histone H3 lysine 4 (H3K4me3) that enhances gene transcription, are well-known histone methylation modified forms. More than 50 histone lysine methyltransferases (HMTs) and demethylases regulate these methylations, resulting in epigenetic gene activation or silencing.

### *14.4.1 Histone Deacetylase*

The 18 types of HDACs are subdivided into four major classes based on sequence homology and catalytic mechanism. HDACs are aberrantly activated in many tumor types and often reduce gene expression associated with lung tumorigenesis. Aberrant HDAC activity enhances cellular proliferation through a number of

signaling pathways including the MYC/MAD and RB/E2F pathways. HDACs have also been reported to be implicated in fibrogenesis in various organs. Guo et al. showed HDAC4-dependent differentiation of normal human lung fibroblasts (NHLFs) to myofibroblasts that requires AKT phosphorylation and demonstrated that AKT activation was indispensable for TGFβ-mediated lung fibroblast-myofibroblast transition [43]. Halder et al. reported that the loss of TGFβ type II receptor expression (TβRII) through histone deacetylation prevents TGF-β-mediated tumor suppressive function [44].

### *14.4.2 Histone Methyltransferase*

HMTs generally contain the SET (suppressor of variegation, enhancer of zeste, trithorax) domain as the catalytic unit, and its dysregulation leads to aberrant histone methylation, resulting in tumorigenesis by oncogene activation and/or inactivation of tumor suppressor genes. Of *HMT* genes, the polycomb group protein *enhancer of zeste homolog 2* (*EZH2*) gene that has HMT activity is known to be overexpressed in many malignant tumors. Polycomb group proteins (PcG), which are transcriptional repressors, contain two distinct protein complexes: polycomb repressive complex (PRC) 1 and PRC2. PRC2 consists of EZH2, its catalytic subunit, the embryonic ectoderm development (EED) protein, and EED-associated HDAC1 and HDAC2. EZH2 acts as an HMT and trimethylates H3K27, thereby leading to epigenetic silencing of genes involved in development, differentiation, and growth. EZH2 also recruits DNMTs to target promoters. EZH2 thus inactivates tumor suppressor genes through both DNA methylation and histone methylation. Therefore, *EZH2* is considered as an oncogene. Indeed, we previously reported that EZH2 expression is associated with poor prognosis in patients with NSCLC and increases potentials of tumor growth and invasiveness in NSCLC cells [45]. Many PRC2 target genes contain CpG islands, and Vire et al. reported that EZH2 directly interacts with DNMTs and is necessary for de novo DNA methylation of PRC2 target gene promoters [46]. Regarding the association of IPF with HMTs, Coward et al. recently demonstrated that in fibroblasts from IPF, G9a HMT-mediated H3K9 methylation and EZH2-mediated H3K27 methylation were markedly increased at the *COX2* promoter, thereby resulting in epigenetic silencing of the *COX2* gene [47]. They also previously demonstrated that defective histone acetylation caused by decreased recruitment of HATs, and increased recruitment of the NCoR, CoREST, and mSin3a transcriptional corepressor complexes to the *COX2* promoter, is responsible for diminished *COX2* gene transcription in IPF. As described in the previous section, COX2/PGE2 function as key antifibrotic mediators by attenuating myofibroblast differentiation and potentially suppressing lung fibrogenesis, whereas these mediators, when overexpressed in lung cancer cells, are known to contribute to tumor angiogenesis.

### *14.4.3 Interferon-γ-Inducible Protein of 10 kDa/Chemokine C-X-C Motif Ligand 10*

Interferon-γ-inducible protein of 10 kDa (IP10)/chemokine C-X-C motif ligand 10 (CXCL10) is secreted by diverse cells including monocytes, fibroblasts, and endothelial cells, and HDACs interact with HMTs that methylate H3K9 in order to maintain chromatin condensation at its promoter region. IP10 has been reported to inhibit tumor growth, metastasis, and angiogenesis in NSCLC [48], while Keane et al. reported that lung tissues and fibroblasts from IPF patients constitutively produced less IP10 than normal fibroblasts, suggesting that IP10 also attenuates angiogenic activity in IPF [49].

Given these findings, histone modification that interacts with diverse pathways and molecules may be directly and indirectly involved in the common pathogenesis of IPF and lung cancer.

## 14.5 MicroRNA in Epigenetic Changes

microRNAs (miRNAs) are a class of noncoding small RNAs that consist of approximately 20–25 nucleotides that bind to the 3′ untranslated region (3′ UTR) of the mRNA of target genes. Once bound to the target mRNA, the mRNA is degraded, and its translation is repressed. A single miRNA targets genes in different pathways, while a single gene is targeted by multiple miRNAs. Therefore, miRNAs play essential roles in numerous cellular and developmental processes, including in intracellular signaling pathways and organ morphogenesis, whereas aberrant miRNA expression is associated with the development and progression of a variety of diseases including cancer. Currently, miRNA is a major focus of research, and in this section, we extensively review the relationship between miRNA and the common pathway of IPF and lung cancer.

### *14.5.1 miR-21*

miR-21, one of the best-characterized miRNAs in tumorigenesis, has been reported to be overexpressed in many types of cancer and to be particularly related to prognosis in never-smokers with NSCLC [50]. miR-21 has also been reported to be upregulated in the lungs of both mice with bleomycin-induced pulmonary fibrosis and in patients with IPF [51]. TGFβ, a key mediator of lung fibrogenesis, upregulates miR-21 expression, thereby promoting the activation of pulmonary fibroblasts, resulting in myofibroblast differentiation. Fibroblastic growth factor-2 (FGF2) also enhances miR-21 expression in human primary fibroblasts. In turn, enhanced miR-21 expression is primarily located in myofibroblasts in IPF.

TGFβ-induced fibrogenic activation of pulmonary fibroblasts through miR-21 is at least partly generated by negative modulation of SMAD7 and reduced SMAD2 phosphorylation. miR-21 is known to positively or negatively regulate the expression and function of diverse tumor-associated genes, including *tropomyosin 1* (*TPM1*), *programmed cell death 4* (*PDCD4*), *PTEN*, *TGFβ*, *nuclear factor I/B* (*NFIB*), a *serpin peptidase inhibitor* (*maspin*), *Sprouty-2* (*Spry2*), *myristoylated alanine-rich C-kinase substrate* (*MARCKS*), *matrix metalloproteinases* (*MMPs*), and *reversion-inducing cysteine-rich protein with kazal motifs* (*RECK*) that is an inhibitor of MMPs. Of these genes, *PDCD4*, *PTEN*, *TGFβ*, and MMP-mediated molecules are commonly associated with IPF and lung cancer.

*PDCD4*, which is considered as a tumor suppressor gene, inhibits the activation of activator protein-1 (AP1). In turn, AP1 that is activated through the RAS/MAPK pathway induces miR-21 expression, whereas RAS downregulates PTEN and PDCD4 in an AP1- and miR-21-dependent manner [52]. On the other hand, miR-21 in fibroblasts was associated with TGFβ-induced differentiation of fibroblasts into myofibroblasts through PDCD4, although this event was reported in cancer stroma [53].

PTEN expression, which is negatively regulated by TGFβ, is reduced in 74 % of NSCLC [54]. White et al. showed that PTEN expression is decreased in fibroblasts isolated from the lungs of IPF patients, that myofibroblasts in IPF have diminished PTEN expression, that inhibition of PTEN *in vivo* promotes fibrosis, and that PTEN prevents myofibroblast differentiation *in vitro* [17].

TGFβ is a potent profibrotic cytokine and has been reported to play a critical role in the pathogenesis of IPF. While TGFβ also induces SMAD-independent signaling, TGFβ signaling that is dependent on SMAD proteins results from TGFβ binding to TβRII, which then phosphorylates and activates TGFβ type I receptor (TβRI) and consequently regulates tumor-associated gene transcription, including the regulation of diverse signaling pathways, the cell cycle, and EMT [55]. Interestingly, TGFβ signaling can exert either tumor suppressive or promoting function according to the conditions to which the cells are exposed.

MMPs, a protein family of zinc-dependent endopeptidases, are classified into subgroups. MMP-mediated degradation of many substrates leads to multiple biological and pathological conditions including wound healing, tumorigenesis, organ fibrosis, and inflammation. A functional imbalance between MMPs and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), can underlie the development of both pulmonary fibrosis and lung cancer [56]. MMP7 is overexpressed in both IPF and NSCLC [57, 58]. MMP2 and MMP9 were not only highly upregulated in the lungs of IPF patients but were also associated with tumor invasion and metastasis [59–61]. On the other hand, increased expression of TIMP1 was found in bleomycin-induced pulmonary fibrosis [62], and TIMP3 was upregulated in IPF patients [63]. Serum levels of TIMP1 and MMP9 were elevated in NSCLC tissues [64].

### 14.5.2 Let-7

The human lethal-7 (let-7) family, which contains 13 members, is another of the best-characterized miRNAs and contributes to development and carcinogenesis. Let-7 is considered as a tumor suppressor and is downregulated in both IPF and lung cancer. Among the let-7 family, a role for let-7d has been reported in many types of cancer and lung diseases. TGFβ reduces let-7d expression, which inhibits high mobility group AT-hook 2 (HMGA2), a target of let-7d that is highly expressed in alveolar epithelial cells (AECs) of IPF patients, thereby preventing EMT [65]. Pandit et al. also reported that SMAD3 binds to the putative let-7d promoter, which may be a potential mechanism by which let-7d inhibition of EMT is prevented [66]. Johnson et al. suggested that let-7 downregulation in lung tumors regulates RAS expression, which might function as a possible oncogenic mechanism [67]. The possible association of let-7 with RAS signaling through HMGA2 may result in antifibrotic phenotypes and oncogenesis.

Cell division cycle 25A (CDC25A) may be another target of let-7 that is associated with both IPF and lung cancer. CDC25A belongs to the CDC2 family of dual-specificity phosphatases and removes the inhibitory phosphates of cyclin-dependent kinases (CDKs), leading to their activation and consequently promoting cell cycle progression and cellular proliferation [68]. Let-7c targets the homeobox A1 gene (HOXA1), resulting in inhibition of CDC25A expression that is frequently increased in NSCLC [69, 70]. CDC25A expression was induced by keratinocyte growth factor (KGF), which also induces proliferation of AECs, whereas TGFβ, a key player in pulmonary fibrogenesis, has been reported to inhibit AEC proliferation induced by KGF [71]. TGFβ also reduces the increased let-7d expression that is found in the AECs of IPF. Let-7c and let-7d may exert reciprocal actions on the development of IPF and pulmonary tumorigenesis.

### 14.5.3 miR-155

miR-155 is produced from processing of the B-cell integration cluster (BIC), which is a noncoding transcript expressed in activated B cells, T cells, monocytes, and macrophages. miR-155 has also been reported to be upregulated in lung cancer and IPF [72, 73], and its expression is decreased by TGFβ. This miRNA reduces keratinocyte growth factor-7 (KGF7), resulting in fibroblast migration through activation of caspase 3 [74]. Coira et al. reported that miR-155 acts as an oncogene by inhibiting SMARCA4 (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 4), the catalytic subunit of the SWI/SNF chromatin-remodeling complex, in lung tumors [75]. miR-155 overexpression downregulates putative tumor suppressor genes including *TP53INP1*, *PTEN*, *PDCD4*, and *SH2 domain-containing inositol 5′-phosphatase 1* (*SHIP1*) [76, 77].

### 14.5.4 miR-29

The miR-29 family consists of miR-29a, miR-29b, and miR-29c and interacts with multiple profibrotic and inflammatory pathways, and its expression is significantly reduced in fibrotic lungs [73]. miR-29 is also one of the TGFβ-associated miRNAs involved in fibrogenesis and inhibits TGFβ-induced ECM synthesis through activation of the PI3K/AKT pathway in human lung fibroblasts [78]. miR-29 is negatively regulated by TGFβ/SMAD signaling through SMAD3 [79], whereas decreased miR-29 upregulates collagens and the genes encoding ECM proteins that are associated with the development of pulmonary fibrogenesis [80]. Therefore, miR-29 is considered to exert antifibrotic activity through regulation of the ECM and EMT. On the other hand, multiple studies have reported that miR-29 is downregulated in lung cancer [72, 81]. Furthermore, Fabbri et al. demonstrated that miR-29 exerts antitumor effects by directly targeting both DNMT3A and DNMT3B, thereby restoring the silenced expression of tumor suppressor genes in lung cancer [82].

