Chapter 5
Air Pollution and Chronic Obstructive Airway Disease

Imre Redai and Angela Haczku

5.1 Introduction

Reigning in fire is regarded as one of the essential steps in the emergence of humans as the dominant species on Earth. Fire provides us with cooked, thus more easily digestible food. It is the source of heating that allowed us to spread to and continue to live at latitudes and altitudes with unfavorable climates. Until the invention of the light bulb, fire was the source of all light between sunset and dawn. Fire based energy fuelled the Industrial Revolution from the eighteen century onwards and allowed us to leave our planet and explore space. Inhaled fire-born pollutants affected and continue to affect the respiratory health of a large portion of humans. Preparing food with the use of open flames producing large quantities of environmental pollutants (lots of smoke that is) remains highly popular: think about backyard barbecues, a platter of smoked meats and cheeses, well roasted coffee beans, or just single malt whisky. On a different scale, industrial mining, chemical processing, emergence of mega-cities with continuously increasing needs in transportation resulted in permanent presence of pollutants like exhaust fumes and ground level ozone in the urban environment. Employees in a wide variety of professions are exposed to inhaled pollutants potentially damaging their lungs. All in all, development of civilization, as we define it, has been presenting a continuous non-physiological challenge for our respiratory tract.

Chronic obstructive airway disease (COPD), the focus of this chapter, is a chronic, progressive, irreversible condition characterized by exacerbations and remissions ultimately leading to respiratory failure and death. Exposure to air

I. Redai, M.D., F.R.C.A. (deceased)

A. Haczku, M.D., Ph.D. (✉)
Translational Lung Biology Center, Pulmonary, Critical Care and Sleep Medicine, University of California, 6510 GBSF, One Shields Avenue, Davis, CA 95616, USA
e-mail: haczku@ucdavis.edu

S.S. Nadadur, J.W. Hollingsworth (eds.), *Air Pollution and Health Effects*,
Molecular and Integrative Toxicology, DOI 10.1007/978-1-4471-6669-6_5

pollutants not only aggravates pre-existing airway disease, but also increases the number of new cases, even in rural areas. Globally, air pollutants now rival tobacco smoke as the leading risk factor for COPD (Arbex et al. 2012). In this review, we discuss emerging epidemiologic evidence of the role of air pollution on COPD and will review the potential cellular-molecular basis of the pollutant-caused pathological changes.

5.2 Pollution and COPD: Historical Perspectives

While a vast body of COPD research has been focusing on the effects of cigarette smoke on the respiratory tract, data are also emerging on the pathogenic function of air pollution in this disease with the hope for prevention and treatment. These studies (initiated by catastrophic events in which a sudden deterioration of air quality resulted in dramatic respiratory effects) have been the driving force behind environmental plans for air quality monitoring and improvement. The lethal industrial haze that occurred in October 1948 in Donora, PA and the 5-day smog that enveloped London and killed close to 12,000 people within 3 months in December 1952 were two environmental disasters that were widely publicized and regarded as the major promoter for the study of air pollution epidemiology (Hunt et al. 2003; Davis et al. 2002; Bell and Davis 2001; Bates 2000). As a result, the US Congress passed the Clean Air Act Amendments in 1970, leading to the establishment of air quality standards.

The earliest study looking into the association of chronic environmental pollutants and morbidity and mortality related to COPD utilized sickness, retirement, and death statistics in the British Civil Service in the 1950s. Postmen delivering mail in areas with higher air pollution (increased incidence of urban fog) have had a significantly greater incidence of absence from work due to chronic bronchitis and were more likely to retire from the service early or die prematurely because of respiratory ailments. Prolonged repeated exposure with longer daily periods was associated with worse outcome on respiratory health: susceptible postmen (working outdoors delivering mail twice a day) on average developed COPD about 20 years earlier in their life than the civil servants who were confined indoors for most of their working hours. Even among civil servants working indoors the incidence of COPD related absence correlated with the air pollution rate of their area of residence (Fairbairn and Reid 1958).

The recognition of the effect of air pollutants on development of COPD took on a new dimension starting in the 1960s with research conducted among non-smokers using biomass fuel for cooking and heating in India, Papua-New Guinea, Central America and Sub-Saharan Africa. An estimated three billion people are today exposed to sustained daily indoor air pollution. Most of these people live either in low-income countries or form the low-income strata of wealthy nations and over 80 % of exposure to air pollutants in this population happens in their own homes (Ezzati and Kammen 2002).