### 14.5.5 miR-30

miR-30 downregulates RAB18, which belongs to the RAS superfamily, resulting in inhibition of NSCLC cell growth [83], whereas miR-30 is downregulated in IPF [66]. WNT1-inducible signaling pathway protein 1 (WISP1) is highly expressed in IPF, where it functions as a pro-fibrotic mediator, whereas miR-30a reverses TGF-β-induced WISP1 expression in lung fibroblasts [84].

### 14.5.6 miR-210

miR-210 is an intronic miRNA located within the genomic loci of transcripts. Its expression is increased in both IPF and lung cancer [85, 86]. Hypoxia-regulated miR-210 mediates gene expression implicated in diverse pathophysiological pathways, such as the cell cycle, apoptosis, angiogenesis, and oxidative metabolism. Bodempudi et al. reported that miR-210 expression is markedly increased in IPF fibroblasts in response to hypoxia, which stimulates fibroblast proliferation in IPF by repressing the cMYC inhibitor, MNT [87]. miR-210 overexpression directly downregulates MNT and indirectly activates cMYC, presumably thereby inhibiting hypoxia-induced cancer cell cycle arrest such as G0/G1 arrest and driving cellular proliferation [88]. On the other hand, Tsuchiya et al. reported that miR-210 overexpression in esophageal squamous cell carcinoma cells directly targets fibroblast growth factor receptor-like 1 (FGFRL1), resulting in induction of cell cycle arrest in both G0/G1 and G2/M phases and subsequent apoptosis [89].

### 14.5.7 miR-199a–5p

miR-199a–5p expression is increased in IPF patients, especially in myofibroblasts and fibroblastic foci. miR-199a–5p that is induced by TGFβ downregulates CAV1 that degrades the TGFβ/TβR complex, consequently promoting TGFβ signaling, ECM production, and myofibroblast differentiation, as well as cellular proliferation, migration, and invasion [90]. A recent report showed that miR-199 also regulates miR-155, which inhibits SMARCA4 that exerts a tumor suppressive function [75].

### 14.5.8 miR-145

miR-145, a putative tumor suppressor, is downregulated in diverse tumors, and its overexpression suppresses the proliferation of human lung adenocarcinoma cells through the EGFR and NUDT1 [91]. On the other hand, Yang et al. reported that miR-145 expression is increased in TGFβ-treated lung fibroblasts and in the lungs of IPF patients and that miR-145 overexpression in lung fibroblasts increased TGFβ-induced αSMA expression by targeting Kruppel-like factor 4 (KLF4), a known negative regulator of αSMA expression [92]. miR-145 exerts reciprocal effects on tumorigenesis and IPF development.

### 14.5.9 miR-200

miR-200 expression downregulates ZEB1 and ZEB2 expression, thereby inhibiting EMT and consequently suppressing distant metastasis in lung cancer [93], although miR-200 enhances metastases in mouse breast cancer cell lines partly through miR-200-mediated downregulation of SEC23A [94]. miR-200 also targets the key pro-angiogenic cytokines, IL-8 and CXCL1, thereby inhibiting tumor angiogenesis. TGFβ decreased miR-200 expression in rat ATII cells, and indeed, miR-200 is downregulated in the lungs of IPF patients [95]. That study also showed that decreased expression of miR-200 regulates the expression of GATA3, ZEB1, and ZEB2 and promotes EMT in AECs.

### 14.5.10 miR-17–92

Reduced miR-17–92 expression interacts with DNMT1, contributing to IPF development [96]. miR-17–92 silencing via DNA methylation is found in lung tissue and fibroblasts from IPF patients, whereas reduced miR-17–92 expression is inversely

correlated with DNMT1 expression. Introduction of the miR-17–92 cluster into fibroblasts of IPF reduced both the expression of fibrotic genes and DNMT1 and DNA methylation of the cluster and normalized cellular phenotype. The review by Osada et al. indicated that cMYC, E2F1/E2F3, and STAT3, which are frequently activated in cancer, transactivate miR-17–92 that is overexpressed in lung cancer, especially in SCLC [97]. miR-17–92 also suppresses PTEN, BIM, TβRII, CTGF, RB, and p21. Increased miR-17–92 expression in tumors targets antiangiogenic and fibrotic genes, many of which are altered in IPF. The biological properties of miR-17–92 may differ between IPF and lung cancer.

### *14.5.11 miR-375*

miR-375 is downregulated in squamous cell carcinoma and upregulated in adenocarcinoma of the lung. Its overexpression leads to inhibition of CLDN1 expression that suppresses cell migration, invasion, and metastasis [98]. On the other hand, miR-375 negatively regulates AEC transdifferentiation through inhibition of the Wnt/β-catenin pathway, and its expression was decreased in the lungs of IPF patients [99].

### *14.5.12 miR-185*

miR-185 induces G1 arrest, thereby inhibiting cellular proliferation in lung cancer [100]. This arrest may be due to miR-185 suppression of *CDK6* and *AKT1* mRNA expression. The expression of miR-185 as well as of Argonaute subfamily proteins, AGO1 and AGO2, a core component of RNA-induced silencing complexes (RISCs), is increased in IPF.

### *14.5.13 miR-154*

miR-154 may target several genes involved in the nuclear factor-κB (NFκB), hypoxia-inducible factor-1 (HIF1), MAPK, NOTCH, and autophagic molecular signaling pathways, and its expression is decreased in the sera of lung cancer patients [101]. In IPF, miR-154 induced by TGFβ inhibits *p15* (*CDKNB2*), a TGF-β-responsive gene, and the Wnt pathway repressors DKK2, DIXDC1, and PPP2CA and increases FZD 4/5/6, LRP, and KREMEN1, consequently inducing fibroblast proliferation and migration [102]. Therefore, miR-154 overexpression may be a positive regulator of the Wnt/β catenin pathway.

Although there are conflicting data regarding the role of miRNAs in pulmonary tumorigenesis and IPF development, miRNA interaction with other miRNAs may

**Table 14.1** Association of microRNAs with tumorigenesis and the development of IPF

| MicroRNA | Tumorigenesis | IPF development | Related molecules |
|---|---|---|---|
| miR-21 | ↑ | ↑ | TPM1, PDCD4, PTEN,TGFβ, NFIB, mapsin, Spry-2, MARCKS |
| | | | MMPs, RECK, SMAD2, SMAD7, FGF2 |
| Let-7 | ↓ | ↓ | TGFβ, HMGA2, SMAD3, RAS, CDC25A |
| miR-155 | ↑ | ↑ | TGFβ, KGF7, SMARCA4, TP53INP1, PTEN, PDCD4, SHIP1 |
| miR-29 | ↓ | ↓ | TGFβ, SMAD3, PI3K/AKT, DNMT3A, DNMT3B |
| miR-30 | ↓ | ↓ | RAS, Rab18, TGFβ, WISP1 |
| miR-210 | ↑? | ↑ | Hypoxia, MNT, FGFRL1 |
| miR-199a–5p | ↑ | ↑ | TGFβ, CAV1, SMARCA4 |
| miR-145 | ↓ | ↑ | EGFR, NUDT1, TGFβ, KLF4 |
| miR-200 | ↓ | ↓ | ZEB1, ZEB2, Sec23a, IL-8, CXCL1, TGFβ, GATA3, PTEN |
| | | | BIM, TGFβRII, CTGF, RB, and p21 |
| miR-17–92 | ↑ | ↓ | DNMT-1, cMYC, E2F1/E2F3, STAT3 |
| miR-375 | ↓ | ↓ | TGFβ/SMAD, CLDN1, FZD8, Wnt/β catenin |
| miR-185 | ↓ | ↑? | CDK6, AKT1, AGO1, AGO2, RISCs |
| miR-154 | ↓? | ↑? | NFκB, HIP-1, MAPK, Notch, TGFβ, p15, DKK2, DIXDC1 |
| | | | PPP2CA, FZD 4/5/6, LRP, KREMEN1, Wnt/β catenin |

be a strong candidate as a common pathogenesis of IPF and lung cancer as described in this section (Table 14.1). Further investigation is warranted.

## 14.6 Signaling Pathways

IPF is characterized by injured and hyperplastic alveolar epithelium, which releases diverse molecules including growth factors, cytokines, and MMPs, causing the activation and proliferation of mesenchymal cells, ECM deposition, and the accumulation of fibroblasts. These processes can lead to basal membrane disruption, fibrin formation, abnormal wound repair, and angiogenesis through multiple signaling pathways, thereby promoting cellular apoptosis or migration. In many lung cancers, these signals can also activate oncogenes or inactivate tumor suppressor genes, leading to oncogenesis through aberrant oncogenic pathways. These findings suggest that common signaling pathways may contribute to the development of both IPF and lung cancer. Indeed, some individual key molecules, as described in the previous sections, are associated with both oncogenesis and fibrogenesis

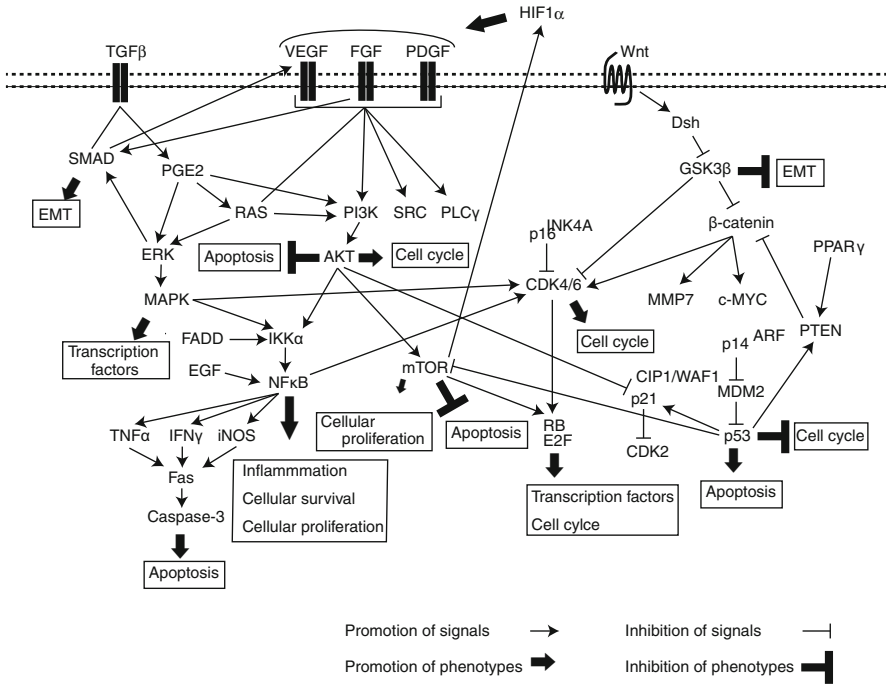


**Fig. 14.1** Potential signaling pathways underlying the common pathogenesis of IPF and lung cancer

through common signaling pathways (Fig. 14.1). Therefore, we further describe noteworthy signaling pathways mentioned in the previous sections.

### *14.6.1 Transforming Growth Factor-β Signaling*

As described in the previous sections, the TGFβ signaling pathway plays important roles in wound healing and fibrogenesis through its cross talk with other signaling pathways and diverse mediators. TGFβ-induced EMT and accumulation of myofibroblasts can be promoted by integrin-dependent activation of SMAD and Wnt/β-catenin signaling [103]. Myofibroblasts are resistant to apoptosis, which promotes fibrogenesis, partly through reduction of the anti-fibrotic prostaglandin E2 (PGE2) in IPF [104]. The features of these phenomena that lead to EMT appear to be similar to those of tumor cells, and myofibroblasts promote cellular infiltration and progression through multiple mediators in a tumor environment.

### 14.6.2 Wnt Signaling

The Wingless-type protein (Wnt) family, which consists of 19 secreted proteins, transmits its signal through activation of multiple pathways. One major Wnt pathway, termed the canonical pathway, inhibits GSK3β, leading to the stabilization and accumulation of β-catenin in the cytosol and its translocation into the nucleus, consequently resulting in enhanced expression of target genes that are associated with diverse diseases. As described in the previous Sect. 14.3.1, the Wnt/β-catenin pathway is one target of TERT regulation. β-catenin transmission of Wnt signals to the nucleus regulates diverse oncogenic genes including *cyclin D1* and *cMYC*, and its overexpression and stabilization can promote oncogenesis. The review by Stewart et al. indicates that expression of WNT1, a Wnt ligand, is correlated with aberrant β-catenin expression and increased expression of cMYC, cyclin D1, VEGFA, MMP7, Ki67, and survivin, resulting in proliferation of NSCLC [105]. The other Wnt pathway, termed the noncanonical pathway, which does not involve β-catenin, is mainly comprised of two types of pathways, the planar cell polarity pathway (Wnt-PCP pathway) and the Wnt-calcium pathway (Wnt/Ca2+ pathway). The combined expression of WNT7A and FZD9 in NSCLC cell lines leads to ERK5 activation, which in turn leads to increased PPARγ expression and activation of Sprouty-4. Sprouty-4 inhibits EMT, consequently inhibiting tumor growth [106, 107]. Indeed, aberrant expression of Wnt ligands and Wnt signaling mediators has been frequently found in NSCLC.

The Wnt/β-catenin pathway also promotes EMT and myofibroblast differentiation that is mediated through TGFβ, thereby contributing to pulmonary fibrogenesis. The Wnt/β-catenin signaling pathway was upregulated in lung tissues of IPF patients. Moreover, β-catenin targets cyclin D1 and MMP7, both of which are considered to be associated with pulmonary fibrogenesis [108].

### 14.6.3 PI3K/AKT/mTOR Signaling

Phosphoinositide 3-kinases (PI3Ks) regulate cellular proliferation, survival, adhesion, and motility. These kinases stimulate PIP3 synthesis on the cell membrane, thereby promoting the PI3K/AKT/mTOR pathway, a downstream signaling pathway composed of multiple receptor tyrosine kinases. The PI3K/AKT/mTOR pathway is activated early in the pathogenesis of pulmonary tumorigenesis through the modulation of multiple signals as follows, resulting in inhibition of apoptosis and cell survival: (1) mutations in *PI3K* or *PTEN* as well as in the *EGFR* or *KRAS* and (2) *PIK3CA* amplification, *PTEN* loss, or *AKT* activation [109]. In fibroblasts of IPF, PI3K/AKT/mTOR signals are aberrantly activated, while PTEN activity is lower than that of normal cells [110]. Furthermore, the PI3K/AKT/mTOR pathway interacts with many other signaling pathways, including those of MAPK and VEGFR, in IPF cells [111].

### 14.6.4 Nuclear Factor-κB Signaling

Cross talk between the NFκB and PI3K/AKT/mTOR signaling pathways may contribute to lung cancer cell survival and proliferation [112]. PI3K/AKT promotes NFκB activity in an IKKα-dependent manner [113], while NFκB is activated by Fas-associated death domain protein (FADD) phosphorylation through IKK, thereby promoting proliferation in lung adenocarcinoma [114]. Furthermore, EGF induces IKK-independent NFκB activation through IκBα phosphorylation in lung adenocarcinoma cells [115]. NFκB activation was associated with *KRAS* mutation, and both lost p53 function and active $KRAS^{G12D}$, the major *RAS* point mutation in lung cancer, constitutively activate NFκB as well as downstream signaling pathways, such as PI3K and MAPK, in lung cancer cells [116]. NFκB activation is also found in the IPF-associated inflammatory process. NFκB-dependent inflammatory mediators, including tumor necrosis factor (TNF)-α, TGFβ, interleukin (IL)-1, inducible nitric oxide synthase (iNOS), and interferon (IFN)-γ, were highly expressed in IPF patients and in animal models of pulmonary fibrosis [117–119]. Previous *in vivo* studies showed that suppression of the NFκB signaling pathway can attenuate bleomycin-induced pulmonary fibrosis, while *in vitro* studies also found that the NFκB signaling pathway contributed to the regulation of TGFβ [119–121].

### 14.6.5 Fibroblast Growth Factor Signaling

Fibroblast growth factors (FGFs) are a family of homologous polypeptide ligands that bind to their cognate FGF receptors (FGFRs) [122]. There are 22 FGF ligands comprising six subfamilies and four FGFR isoforms that are differentially activated by FGF ligands in conjunction with the scaffold protein heparan sulfate proteoglycan. Binding of FGF ligands to FGFRs transmits signals associated with angiogenesis as well as with cellular migration and proliferation, and the FGF signaling pathway is involved in the pathogenesis of diverse diseases. However, FGF signaling exerts reciprocal effects on tumor promoting and suppressive activities, which are dependent on the tumor type. Regarding IPF, TGFβ released from AECs induces the proliferation of pulmonary fibroblasts through FGF2, which promotes phosphorylation of p38 MAPK and JNK [123], and high FGF2 levels have been found in the bronchoalveolar lavage fluid and serum of IPF patients [124]. Many NSCLC cells showed elevated FGF2 levels, which in turn promote the growth of these tumor cells by intracrine mechanisms [125]. FGF2 also contributes to angiogenesis and tumor proliferation in many types of cancer, and FGF2-mediated autocrine and paracrine signaling can potently promote oncogenesis.

Another FGF, FGF1, exerts antifibrotic activity through downregulation of collagen expression and antagonization of some TGFβ-mediated profibrotic functions [126]. FGF1 was also shown to restore TGFβ-induced EMT in AECs through

dephosphorylation of the SMAD2 phosphorylation that was induced by the MEK/ERK pathway. FGF1-mediated activation of FGFR signaling induces the recruitment and activation of SRC homology (SH2)- or phosphotyrosine (PTB)-containing proteins, thereby activating multiple signaling pathways including PI3K/AKT, MEK1/2-ERK, and p38MAPK [127]. Recently, Daly et al. reported that low levels of FGF1 are associated with favorable outcomes in stage I lung adenocarcinoma [128].

### *14.6.6 Fas/FasL Signaling*

Fas, a cell surface death receptor of the TNF receptor (TNFR) superfamily, paradoxically promotes both survival/differentiation and apoptosis through the modulation of immune responses. Low to absent staining of Fas was detected in fibroblastic cells of fibroblast foci from IPF patients [129]. Exposure to the proinflammatory cytokines, TNF-α and IFNγ, increases Fas expression in an NFκB- and MAPK-dependent manner, thereby sensitizing fibroblasts to Fas-induced apoptosis and reversing the resistance of lung fibroblasts to apoptosis, which is mediated by a prosurvival effect of TGFβ. Aberrant Fas/Fas ligand (FasL) expression is found in many lung cancer cells and samples [130], suggesting its contribution to lung carcinogenesis.

### *14.6.7 Vascular Endothelial Growth Factor Signaling*

The vascular endothelial growth factor (VEGF) signaling pathway is well characterized. VEGF ligands (VEGFA to VEGFE and placental growth factor) induced by hypoxia, growth factors, and cytokines interact with VEGF receptors (VEGFR1–3), especially with VEGFR2 that activates the PI3K/AKT pathway; promotes cellular proliferation, migration, and survival as well as angiogenesis; and inhibits apoptosis. VEGF is highly expressed in lung cancer, and its expression is associated with poor prognosis [131]. While normal wound healing requires angiogenesis, aberrant neovascularization is often found in IPF tissues, suggesting that VEGF signaling is associated with the development of IPF. Furthermore, Kobayashi et al. showed that SMAD3 signaling mediates TGFβ-induced VEGFA production in human lung fibroblasts [132].

### *14.6.8 Platelet-Derived Growth Factor Signaling*

The platelet-derived growth factor (PDGF) family, which consists of PDGFA to PDGFD, promotes cellular proliferation, invasion, and angiogenesis as well as

wound healing and proliferation of mesenchymal cells. Enhanced PDGF expression and activation of its signaling have been reported in different types of cancer and in fibrotic disorders. Dimeric PDGFs bind to the receptors PDGFRα and PDGFRβ, thereby transmitting signaling through PI3K, SRC, phospholipase C-γ, and RAS pathways in both an autocrine and a paracrine manner [133]. PDGFA and PDGFC paracrine signaling was associated with fibroblastic tumor infiltration in NSCLC cell lines [134]. Furthermore, PDGF signaling, which partly overlaps with VEGF signaling, activates cancer-associated fibroblasts (CAFs) and recruits VEGF-producing stromal fibroblasts, leading to both tumorigenesis and angiogenesis [135]. PDGF that is synthesized by alveolar macrophages is a potent mitogenic and chemotactic factor for fibroblasts. Previous *in vitro* studies showed that PDGF interacts with several fibrotic mediators including TGFβ, IL-1, TNF-α, FGF, and thrombin, thereby promoting fibrogenesis. Macrophages and fibroblasts from IPF patients produce PDGF, whereas PDGFB and PDGFR mRNAs are highly expressed in hyperplasic ATII cells in IPF [136]. PDGF/PDGFR signaling can at least partly interact with VEGF/VEGFR and FGF/FGFR signaling pathways, and the intricate cross talk between these pathways may contribute to the common pathogenesis of IPF and lung cancer.

### *14.6.9 RAS/RAF/MEK/MAPK Signaling*

Signaling of the RAS/RAF/MEK/MAPK pathway is one of the most extensively characterized signals and modulates cellular migration, proliferation, and apoptosis; its aberrant signals are therefore involved in the development of diverse diseases. In particular, this pathway is frequently activated in lung cancer, most commonly via *KRAS* mutations in approximately 20 % of lung cancers, particularly in adenocarcinomas in smokers [137]. The RAS/RAF/MEK/MAPK pathway has also been associated with the development of IPF. Many molecules and pathways, as well as most signals described in this section, can converge, regulate, or interact with the RAS/RAF/MEK/MAPK pathway.

### *14.6.10 Signaling Through Connexin*

Gap junctions are composed of protein complexes including connexins that characterize cell-cell communication, and their alteration is tightly associated with cellular proliferation, tissue repair, and tumor growth. Vancheri et al. reported the possible role of connexins, especially connexin 43 (CX43), in the common pathogenesis of IPF and lung cancer [138].

Multiple pathways that are mutually dependent interact with one another, thereby regulating the signals that can lead to inflammatory processes and tumorigenesis. Therefore, a possible common pathway of IPF and lung cancer may

provide a therapeutic perspective on these comorbid disorders. For example, nintedanib that targets PDGFRα and PDGFRβ, VEGFR1 to VEGFR3, and FGFR1 to FGFR3 has therapeutic potential for both IPF and NSCLC based on the phase III trials, INPULSIS-1 and INPULSIS-2, for IPF and LUME-Lung 1 for NSCLC [139, 140].

## 14.7 Conclusion

Both IPF and lung cancer are heterogeneous disease groups, and furthermore, multiple pathways and diverse molecules that interact with one another can be associated with both diseases, raising the complexity of the pathogenesis of these diseases. However, we often encounter patients with lung cancer comorbid with IPF in clinical practice, and as described in Sect. 14.1, lung cancer occurs in 4.4–38 % of patients with interstitial pneumonia according to previous reports. Possible commonality in the pathogenesis of IPF and lung cancer has been discussed in this chapter, suggesting that in this context, there may be a common pathway that contributes to the development of IPF and lung cancer. Diverse signals and molecules can transmit individual signaling pathways, converge on a common pathway, and promote inflammatory processes in IPF and lung tumorigenesis. These phenomena may lead to a high frequency of comorbid IPF and lung cancer. Therefore, an efficacious therapeutic strategy for both diseases that targets such a possible common pathway may be exploited in the future, although it has already been attempted, in part. In particular, although the incidence of lung cancer with IPF is steadily increasing, there are few reports regarding its treatment. For more efficacious and efficient therapy for IPF and lung cancer, a more fundamental pathway that underlies the development of both diseases needs to be determined.