In addition to the detrimental effects of chronic exposure to air pollutants, some of the most devastating outcomes of acute exposure to air pollution were observed in patients with preexisting obstructive airway disease (Zanobetti et al. 2008). In December 1991 Londoners experienced an air pollution episode with mortality sharply increasing for all causes (excluding accidents). In the elderly over 65, but not in children (0–14), the relative risk of hospital admission during this episode was increased for all respiratory diseases (1.19), but it was significantly greater for documented exacerbations of chronic obstructive lung diseases (1.43) (Anderson et al. 1995). In a different study, the effects of traffic related pollution on respiratory symptoms were delayed in children, but were more immediate in the elderly (Halonen et al. 2008). These studies suggested that the acute effects of air pollution are more severe in the elderly who are suffering from COPD. Indeed acute exposure to air pollution is now considered a main contributor to mortality in COPD patients (Cazzola et al. 2007).

5.3 The Role of Outdoor Air Pollutants in COPD

The major pollutants that are significantly associated with respiratory failure include NOx, SO_2, particulate matter (PM) and CO (Stieb et al. 2002). All of these are listed in the six criteria pollutants (nitrogen oxides, sulfur oxides, particulate matter, ozone, carbon monoxide, and lead) for which the US EPA established the National Air Quality Standards.

Nitrogen dioxide (NO_2) is a toxic gas that can be produced by fossil fuel combustion or industrial activities. The December 1991 air pollution incident in London came with record high nitrogen dioxide levels associated with black smoke. Elderly patients suffering from COPD showed a significantly increased sensitivity to this pollutant manifested in increased hospital admission (Anderson et al. 1995).

Particulate matter contains particles with size less than 10 μm in aerodynamic diameter (PM_{10}). These particles contain a mixture of inhalable material from dust, smoke, soot, and combustion, are small enough to reach the lower airways and induce/maintain chronic inflammation. Halonen et al. studied the effects of urban PM in air pollution on asthma and COPD. They found that traffic related $PM_{2.5}$ (≤2.5 μm in aerodynamic diameter) caused delayed respiratory effects (hospital emergency room visits for asthma) in children ≤15 years of age. Meanwhile, $PM_{2.5}$ accumulation was associated with acute respiratory effects (hospital emergency room visits for a combination of asthma and COPD) in adults (15–65) and the elderly (≥65 years of age) (Halonen et al. 2008). That elderly, COPD patients might have a heightened sensitivity to traffic related fine particles ($PM_{2.5}$) in comparison with healthy individuals has been confirmed by additional investigations (Zanobetti et al. 2008).

It is interesting to note that a single cigarette exposes COPD patients (the majority of whom have been smokers) to ~15,000–40,000 μg of PM of similar size and composition to what is found in traffic related pollution. Given that during an

average exposure the inhaled PM amount does not exceed 720 μg, the underlying mechanism of such sensitivity of the COPD patients to traffic related air pollution remains obscure and somewhat baffling. Nonetheless, to provide a greater awareness of the PM levels, the U.S. Environmental Protection Agency now includes levels of air pollution particles in an air quality index (Sint et al. 2008).

The role of outdoor, generally urban or traffic-related air pollution in triggering acute exacerbations and worsening symptoms in patients suffering from various degrees of COPD is well established (Sunyer 2001). In contrast, the association of chronic, life-long exposure to the same outdoor air pollution with the risk of developing COPD is far less clear and even recent studies have remained largely inconclusive (Schikowski et al. 2014). No single pollutant or pollutants have been identified as causative agents in traffic-related COPD. Measuring exposure to pollutants, like nitrogen oxides (NO_2 in particular), ozone (O_3), SO_2, and PM correlated (or not) with prevalence of COPD equally, to just measuring the distance of the patient's abode from a main road (Götschi et al. 2008). Long term continuous exposure to low-grade air pollution on the lungs however was shown to lead to increased mortality of COPD patients related to both cardiovascular and respiratory causes (Jerrett et al. 2009; Krewski 2009; Katsouyanni et al. 2009).