## References

1. Kawasaki H, Nagai K, Yokose T, Yoshida J, Nishimura M, Takahashi K, et al. Clinicopathological characteristics of surgically resected lung cancer associated with idiopathic pulmonary fibrosis. J Surg Oncol. 2001;76(1):53–7.
2. Lawson WE, Loyd JE. The genetic approach in pulmonary fibrosis: can it provide clues to this complex disease? Proc Am Thorac Soc. 2006;3(4):345–9.
3. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356 (13):1317–26.
4. Gansner JM, Rosas IO. Telomeres in lung disease. Transl Res. 2013;162(6):343–52.
5. Jang JS, Choi YY, Lee WK, Choi JE, Cha SI, Kim YJ, et al. Telomere length and the risk of lung cancer. Cancer Sci. 2008;99(7):1385–9.
6. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, et al. Lung cancer susceptibility locus at 5p15.33. Nat Genet. 2008;40(12):1404–6.

7. Ma X, Gong R, Wang R, Pan Y, Cai D, Pan B, et al. Recurrent TERT promoter mutations in non-small cell lung cancers. Lung Cancer. 2014;86(3):369–73.
8. Liu T, Hu B, Chung MJ, Ullenbruch M, Jin H, Phan SH. Telomerase regulation of myofibroblast differentiation. Am J Respir Cell Mol Biol. 2006;34(5):625–33.
9. Wang Y, Kuan PJ, Xing C, Cronkhite JT, Torres F, Rosenblatt RL, et al. Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet. 2009;84(1):52–9.
10. Nogee LM, Dunbar 3rd AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med. 2001;344(8):573–9.
11. Jiang F, Yin Z, Caraway NP, Li R, Katz RL. Genomic profiles in stage I primary non small cell lung cancer using comparative genomic hybridization analysis of cDNA microarrays. Neoplasia. 2004;6(5):623–35.
12. Rodenhuis S, Slebos RJ. Clinical significance of ras oncogene activation in human lung cancer. Cancer Res. 1992;52(9 Suppl):2665s–9.
13. Takahashi T, Munakata M, Ohtsuka Y, Nisihara H, Nasuhara Y, Kamachi-Satoh A, et al. Expression and alteration of ras and p53 proteins in patients with lung carcinoma accompanied by idiopathic pulmonary fibrosis. Cancer. 2002;95(3):624–33.
14. Verri C, Roz L, Conte D, Liloglou T, Livio A, Vesin A, et al. Fragile histidine triad gene inactivation in lung cancer: the European Early Lung Cancer project. Am J Respir Crit Care Med. 2009;179(5):396–401.
15. Rabinovich EI, Kapetanaki MG, Steinfeld I, Gibson KF, Pandit KV, Yu G, et al. Global methylation patterns in idiopathic pulmonary fibrosis. PLoS One. 2012;7(4):e33770.
16. Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. J Thorac Dis. 2013;5 Suppl 5:S479–90.
17. White ES, Atrasz RG, Hu B, Phan SH, Stambolic V, Mak TW, et al. Negative regulation of myofibroblast differentiation by PTEN (Phosphatase and Tensin Homolog Deleted on chromosome 10). Am J Respir Crit Care Med. 2006;173(1):112–21.
18. Wang XM, Zhang Y, Kim HP, Zhou Z, Feghali-Bostwick CA, Liu F, et al. Caveolin-1: a critical regulator of lung fibrosis in idiopathic pulmonary fibrosis. J Exp Med. 2006;203 (13):2895–906.
19. Racine C, Belanger M, Hirabayashi H, Boucher M, Chakir J, Couet J. Reduction of caveolin 1 gene expression in lung carcinoma cell lines. Biochem Biophys Res Commun. 1999;255 (3):580–6.
20. Engelman JA, Wykoff CC, Yasuhara S, Song KS, Okamoto T, Lisanti MP. Recombinant expression of caveolin-1 in oncogenically transformed cells abrogates anchorage-independent growth. J Biol Chem. 1997;272(26):16374–81.
21. Ho CC, Huang PH, Huang HY, Chen YH, Yang PC, Hsu SM. Up-regulated caveolin-1 accentuates the metastasis capability of lung adenocarcinoma by inducing filopodia formation. Am J Pathol. 2002;161(5):1647–56.
22. Yoo SH, Park YS, Kim HR, Sung SW, Kim JH, Shim YS, et al. Expression of caveolin-1 is associated with poor prognosis of patients with squamous cell carcinoma of the lung. Lung Cancer. 2003;42(2):195–202.
23. Li L, Ren CH, Tahir SA, Ren C, Thompson TC. Caveolin-1 maintains activated Akt in prostate cancer cells through scaffolding domain binding site interactions with and inhibition of serine/threonine protein phosphatases PP1 and PP2A. Mol Cell Biol. 2003;23 (24):9389–404.
24. Sunaga N, Miyajima K, Suzuki M, Sato M, White MA, Ramirez RD, et al. Different roles for caveolin-1 in the development of non-small cell lung cancer versus small cell lung cancer. Cancer Res. 2004;64(12):4277–85.
25. Sanders YY, Ambalavanan N, Halloran B, Zhang X, Liu H, Crossman DK, et al. Altered DNA methylation profile in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186(6):525–35.

26. Ohta H, Chiba S, Ebina M, Furuse M, Nukiwa T. Altered expression of tight junction molecules in alveolar septa in lung injury and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2012;302(2):L193–205.
27. Paschoud S, Bongiovanni M, Pache JC, Citi S. Claudin-1 and claudin-5 expression patterns differentiate lung squamous cell carcinomas from adenocarcinomas. Mod Pathol. 2007;20 (9):947–54.
28. Lee T, Park JY, Lee HY, Cho YJ, Yoon HI, Lee JH, et al. Lung cancer in patients with idiopathic pulmonary fibrosis: clinical characteristics and impact on survival. Respir Med. 2014;108(10):1549–55.
29. Zeini M, Traves PG, Lopez-Fontal R, Pantoja C, Matheu A, Serrano M, et al. Specific contribution of p19(ARF) to nitric oxide-dependent apoptosis. J Immunol. 2006;177 (5):3327–36.
30. Vyas-Read S, Shaul PW, Yuhanna IS, Willis BC. Nitric oxide attenuates epithelial-mesenchymal transition in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2007;293(1):L212–21.
31. Huang SK, Scruggs AM, McEachin RC, White ES, Peters-Golden M. Lung fibroblasts from patients with idiopathic pulmonary fibrosis exhibit genome-wide differences in DNA methylation compared to fibroblasts from nonfibrotic lung. PLoS One. 2014;9(9):e107055.
32. Chaussade L, Eymin B, Brambilla E, Gazzeri S. Expression of p15 and p15.5 products in neuroendocrine lung tumours: relationship with p15(INK4b) methylation status. Oncogene. 2001;20(45):6587–96.
33. Li Z, Qu L, Dong Q, Huang B, Li H, Tang Z, et al. Overexpression of CARMA3 in non-small-cell lung cancer is linked for tumor progression. PLoS One. 2012;7(5):e36903.
34. Gu C, Lu J, Cui T, Lu C, Shi H, Xu W, et al. Association between MGMT promoter methylation and non-small cell lung cancer: a meta-analysis. PLoS One. 2013;8(9):e72633.
35. Huang M, Stolina M, Sharma S, Mao JT, Zhu L, Miller PW, et al. Non-small cell lung cancer cyclooxygenase-2-dependent regulation of cytokine balance in lymphocytes and macrophages: up-regulation of interleukin 10 and down-regulation of interleukin 12 production. Cancer Res. 1998;58(6):1208–16.
36. Bozyk PD, Moore BB. Prostaglandin E2 and the pathogenesis of pulmonary fibrosis. Am J Respir Cell Mol Biol. 2011;45(3):445–52.
37. Fireman E, Ben Efraim S, Greif J, Alguetti A, Ayalon D, Topilsky M. Correlation between PGE2 production and suppressor activity of alveolar macrophages from patients with interstitial lung diseases. Immunol Lett. 1988;18(2):159–65.
38. Kolodsick JE, Peters-Golden M, Larios J, Toews GB, Thannickal VJ, Moore BB. Prostaglandin E2 inhibits fibroblast to myofibroblast transition via E. prostanoid receptor 2 signaling and cyclic adenosine monophosphate elevation. Am J Respir Cell Mol Biol. 2003;29(5):537–44.
39. Jiang J, Dingledine R. Prostaglandin receptor EP2 in the crosshairs of anti-inflammation, anti-cancer, and neuroprotection. Trends Pharmacol Sci. 2013;34(7):413–23.
40. Wang P, Gao Q, Suo Z, Munthe E, Solberg S, Ma L, et al. Identification and characterization of cells with cancer stem cell properties in human primary lung cancer cell lines. PLoS One. 2013;8(3):e57020.
41. Sanders YY, Pardo A, Selman M, Nuovo GJ, Tollefsbol TO, Siegal GP, et al. Thy-1 promoter hypermethylation: a novel epigenetic pathogenic mechanism in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2008;39(5):610–18.
42. Shahbazi J, Lock R, Liu T. Tumor Protein 53-Induced Nuclear Protein 1 Enhances p53 Function and Represses Tumorigenesis. Front Genet. 2013;4:80.
43. Guo W, Shan B, Klingsberg RC, Qin X, Lasky JA. Abrogation of TGF-beta1-induced fibroblast-myofibroblast differentiation by histone deacetylase inhibition. Am J Physiol Lung Cell Mol Physiol. 2009;297(5):L864–70.

44. Halder SK, Cho YJ, Datta A, Anumanthan G, Ham AJ, Carbone DP, et al. Elucidating the mechanism of regulation of transforming growth factor beta Type II receptor expression in human lung cancer cell lines. Neoplasia. 2011;13(10):912–22.
45. Huqun, Ishikawa R, Zhang J, Miyazawa H, Goto Y, Shimizu Y, et al. Enhancer of zeste homolog 2 is a novel prognostic biomarker in nonsmall cell lung cancer. Cancer. 2012;118 (6):1599–606.
46. Vire E, Brenner C, Deplus R, Blanchon L, Fraga M, Didelot C, et al. The Polycomb group protein EZH2 directly controls DNA methylation. Nature. 2006;439(7078):871–4.
47. Coward WR, Feghali-Bostwick CA, Jenkins G, Knox AJ, Pang L. A central role for G9a and EZH2 in the epigenetic silencing of cyclooxygenase-2 in idiopathic pulmonary fibrosis. FASEB J. 2014;28(7):3183–96.
48. Arenberg DA, Kunkel SL, Polverini PJ, Morris SB, Burdick MD, Glass MC, et al. Interferon-gamma-inducible protein 10 (IP-10) is an angiostatic factor that inhibits human non-small cell lung cancer (NSCLC) tumorigenesis and spontaneous metastases. J Exp Med. 1996;184 (3):981–92.
49. Keane MP, Arenberg DA, Lynch 3rd JP, Whyte RI, Iannettoni MD, Burdick MD, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. J Immunol. 1997;159(3):1437–43.
50. Gao W, Yu Y, Cao H, Shen H, Li X, Pan S, et al. Deregulated expression of miR-21, miR-143 and miR-181a in non small cell lung cancer is related to clinicopathologic characteristics or patient prognosis. Biomed Pharmacother. 2010;64(6):399–408.
51. Liu G, Friggeri A, Yang Y, Milosevic J, Ding Q, Thannickal VJ, et al. miR-21 mediates fibrogenic activation of pulmonary fibroblasts and lung fibrosis. J Exp Med. 2010;207 (8):1589.
52. Talotta F, Cimmino A, Matarazzo MR, Casalino L, De Vita G, D'Esposito M, et al. An autoregulatory loop mediated by miR-21 and PDCD4 controls the AP-1 activity in RAS transformation. Oncogene. 2009;28(1):73–84.
53. Yao Q, Cao S, Li C, Mengesha A, Kong B, Wei M. Micro-RNA-21 regulates TGF-beta-induced myofibroblast differentiation by targeting PDCD4 in tumor-stroma interaction. Int J Cancer. 2011;128(8):1783–92.
54. Marsit CJ, Zheng S, Aldape K, Hinds PW, Nelson HH, Wiencke JK, et al. PTEN expression in non-small-cell lung cancer: evaluating its relation to tumor characteristics, allelic loss, and epigenetic alteration. Hum Pathol. 2005;36(7):768–76.
55. Feng XH, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol. 2005;21:659–93.
56. Vandenbroucke RE, Dejonckheere E, Libert C. A therapeutic role for matrix metalloproteinase inhibitors in lung diseases? Eur Respir J. 2011;38(5):1200–14.
57. Zuo F, Kaminski N, Eugui E, Allard J, Yakhini Z, Ben-Dor A, et al. Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. Proc Natl Acad Sci U S A. 2002;99(9):6292–7.
58. Shah SA, Spinale FG, Ikonomidis JS, Stroud RE, Chang EI, Reed CE. Differential matrix metalloproteinase levels in adenocarcinoma and squamous cell carcinoma of the lung. J Thorac Cardiovasc Surg. 2010;139(4):984–90; discussion 90.
59. Suga M, Iyonaga K, Okamoto T, Gushima Y, Miyakawa H, Akaike T, et al. Characteristic elevation of matrix metalloproteinase activity in idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2000;162(5):1949–56.
60. Wang L, Antonini JM, Rojanasakul Y, Castranova V, Scabilloni JF, Mercer RR. Potential role of apoptotic macrophages in pulmonary inflammation and fibrosis. J Cell Physiol. 2003;194(2):215–24.
61. Reichenberger F, Eickelberg O, Wyser C, Perruchoud AP, Roth M, Tamm M. Distinct endobronchial expression of matrix-metalloproteinases (MMP) and their endogenous inhibitors in lung cancer. Swiss Med Wkly. 2001;131(19–20):273–9.

62. Swiderski RE, Dencoff JE, Floerchinger CS, Shapiro SD, Hunninghake GW. Differential expression of extracellular matrix remodeling genes in a murine model of bleomycin-induced pulmonary fibrosis. Am J Pathol. 1998;152(3):821–8.
63. Garcia-Alvarez J, Ramirez R, Checa M, Nuttall RK, Sampieri CL, Edwards DR, et al. Tissue inhibitor of metalloproteinase-3 is up-regulated by transforming growth factor-beta1 in vitro and expressed in fibroblastic foci in vivo in idiopathic pulmonary fibrosis. Exp Lung Res. 2006;32(5):201–14.
64. Safranek J, Pesta M, Holubec L, Kulda V, Dreslerova J, Vrzalova J, et al. Expression of MMP-7, MMP-9, TIMP-1 and TIMP-2 mRNA in lung tissue of patients with non-small cell lung cancer (NSCLC) and benign pulmonary disease. Anticancer Res. 2009;29(7):2513–17.
65. Huleihel L, Ben-Yehudah A, Milosevic J, Yu G, Pandit K, Sakamoto K, et al. Let-7d microRNA affects mesenchymal phenotypic properties of lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2014;306(6):L534–42.
66. Pandit KV, Corcoran D, Yousef H, Yarlagadda M, Tzouvelekis A, Gibson KF, et al. Inhibition and role of let-7d in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2010;182(2):220–9.
67. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, et al. RAS is regulated by the let-7 microRNA family. Cell. 2005;120(5):635–47.
68. Mailand N, Podtelejnikov AV, Groth A, Mann M, Bartek J, Lukas J. Regulation of G(2)/M events by Cdc25A through phosphorylation-dependent modulation of its stability. EMBO J. 2002;21(21):5911–20.
69. Wu W, Fan YH, Kemp BL, Walsh G, Mao L. Overexpression of cdc25A and cdc25B is frequent in primary non-small cell lung cancer but is not associated with overexpression of c-myc. Cancer Res. 1998;58(18):4082–5.
70. Zhan M, Qu Q, Wang G, Liu YZ, Tan SL, Lou XY, et al. Let-7c inhibits NSCLC cell proliferation by targeting HOXA1. Asian Pac J Cancer Prev. 2013;14(1):387–92.
71. Zhang F, Nielsen LD, Lucas JJ, Mason RJ. Transforming growth factor-beta antagonizes alveolar type II cell proliferation induced by keratinocyte growth factor. Am J Respir Cell Mol Biol. 2004;31(6):679–86.
72. Yanaihara N, Caplen N, Bowman E, Seike M, Kumamoto K, Yi M, et al. Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell. 2006;9(3):189–98.
73. Pandit KV, Milosevic J, Kaminski N. MicroRNAs in idiopathic pulmonary fibrosis. Transl Res. 2011;157(4):191–9.
74. Pottier N, Maurin T, Chevalier B, Puissegur MP, Lebrigand K, Robbe-Sermesant K, et al. Identification of keratinocyte growth factor as a target of microRNA-155 in lung fibroblasts: implication in epithelial-mesenchymal interactions. PLoS One. 2009;4(8):e6718.
75. Coira IF, Rufino-Palomares EE, Romero OA, Peinado P, Metheetrairut C, Boyero-Corral L et al. Expression inactivation of SMARCA4 by microRNAs in lung tumors. Hum Mol Genet. 2015;24:1400–9.
76. Seux M, Peuget S, Montero MP, Siret C, Rigot V, Clerc P, et al. TP53INP1 decreases pancreatic cancer cell migration by regulating SPARC expression. Oncogene. 2011;30 (27):3049–61.
77. Yamanaka Y, Tagawa H, Takahashi N, Watanabe A, Guo YM, Iwamoto K, et al. Aberrant overexpression of microRNAs activate AKT signaling via down-regulation of tumor suppressors in natural killer-cell lymphoma/leukemia. Blood. 2009;114(15):3265–75.
78. Yang T, Liang Y, Lin Q, Liu J, Luo F, Li X, et al. miR-29 mediates TGFbeta1-induced extracellular matrix synthesis through activation of PI3K-AKT pathway in human lung fibroblasts. J Cell Biochem. 2013;114(6):1336–42.
79. Xiao J, Meng XM, Huang XR, Chung AC, Feng YL, Hui DS, et al. miR-29 inhibits bleomycin-induced pulmonary fibrosis in mice. Mol Ther. 2012;20(6):1251–60.
80. Cushing L, Kuang P, Lu J. The role of miR-29 in pulmonary fibrosis. Biochem Cell Biol. 2015;93:1–10.

81. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci U S A. 2006;103(7):2257–61.
82. Fabbri M, Garzon R, Cimmino A, Liu Z, Zanesi N, Callegari E, et al. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proc Natl Acad Sci U S A. 2007;104(40):15805–10.
83. Zhong K, Chen K, Han L, Li B. MicroRNA-30b/c inhibits non-small cell lung cancer cell proliferation by targeting Rab18. BMC Cancer. 2014;14:703.
84. Berschneider B, Ellwanger DC, Baarsma HA, Thiel C, Shimbori C, White ES, et al. miR-92a regulates TGF-beta1-induced WISP1 expression in pulmonary fibrosis. Int J Biochem Cell Biol. 2014;53:432–41.
85. Oak SR, Murray L, Herath A, Sleeman M, Anderson I, Joshi AD, et al. A micro RNA processing defect in rapidly progressing idiopathic pulmonary fibrosis. PLoS One. 2011;6(6):e21253.
86. Puissegur MP, Mazure NM, Bertero T, Pradelli L, Grosso S, Robbe-Sermesant K, et al. miR-210 is overexpressed in late stages of lung cancer and mediates mitochondrial alterations associated with modulation of HIF-1 activity. Cell Death Differ. 2011;18(3):465.
87. Bodempudi V, Hergert P, Smith K, Xia H, Herrera J, Peterson M, et al. miR-210 promotes IPF fibroblast proliferation in response to hypoxia. Am J Physiol Lung Cell Mol Physiol. 2014;307(4):L283–94.
88. Zhang Z, Sun H, Dai H, Walsh RM, Imakura M, Schelter J, et al. MicroRNA miR-210 modulates cellular response to hypoxia through the MYC antagonist MNT. Cell Cycle. 2009;8(17):2756–68.
89. Tsuchiya S, Fujiwara T, Sato F, Shimada Y, Tanaka E, Sakai Y, et al. MicroRNA-210 regulates cancer cell proliferation through targeting fibroblast growth factor receptor-like 1 (FGFRL1). J Biol Chem. 2011;286(1):420–8.
90. Lino Cardenas CL, Henaoui IS, Courcot E, Roderburg C, Cauffiez C, Aubert S, et al. miR-199a-5p Is upregulated during fibrogenic response to tissue injury and mediates TGFbeta-induced lung fibroblast activation by targeting caveolin-1. PLoS Genet. 2013;9(2):e1003291.
91. Cho WC, Chow AS, Au JS. MiR-145 inhibits cell proliferation of human lung adenocarcinoma by targeting EGFR and NUDT1. RNA Biol. 2011;8(1):125–31.
92. Yang S, Cui H, Xie N, Icyuz M, Banerjee S, Antony VB, et al. miR-145 regulates myofibroblast differentiation and lung fibrosis. FASEB J. 2013;27(6):2382–91.
93. Pecot CV, Rupaimoole R, Yang D, Akbani R, Ivan C, Lu C, et al. Tumour angiogenesis regulation by the miR-200 family. Nat Commun. 2013;4:2427.
94. Korpal M, Ell BJ, Buffa FM, Ibrahim T, Blanco MA, Celia-Terrassa T, et al. Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization. Nat Med. 2012;17(9):1101–8.
95. Yang S, Banerjee S, de Freitas A, Sanders YY, Ding Q, Matalon S, et al. Participation of miR-200 in pulmonary fibrosis. Am J Pathol. 2012;180(2):484–93.
96. Dakhlallah D, Batte K, Wang Y, Cantemir-Stone CZ, Yan P, Nuovo G, et al. Epigenetic regulation of miR-17 ~ 92 contributes to the pathogenesis of pulmonary fibrosis. Am J Respir Crit Care Med. 2013;187(4):397–405.
97. Osada H, Takahashi T. let-7 and miR-17-92: small-sized major players in lung cancer development. Cancer Sci. 2010;102(1):9–17.
98. Yoda S, Soejima K, Hamamoto J, Yasuda H, Nakayama S, Satomi R, et al. Claudin-1 is a novel target of miR-375 in non-small-cell lung cancer. Lung Cancer. 2014;85(3):366–72.
99. Wang Y, Huang C, Reddy Chintagari N, Bhaskaran M, Weng T, Guo Y, et al. miR-375 regulates rat alveolar epithelial cell trans-differentiation by inhibiting Wnt/beta-catenin pathway. Nucleic Acids Res. 2013;41(6):3833–44.
100. Takahashi Y, Forrest AR, Maeno E, Hashimoto T, Daub CO, Yasuda J. MiR-107 and MiR-185 can induce cell cycle arrest in human non small cell lung cancer cell lines. PLoS One. 2009;4(8):e6677.

101. Huang J, Wu J, Li Y, Li X, Yang T, Yang Q, et al. Deregulation of serum microRNA expression is associated with cigarette smoking and lung cancer. Biomed Res Int. 2014;2014:364316.
102. Milosevic J, Pandit K, Magister M, Rabinovich E, Ellwanger DC, Yu G, et al. Profibrotic role of miR-154 in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2012;47(6):879–87.
103. Kim KK, Wei Y, Szekeres C, Kugler MC, Wolters PJ, Hill ML, et al. Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis. J Clin Invest. 2009;119(1):213–24.
104. Thomas PE, Peters-Golden M, White ES, Thannickal VJ, Moore BB. PGE(2) inhibition of TGF-beta1-induced myofibroblast differentiation is Smad-independent but involves cell shape and adhesion-dependent signaling. Am J Physiol Lung Cell Mol Physiol. 2007;293 (2):L417–28.
105. Stewart DJ. Wnt signaling pathway in non-small cell lung cancer. J Natl Cancer Inst. 2013;106(1):djt356.
106. Winn RA, Van Scoyk M, Hammond M, Rodriguez K, Crossno Jr JT, Heasley LE, et al. Antitumorigenic effect of Wnt 7a and Fzd 9 in non-small cell lung cancer cells is mediated through ERK-5-dependent activation of peroxisome proliferator-activated receptor gamma. J Biol Chem. 2006;281(37):26943–50.
107. Tennis MA, Van Scoyk MM, Freeman SV, Vandervest KM, Nemenoff RA, Winn RA. -Sprouty-4 inhibits transformed cell growth, migration and invasion, and epithelial-mesenchymal transition, and is regulated by Wnt7A through PPARgamma in non-small cell lung cancer. Mol Cancer Res. 2010;8(6):833–43.
108. Konigshoff M, Balsara N, Pfaff EM, Kramer M, Chrobak I, Seeger W, et al. Functional Wnt signaling is increased in idiopathic pulmonary fibrosis. PLoS One. 2008;3(5):e2142.
109. Larsen JE, Minna JD. Molecular biology of lung cancer: clinical implications. Clin Chest Med. 2011;32(4):703–40.
110. Xia H, Khalil W, Kahm J, Jessurun J, Kleidon J, Henke CA. Pathologic caveolin-1 regulation of PTEN in idiopathic pulmonary fibrosis. Am J Pathol. 2010;176(6):2626–37.
111. Yan Z, Kui Z, Ping Z. Reviews and prospectives of signaling pathway analysis in idiopathic pulmonary fibrosis. Autoimmun Rev. 2014;13(10):1020–5.
112. Tsurutani J, Castillo SS, Brognard J, Granville CA, Zhang C, Gills JJ, et al. Tobacco components stimulate Akt-dependent proliferation and NFkappaB-dependent survival in lung cancer cells. Carcinogenesis. 2005;26(7):1182–95.
113. Gustin JA, Ozes ON, Akca H, Pincheira R, Mayo LD, Li Q, et al. Cell type-specific expression of the IkappaB kinases determines the significance of phosphatidylinositol 3-kinase/Akt signaling to NF-kappa B activation. J Biol Chem. 2004;279(3):1615–20.
114. Chen G, Bhojani MS, Heaford AC, Chang DC, Laxman B, Thomas DG, et al. Phosphorylated FADD induces NF-kappaB, perturbs cell cycle, and is associated with poor outcome in lung adenocarcinomas. Proc Natl Acad Sci U S A. 2005;102(35):12507–12.
115. Sethi G, Ahn KS, Chaturvedi MM, Aggarwal BB. Epidermal growth factor (EGF) activates nuclear factor-kappaB through IkappaBalpha kinase-independent but EGF receptor-kinase dependent tyrosine 42 phosphorylation of IkappaBalpha. Oncogene. 2007;26(52):7324–32.
116. Meylan E, Dooley AL, Feldser DM, Shen L, Turk E, Ouyang C, et al. Requirement for NF-kappaB signalling in a mouse model of lung adenocarcinoma. Nature. 2009;462 (7269):104–7.
117. Willis BC, Liebler JM, Luby-Phelps K, Nicholson AG, Crandall ED, du Bois RM, et al. Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor-beta1: potential role in idiopathic pulmonary fibrosis. Am J Pathol. 2005;166(5):1321–32.
118. Wan YY, Tian GY, Guo HS, Kang YM, Yao ZH, Li XL, et al. Endostatin, an angiogenesis inhibitor, ameliorates bleomycin-induced pulmonary fibrosis in rats. Respir Res. 2013;14 (1):56.

119. Zhu T, Zhang W, Xiao M, Chen H, Jin H. Protective role of andrographolide in bleomycin-induced pulmonary fibrosis in mice. Int J Mol Sci. 2013;14(12):23581–96.
120. Lin X, Sime PJ, Xu H, Williams MA, LaRussa L, Georas SN, et al. Yin yang 1 is a novel regulator of pulmonary fibrosis. Am J Respir Crit Care Med. 2010;183(12):1689–97.
121. Chitra P, Saiprasad G, Manikandan R, Sudhandiran G. Berberine attenuates bleomycin induced pulmonary toxicity and fibrosis via suppressing NF-kappaB dependant TGF-beta activation: a biphasic experimental study. Toxicol Lett. 2013;219(2):178–93.
122. Kelleher FC, O'Sullivan H, Smyth E, McDermott R, Viterbo A. Fibroblast growth factor receptors, developmental corruption and malignant disease. Carcinogenesis. 2013;34 (10):2198–205.
123. Khalil N, Xu YD, O'Connor R, Duronio V. Proliferation of pulmonary interstitial fibroblasts is mediated by transforming growth factor-beta1-induced release of extracellular fibroblast growth factor-2 and phosphorylation of p38 MAPK and JNK. J Biol Chem. 2005;280 (52):43000–9.
124. Inoue Y, King Jr TE, Tinkle SS, Dockstader K, Newman LS. Human mast cell basic fibroblast growth factor in pulmonary fibrotic disorders. Am J Pathol. 1996;149(6):2037–54.
125. Kuhn H, Kopff C, Konrad J, Riedel A, Gessner C, Wirtz H. Influence of basic fibroblast growth factor on the proliferation of non-small cell lung cancer cell lines. Lung Cancer. 2004;44(2):167–74.
126. Ramos C, Montano M, Becerril C, Cisneros-Lira J, Barrera L, Ruiz V, et al. Acidic fibroblast growth factor decreases alpha-smooth muscle actin expression and induces apoptosis in human normal lung fibroblasts. Am J Physiol Lung Cell Mol Physiol. 2006;291(5):L871–9.
127. Dailey L, Ambrosetti D, Mansukhani A, Basilico C. Mechanisms underlying differential responses to FGF signaling. Cytokine Growth Factor Rev. 2005;16(2):233–47.
128. Daly S, Kubasiak JC, Rinewalt D, Pithadia R, Basu S, Fhied C, et al. Circulating angiogenesis biomarkers are associated with disease progression in lung adenocarcinoma. Ann Thorac Surg. 2014;98(6):1968–75; discussion 75.
129. Wynes MW, Edelman BL, Kostyk AG, Edwards MG, Coldren C, Groshong SD, et al. Increased cell surface Fas expression is necessary and sufficient to sensitize lung fibroblasts to Fas ligation-induced apoptosis: implications for fibroblast accumulation in idiopathic pulmonary fibrosis. J Immunol. 2011;187(1):527–37.
130. Niehans GA, Brunner T, Frizelle SP, Liston JC, Salerno CT, Knapp DJ, et al. Human lung carcinomas express Fas ligand. Cancer Res. 1997;57(6):1007–12.
131. Zhan P, Wang J, Lv XJ, Wang Q, Qiu LX, Lin XQ, et al. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: a systematic review with meta-analysis. J Thorac Oncol. 2009;4(9):1094–103.
132. Kobayashi T, Liu X, Wen FQ, Fang Q, Abe S, Wang XQ, et al. Smad3 mediates TGF-beta1 induction of VEGF production in lung fibroblasts. Biochem Biophys Res Commun. 2005;327 (2):393–8.
133. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008;22(10):1276–312.
134. Tejada ML, Yu L, Dong J, Jung K, Meng G, Peale FV, et al. Tumor-driven paracrine platelet-derived growth factor receptor alpha signaling is a key determinant of stromal cell recruitment in a model of human lung carcinoma. Clin Cancer Res. 2006;12(9):2676–88.
135. Dong J, Grunstein J, Tejada M, Peale F, Frantz G, Liang WC, et al. VEGF-null cells require PDGFR alpha signaling-mediated stromal fibroblast recruitment for tumorigenesis. EMBO J. 2004;23(14):2800–10.
136. Nagaoka I, Trapnell BC, Crystal RG. Upregulation of platelet-derived growth factor-A and -B gene expression in alveolar macrophages of individuals with idiopathic pulmonary fibrosis. J Clin Invest. 1990;85(6):2023–7.
137. Downward J. Targeting RAS, signalling pathways in cancer therapy. Nat Rev Cancer. 2003;3 (1):11–22.

138. Vancheri C. Common pathways in idiopathic pulmonary fibrosis and cancer. Eur Respir Rev. 2013;22(129):265–72.
139. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
140. Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014;15(2):143–55.

# Chapter 15
# Acute Exacerbation of Interstitial Pneumonia After Pulmonary Resection for Lung Cancer

## Can Acute Exacerbation of IPF Be Predicted Preoperatively?

**Hiroshi Date**

**Abstract** Interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer. However, the contribution of anticancer therapies is unclear because these therapies including surgery may trigger acute exacerbation (AE) and are confounded by the progressive nature and poor prognoses of ILDs. We conducted a large ($n = 1{,}763$) retrospective multi-institutional study to identify the predictors of AE and to identify the predictors of long-term survival after surgical resection for lung cancer. AE occurred in 9.3 % of patients and its mortality was 43.9 %. With multivariate analysis, the following seven risk factors of AE were identified: anatomical surgical resection, male sex, history of AE, preoperative steroid use, high serum sialylated carbohydrate antigen KL-6 level, usual interstitial pneumonia appearance on CT, and reduced percent-predicted vital capacity (%VC). Unfortunately, no effective prophylactic medication could be identified.

The overall 5-year survival was 40 %, which was poorer than the historical control. The multivariate analysis revealed that wedge resection, %VC$<$80 %, and lower lobe cancer were identified as predictors of poor survival. Of note, wedge resection reduced death caused by respiratory failure but resulted in poorer long-term prognosis than lobectomy because of higher incidence of cancer recurrence.

We further developed a simple risk scoring system for predicting AE by giving weight to each seven risk factors. Using this risk score system, surgeons can assess the risk of AE in each patient preoperatively and may choose appropriate surgical procedure in routine clinical practice.

**Keywords** Acute exacerbation • Interstitial pneumonia • Idiopathic pulmonary fibrosis • Lung cancer

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## 15.1 Introduction

It is well known that interstitial lung diseases (ILDs) are associated with an increased risk of lung cancer [1, 2]. Therapeutic strategies for lung cancer patients with ILDs should be chosen carefully, as any interventions may trigger exacerbation of ILDs [3, 4]. Pulmonary resection has been shown to be associated with high postoperative morbidity and mortality in these patients. Postoperative acute exacerbation (AE) of interstitial pneumonia is the most fearful complication and is associated with mortality rates between 33.3 % and 100 % [5–8]. In addition to treatment-related morbidity and mortality, the prognosis of ILDs itself—particularly in idiopathic pulmonary fibrosis (IPF) patients—can be a life-limiting factor. IPF is generally unresponsive to medical treatment, and patients have an extremely limited prognosis with an expected survival from 2 to 3 years after diagnosis [9–13]. Whether pulmonary resections should be performed for lung cancer patients with fibrosis remains a matter of debate [8, 14–16].

To determine the most appropriate treatment strategy, a reliable assessment of the risks and benefits of the various interventions is required. It was for this purpose that we first conducted a large-scale multi-institutional retrospective cohort study at the initiative of the Japanese Association for Chest Surgery starting from 2010.

## 15.2 A Typical Case of Acute Exacerbation After Pulmonary Resection for Lung Cancer

A 69-year-old man presented a right middle lobe mass. A high-resolution CT scan revealed a solid mass with a diameter of 25 mm in the middle lobe (Fig. 15.1a). Basal slice of the CT showed bilateral subpleural interstitial reticular opacities with mild honeycombing (Fig. 15.1b). Transbronchial lung biopsy was performed for the middle lobe mass resulting in the diagnosis of adenocarcinoma of the lung. Further work-ups showed no evidence of metastasis and his clinical staging was determined to be c-T1bN0M0, c-Stage Ia. He had a 30-pack-year history of cigarette smoking, but preoperative respiratory function and blood gas analysis were normal. He underwent a straightforward right middle lobectomy with radical lymph node dissection by video-assisted thoracoscopic surgery. Early postoperative course was uneventful and he was discharged on day 7. Pathologic examination of the middle lobe showed adenocarcinoma associated with usual interstitial pneumonia. He was readmitted with aggressive dyspnea on day 19. CT scan of the chest showed newly developed bilateral gland-grass opacities on top of the preexisting fibrotic shadow (Fig. 15.1c, d). He was diagnosed with acute exacerbation of the interstitial pneumonia and treated with maximal medical treatment including steroid pulse and sivelestat sodium hydrate resulting in little improvement. He died on day 59 by respiratory failure.

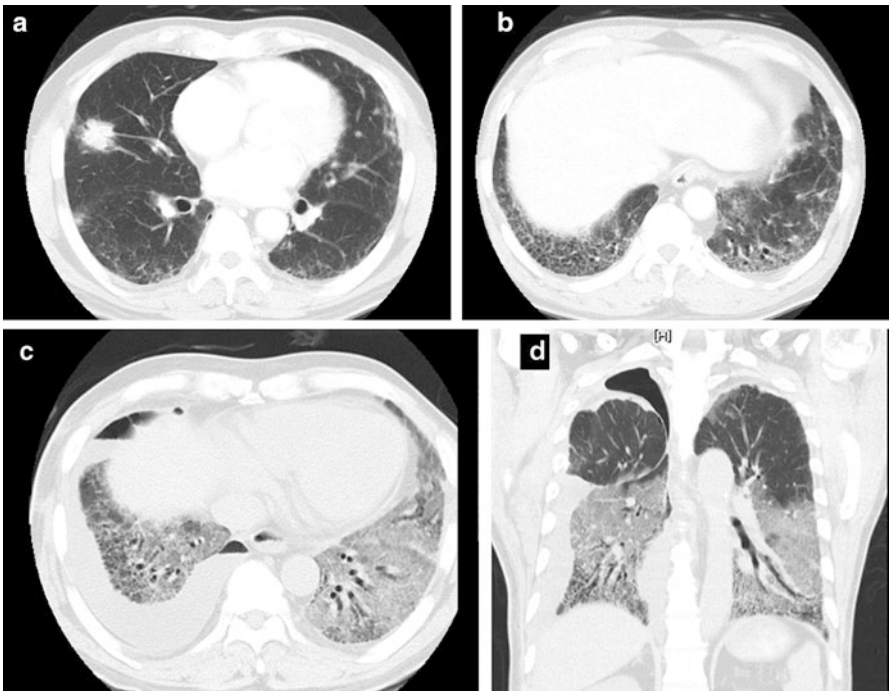


**Fig. 15.1** A typical case of acute exacerbation after pulmonary resection for lung cancer. (**a**) A solid mass of adenocarcinoma in the middle lobe. (**b**) Basal slice of the CT demonstrating bilateral subpleural interstitial reticular opacities with mild honeycombing. (**c**, **d**) Newly developed bilateral gland-grass opacities on top of the preexisting fibrotic shadow on day 19 after middle lobectomy

## 15.3 Risk Factor for Acute Exacerbation

Acute exacerbation (AE) is characterized by diffuse and rapid alveolar damage superimposed on a background of preexisting fibrotic change, which most likely occurs as a result of a massive lung injury due to some unknown etiologic agents. Some unknown etiologic agents of AE can be induced by pulmonary resection. Several investigators have reported on possible AE risk predictors, such as low DLCO [6], low %VC [17, 18], high KL-6 [19], high CRP [20], high LDH [18], poor performance status [7], and positive intraoperative water balance [20]. However, all these previous studies were single institutional retrospective studies, and their sample size were less than 100, which were too small to draw any conclusions.

AE has been shown to be the major cause of death for lung cancer patients after pulmonary resection in a report cumulating over 10,000 cases from the Japanese Joint Committee for Lung Cancer Registration and in the 2009 annual report of the Japanese Association for Thoracic Surgery [21, 22]. It was for reason that we first conducted a large-scale multi-institutional retrospective cohort study at the

initiative of the Japanese Association for Chest Surgery starting from 2010 [23]. The original data for analysis were obtained from non-small cell lung cancer patients who had undergone pulmonary resection and presented with a clinical diagnosis of ILDs between January 2000 and December 2009 at 64 institutions throughout Japan. The primary end point for outcome analysis was postoperative AE of interstitial pneumonitis within 30 days after pulmonary resection. Medical records of the patients were reviewed for about 80 clinicopathological factors.

Diagnoses of ILDs were confirmed based on a combination of clinical and radiologic findings according to the clinical criteria proposed by the Japanese Respiratory Society [17], which are consistent with the guidelines of the American Thoracic Society in 2011 [12]. The cases were categorized into two groups according to their radiological appearance on CT scan: (1) usual interstitial pneumonia (UIP) pattern, characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with multiple equal-sized cystic lesions of 2–10 mm diameter with a thick wall; and (2) non-UIP pattern, characterized by the presence of basal-predominant ground-glass opacities and infiltrative shadows inconsistent with UIP patterns.

AE caused by pulmonary resection was defined based on criteria proposed by Yoshimura et al. and ATS Guidelines [12, 24]. These criteria were (1) onset within 30 days after pulmonary resection, (2) intensified dyspnea, (3) increase in the interstitial shadow on chest radiograph and chest CT scan, (4) decrease in arterial oxygen tension of more than 10 mmHg under similar conditions, (5) no evidence of pulmonary infection, and (6) exclusion of alternative causes such as cardiac failure, pulmonary embolism, or other identifiable causes of lung injury. Exacerbations occurring from 31 days onward were defined as chronic exacerbations.

Data were obtained from 1,763 patients with surgically treated lung cancer with ILDs. Among these, 164 patients (9.3 %) developed postoperative AE within 30 days after the operation. The majority of the patients developed AE within 10 days after operation, with postoperative day 4 showing the highest frequency of AE. Within the patients developing AE, 72 of them (43.9 %) died.

With multivariate analysis, the following seven independent risk factors of AE were identified: surgical procedures, male sex, history of exacerbation, preoperative steroid use, serum sialylated carbohydrate antigen KL-6 levels, usual interstitial pneumonia appearance on CT scan, and reduced percent-predicted vital capacity (Table 15.1). Surgical procedures showed the strongest association with AE. The lobectomy/segmentectomy group and the bilobectomy/pneumonectomy group were both more likely to develop AE than the wedge resection group, with ORs of 3.83 and 5.70, respectively. Neoadjuvant treatment and video-assisted thoracoscopic surgery showed no association with AE in our study. The effect of perioperative prophylactics such as steroids and sivelestat was not confirmed in this study.

**Table 15.1** Risk factors of acute exacerbation (multivariate analysis)

| Factors | Patients (*n*) | AE (%) | OR | *P* value |
|---|---|---|---|---|
| Surgical procedure | | | | |
| Wedge resection | 275 | 10 (3.6) | 1 | |
| Segmentectomy/lobectomy | 1,386 | 138 (10.0) | 3.83 | 0.0001 |
| Bilobectomy/pneumonectomy | 94 | 15 (16.0) | 5.7 | 0.0001 |
| Unknown | 8 | | | |
| KL-6 | | | | |
| <1,000 U/mL | 834 | 68 (8.2) | 1 | |
| ≧1,000 U/ml | 209 | 34 (16.3) | 2.14 | 0.0013 |
| Unknown | 720 | | | |
| Sex | | | | |
| Male | 1,593 | 158 (9.9) | 1 | |
| Female | 170 | 6 (3.5) | 0.3 | 0.0047 |
| %VC | | | | |
| <80 % | 263 | 36 (13.7) | 1 | |
| ≧80 % | 1,478 | 126 (8.5) | 0.63 | 0.0308 |
| Unknown | | | | |
| History of AE | | | | |
| No | 1,741 | 158 (9.1) | 1 | |
| Yes | 20 | 6 (30.0) | 3.24 | 0.0387 |
| Unknown | 2 | | | |
| Preoperative steroid use | | | | |
| No | 1,651 | 14.4 (8.7) | 1 | |
| Yes | 103 | 20 (19.4) | 2.46 | 0.0031 |
| Unknown | 9 | | | |
| CT findings | | | | |
| UIP pattern | 1,300 | 134 (10.3) | 1 | |
| non-UIP pattern | 463 | 30 (6.5) | 0.59 | 0.0143 |

## 15.4 Long-Term Survival

Achieving long-term survival after surgical resection for lung cancer patients with ILDs is not easy due to several reasons. Firstly, AE may occur in early postoperative period as shown in the previous section. Secondly, ILD itself has poor prognosis in general. Especially, the median survival of the patients with IPF reportedly ranges only 2–4.2 years from the date of diagnosis [12, 25, 26]. Thirdly, cancer arising from ILDs may have aggressive nature.

Because of these considerations, determining the surgical indication for lung cancer patients with ILDs is not easy. Besides their impaired pulmonary reserve, it is not clear whether pulmonary resection is beneficial or harmful for each individual. Although there is a general understanding that the prognosis of lung cancer patients with ILDs is poor, existing evidence to support these conclusions used to be based on a few studies with comparatively small number of patients (14–56 cases)

[5, 14, 16, 27–30]. In our previous report using data from 61 institutes in Japan on 1,763 lung cancer cases who had ILDs, we studied the morbidity and mortality rate of pulmonary-resected patients and identified seven risk factors for postoperative acute exacerbation of pulmonary fibrosis [23]. Using the same cohort, we have analyzed their long-term survival and the probable factors influencing their survival [31].

The overall 5-year survival after surgical resection for lung cancer patients with ILDs was 40 %. The leading cause of death was cancer recurrence (50.2 %), followed by respiratory failure (26.8 %). The 5-year survivals were 59 %, 42 %, 43 %, 29 %, 25 %, 17 %, and 16 % for patients with p-stage Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, respectively. These were substantially poorer than the recent figures reported by the Japanese Joint Committee for Lung Cancer Registration for general patients (Table 15.2) [32]. These poorer survival rates are likely due to the high incidence of cancer recurrence, combined with the poor survival rate of ILD itself.

Multivariable analysis revealed that the type of surgical procedure, percent-predicted vital capacity (%VC), and tumor locations were independent predictors for survival (Table 15.3). Long-term survival of stage Ia patients who had undergone wedge resections was poorer than that of lobectomy patients (Fig. 15.2). The estimated survival curve of the wedge resection group crossed that of the lobectomy group 1 year after the surgery, and the survival of the wedge resection group was significantly poorer than that of the lobectomy group (log-rank test, $p = 0.0008$). These observations can be explained by the fact that the wedge resection group was less likely to develop AE, but had a higher cancer recurrence rate than that of the lobectomy group. The 5-year survival of the stage Ia patients with %VC $<$ or $=$ 80 % was 20 %, whereas those with %VC $>$ 80 % was 64.3 % (log-rank test, $p < 0.0001$). For patients with poor predictors of survival, such as predicted percent vital capacity of 80 % or less, surgical resection should be limited.

## 15.5 Risk Score

We aimed to derive a simple risk scoring system to predict AE after pulmonary resection with two potential uses: firstly to allow pulmonologists and surgeons to assess the risk of pulmonary resection when considering anticancer therapy for lung cancer patients with ILDs and secondly to provide patients proper risk information before the surgery.

We included seven predictors in our scoring system; each of them can be reliably and routinely ascertained in typical clinical settings. These predictors, including history of AE, surgical procedures, CT findings, preoperative steroid use, gender, serum KL-6 level, and percent-predicted vital capacity, were identified as independent risk factors for postoperative AE in our previous study [23]. We derived a risk score system by giving weight to each factor. A logistic regression model was employed to develop a risk prediction model for AE [33].

**Table 15.2** Five-year survival rate after surgical resection

| p-Stage | Patients with ILDs (%) | General patients (%) |
|---|---|---|
| All | 40 | 70 |
| Ia | 59 | 87 |
| Ib | 42 | 74 |
| IIa | 43 | 62 |
| IIb | 29 | 50 |
| IIIa | 25 | 41 |
| IIIb | 17 | 28 |
| IV | 16 | 28 |

**Table 15.3** Cox proportional hazard regression analysis for survival

| Categories | Cases | HR | *P* value |
|---|---|---|---|
| %VC | 1,656 | 0.98 | <0.001 |
| Procedures | | | |
| Wedge resection | 250 | 1 | |
| Lobectomy | 1,209 | 0.704 | 0.002 |
| Tumor location | | | |
| Upper lobe | 649 | 1 | |
| Lower lobe | 928 | 1.409 | <0.001 |

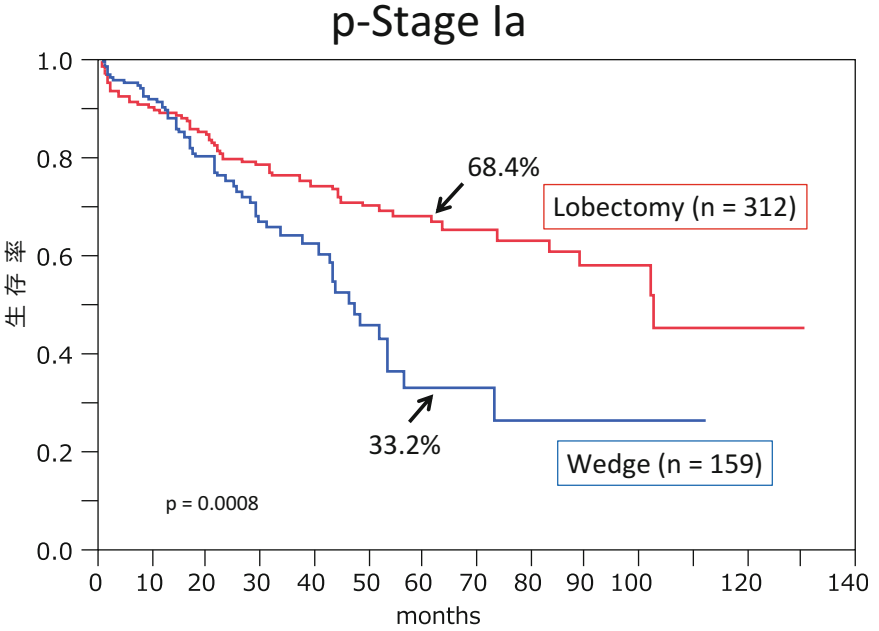


**Fig. 15.2** Survival of stage Ia patients with interstitial lung diseases who underwent surgical resection

**Table 15.4** Risk score of acute exacerbation after surgical resection for lung cancer

| | | | | |
|---|---|---|---|---|
| FHistory of AE | Yes | 5 | No | 0 |
| Surgical procedure | Non-wedge | 4 | Wedge | 0 |
| CT findings | UIP | 4 | Non-UIP | 0 |
| Sex | Male | 3 | Female | 0 |
| Preoperative steroid use | Yes | 3 | No | 0 |
| KL-6 | ≧1,000 U/mL | 2 | <1,000 U/mL | 0 |
| %VC | <80 % | 1 | ≧80 % | 0 |

A risk score (RS) as shown in Table 15.4 was derived as the following equation:

$$\begin{aligned} \mathrm{RS} = {} & 5\,(\mathrm{History\ of\ AE:\ yes}) \\ & + 4\,(\mathrm{Surgical\ procedure:\ non\text{-}wedge}) \\ & + 4\,(\mathrm{CT\ findings:\ UIP\ pattern}) \\ & + 3\,(\mathrm{Preoperative\ steroid\ use:\ yes}) \\ & + 3\,(\mathrm{Gender:\ male}) \\ & + 2\,(\mathrm{KL\text{-}6:}\ > 1,000\,\mathrm{U/mL}) \\ & + 1\,(\%\mathrm{VC:}\ \leq 80) \end{aligned}$$

RS of patients ranged between 0 and 22 and the relationship between RS and predicted probability of AE is shown in Table 15.5. On the basis of the predicted probabilities for AE, patients were classified into three risk groups, i.e., low-risk group (RS: 0–10; predicted probability of AE <10 %), intermediate-risk group (RS: 11–14; predicted probability of AE 10–25 %), and high-risk group (RS: 15–22; predicted probability of AE >25 %).

Using this risk score system, surgeons can assess the risk of AE in each patient preoperatively and may choose appropriate surgical procedure in routine clinical practice. Only the type of surgical procedure among the seven risk factors can be modified based on the patient's potential risk and curability. For the patients stratified in the high-risk group of whom the predicted AE incidence is over 25 %, the surgeon should deliberately downgrade the procedure from lobectomy to wedge resection or should not operate. For the patients stratified in the high-risk group, by changing surgical procedure from lobectomy to wedge resection, a reduction of four points shall be realized in the risk score, resulting in a 20–30 % reduction of predicted AE risk. However, we should also take into account that the conversion to the limited wedge resection possibly brings cancer recurrence which results in less favorable long-term prognosis as shown in the previous section. For those identified as high-risk patients in our risk scoring system, it is a matter of argument if there is an alternative therapeutic modality other than the type of surgical procedure. Chemotherapy and radiation also have been shown to provoke acute deterioration of ILDs with high mortality [34].

Unfortunately, no prophylactic treatment with clear efficacy for AE has been identified so far [23]. Stratifying the patients and identifying those at high risk are very relevant to preventing or to decreasing the mortality of postoperative AE. Early detection of AE may lead to more effective treatment, including high-

**Table 15.5** Risk score and predicted probability of acute exacerbation

| Risk score | Predicted probability of AE (%) | Patient's risk |
|---|---|---|
| 0 | 0.4 % | Low risk |
| 1 | 0.5 % | |
| 2 | 0.7 % | |
| 3 | 0.9 % | |
| 4 | 1.3 % | |
| 5 | 1.8 % | |
| 6 | 2.4 % | |
| 7 | 3.3 % | |
| 8 | 4.4 % | |
| 9 | 6.0 % | |
| 10 | 8.0 % | |
| 11 | 10.7 % | Intermediate risk |
| 12 | 14.1 % | |
| 13 | 18.4 % | |
| 14 | 23.6 % | |
| 15 | 29.8 % | |
| 16 | 36.8 % | High risk |
| 17 | 44.5 % | |
| 18 | 52.4 % | |
| 19 | 60.2 % | |
| 20 | 67.5 % | |
| 21 | 74.0 % | |
| 22 | 79.6 % | |

dose corticosteroid administration, although its use is not well evaluated. Those identified as being in the intermediate- or high-risk group in our proposed risk scoring system are recommended to have intensive surveillance, such as a routine chest CT scan on postoperative day 4 or 5, the most likely time of AE onset [23]. Another future application for this scoring system is the identification of patients who should be treated prophylactically. Pulmonary fibrosis study group recently reported that pirfenidone, an antifibrotic agent, significantly reduced disease progression in a phase III trial of pirfenidone for patients with IPF [35]. Now a prospective study on the prophylactic effect of pirfenidone is being carried out in Japan. In the same way, nintedanib (BIBF1120), a tyrosine kinase inhibitor which reportedly reduces the progression of fibrosis and AE for IPF patients [36], may be selectively administered for those at high risk of AE.

## References

1. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. 2000;161:5–8.

2. Harris JM, Johnston ID, Rudd R, Taylor AJ, Cullinan P. Cryptogenic fibrosing alveolitis and lung cancer: the BTS study. Thorax. 2010;65:70–6.
3. Minegishi Y, Takenaka K, Mizutani H, Sudoh J, Noro R, Okano T, et al. Exacerbation of idiopathic interstitial pneumonias associated with lung cancer therapy. Intern Med. 2009;48:665–72.
4. Isobe K, Hata Y, Sakamoto S, Takai Y, Shibuya K, Homma S. Clinical characteristics of acute respiratory deterioration in pulmonary fibrosis associated with lung cancer following anti-cancer therapy. Respirology. 2010;15:88–92.
5. Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. J Thorac Cardiovasc Surg. 2003;126:1141–6.
6. Kumar P, Goldstraw P, Yamada K, Nicholson AG, Wells AU, Hansell DM, et al. Pulmonary fibrosis and lung cancer: risk and benefit analysis of pulmonary resection. J Thorac Cardiovasc Surg. 2003;125:1321–7.
7. Koizumi K, Hirata T, Hirai K, Mikami I, Okada D, Yamagishi S, et al. Surgical treatment of lung cancer combined with interstitial pneumonia: the effect of surgical approach on postoperative acute exacerbation. Ann Thorac Cardiovasc Surg. 2004;10:340–6.
8. Watanabe A, Kawaharada N, Higami T. Postoperative acute exacerbation of ipf after lung resection for primary lung cancer. Pulm Med. 2011;2011:960316.
9. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;157:199–203.
10. Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000;162:2213–7.
11. Rudd RM, Prescott RJ, Chalmers JC, Johnston ID. British thoracic society study on cryptogenic fibrosing alveolitis: response to treatment and survival. Thorax. 2007;62:62–6.
12. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ats/ers/jrs/alat statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
13. Ley B, Collard HR, King Jr TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
14. Fujimoto T, Okazaki T, Matsukura T, Hanawa T, Yamashita N, Nishimura K, et al. Operation for lung cancer in patients with idiopathic pulmonary fibrosis: surgical contraindication? Ann Thorac Surg. 2003;76:1674–8.
15. Nakajima J, Takamoto S, Murakawa T, Fukami T, Sano A. Is interstitial pneumonia in patients with collagen diseases a contraindication to lung cancer surgery? Surg Today. 2007;37:14–8.
16. Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? J Thorac Cardiovasc Surg. 2008;136:1357–63.
17. Kushibe K, Kawaguchi T, Takahama M, Kimura M, Tojo T, Taniguchi S. Operative indications for lung cancer with idiopathic pulmonary fibrosis. Thorac Cardiovasc Surg. 2007;55:505–8.
18. Shintani Y, Ohta M, Iwasaki T, Ikeda N, Tomita E, Kawahara K, et al. Predictive factors for postoperative acute exacerbation of interstitial pneumonia combined with lung cancer. Gen Thorac Cardiovasc Surg. 2010;58:182–5.
19. Yano M, Sasaki H, Moriyama S, Hikosaka Y, Yokota K, Kobayashi S, et al. Post-operative acute exacerbation of pulmonary fibrosis in lung cancer patients undergoing lung resection. Interact Cardiovasc Thorac Surg. 2012;14:146–50.
20. Mizuno Y, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K, et al. The importance of intraoperative fluid balance for prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. Eur J Cardiothorac Surg. 2012;41:e161–5.

21. Sawabata N, Fujii Y, Asamura H, Nomori H, Nakanishi Y, Eguchi K, et al. Lung cancer in Japan: analysis of lung cancer registry cases resected in 2004. Haigan. 2010;50:875–88.
22. Sakata R, Fujii Y, Kuwano H. Thoracic and cardiovascular surgery in Japan during 2008: annual report by the Japanese association for thoracic surgery. Gen Thorac Cardiovasc Surg. 2010;58:356–83.
23. Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, Fujii Y, Mitsudomi T, Yoshimura M, Maniwa T, Suzuki K, Kataoka K, Sugiyama Y, Kondo T, Date H, Japanese Association for Chest Surgery. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg. 2014;147(5):1604–11.
24. Yoshimura K, Nakatani T, Nakamori Y, Chonabayashi N, Tachibana A, Nakata K, et al. Acute exacerbation in idiopathic interstitial pneumonia. Nihon Kyobu Shikkan Gakkai Zasshi. 1984;22:1012–20.
25. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1994;149:450–4.
26. Mapel DW, Hunt WC, Utton R, Baumgartner KB, Samet JM, Coultas DB. Idiopathic pulmonary fibrosis: survival in population based and hospital based cohorts. Thorax. 1998;53:469–76.
27. Saito Y, Kawai Y, Takahashi N, Ikeya T, Murai K, Kawabata Y, et al. Survival after surgery for pathologic stage IA non-small cell lung cancer associated with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2011;92:1812–7.
28. Kawasaki H, Nagai K, Yoshida J, Nishimura M, Nishiwaki Y. Postoperative morbidity, mortality, and survival in lung cancer associated with idiopathic pulmonary fibrosis. J Surg Oncol. 2002;81:33–7.
29. Martinod E, Azorin JF, Sadoun D, Destable MD, Le Toumelin P, Longchampt E, et al. Surgical resection of lung cancer in patients with underlying interstitial lung disease. Ann Thorac Surg. 2002;74:1004–7.
30. Okamoto T, Gotoh M, Masuya D, Nakashima T, Liu D, Kameyama K, et al. Clinical analysis of interstitial pneumonia after surgery for lung cancer. Jpn J Thorac Cardiovasc Surg. Official publication of the Japanese Association for Thoracic Surgery = Nihon Kyobu Geka Gakkai zasshi. 2004;52:323–9.
31. Sato T, Watanabe A, Kondo H, Kanzaki M, Okubo K, Yokoi K, Matsumoto K, Marutsuka T, Shinohara H, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Meinoshin O, Date H, Japanese Association for Chest Surgery. Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases. J Thorac Cardiovasc Surg. 2015;149(1):64–9.
32. Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 2011;6:1229–35.
33. Sato T, Kondo H, Watanabe A, Nakajima J, Niwa H, Horio H, Okami J, Okumura N, Sugio K, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Kondo T, Date H. A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients. Gen Thorac Cardiovasc Surg. 2015;63(3):164–72.
34. Kenmotsu H, Naito T, Kimura M, Ono A, Shukuya T, Nakamura Y, et al. The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. J Thorac Oncol. 2011;6:1242–6.
35. King Jr TE, Bradfold WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, ASCEND Study Group, et al. A phase 3 trial of pirfenidone with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
36. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–87.