Whether chronic low-grade exposure (which perhaps maintains a low level activation of the inflammatory process in the airways) or intermittent high-level exposure to pollutants (causing exacerbation of symptoms and flare up of the inflammatory process) is the main contributor to the development of COPD (Arbex et al. 2009) remains unclear. Perhaps both have a role but their relative impact in the induction and natural progression of the disease will need to be clarified by future studies both in the laboratory and in the field. This problem is further confounded by the possible link of childhood exposure to environmental air pollution and delayed or incomplete lung development and its contribution to the emergence of COPD in later life (Gauderman et al. 2004).

5.4 Indoor Air Pollutants and COPD

Most of the research in COPD has been focusing on the association of this disease with chronic cigarette smoking and most of our understanding is based on clinical experience, animal models, diagnostic test, drugs, and therapeutic interventions all associated with cigarette smoke as a causative agent. Cigarette smoke exposes the smoker to high concentrations of airborne noxious agents for a short period of time in repeat intervals. On the other hand most chronic environmental airborne pollutants elicit their effect on the lung by sustained, low-grade exposure; sometimes this exposure is constant during almost the entire life of the subject. The most common current environmental pollutant with epidemiological link to COPD is biomass fuel smoke with about half the population of the planet being exposed to biomass fuel smoke on a daily basis. The studies on indoor air pollution started in the 1960s with research into household COPD in non-smokers and its relation to biomass fuel use

in India, Papua-New Guinea, Central America and Sub-Saharan Africa (Ezzati and Kammen 2002). Indoor air pollution is the result of a combination of burning biomass fuel (twigs, wood, animal dung, straw, peat and coal) with poor stove design (often open fire) and poor ventilation (lack of a chimney and often even windows). The smoke generated by these fires contains high concentrations of CO, nitrogen and sulfur oxides, aldehydes, and PM_{10}. Field studies have reported average concentrations of airborne particles and agents of several magnitudes above the recommended 150 $\mu g/m^3$ with inhabitants of these homes exposed to pollutants for long hours every day (Ezzati and Kammen 2002). Women and small children are disproportionately represented in the affected population and the worldwide prevalence of COPD in women and chronic respiratory ailments in small children is strongly associated with exposure to biomass fuel smoke (Torres-Duque et al. 2008). The importance of biomass smoke exposure is underscored by the finding that in women 30-years exposure to either biomass smoke or cigarette-smoking results in the same likelihood of developing COPD (Sezer et al. 2006). There are no significant differences in histopathological findings in the lungs (which include anthracosis, chronic bronchitis, centrolobular emphysema, bronchial squamous cell metaplasia and hypertrophic remodeling of the pulmonary vascular tree) between patients with wood smoke-associated lung disease and those of smokers at the time of death (Moran-Mendoza et al. 2008).

As of now, COPD and chronic bronchitis are the third highest cause of death in the World. The contribution of widespread exposure to biomass fuel smoke to COPD and ways to limit or eliminate it remains a significant public health issue in times of increasing energy costs (Po et al. 2011). A large fraction of this cost will affect the wider international community, as most of the affected inhabit low or very low-income countries already dependent on foreign aid and other forms of help.

5.5 Occupational Exposure and COPD

COPD associated with workplace exposure is notoriously difficult to detect for two reasons. Firstly, COPD is strongly associated with common non-occupational exposures like cigarette smoking often practiced in the same environmental setting ("cigarette break"). Secondly, the dose-response and time exposure relations with the disease are complex (Balmes et al. 2003). Inhalational exposure at the workplace consists of a mixture of airborne particles, fumes, and toxic gases. Some components like cadmium and vanadium are proven direct causative agents in emphysema and chronic bronchitis, respectively. Similarly to cigarette smoke (that contains over 400 potentially toxic components neither of which has been identified as a single most important causative agent in COPD), the etiological role of occupational exposure in COPD has been better ascertained by epidemiological studies than laboratory experiments.

Observing decline in FEV_1 over a period of years in workers employed in industries like coal and hard-rock mining, cement and concrete manufacturing,

construction (especially of tunnels), and agricultural activities has indicated the causative role of dust particles in occupational COPD (Becklake 1989). It is estimated that the population burden of occupational exposure for COPD is in the range of 15 % in developed countries (Balmes et al. 2003) with the related annual health expenditure at the beginning of this millennium in the United States alone of about $5 billion (Leigh et al. 2002). Excess occurrence of COPD among the general US population was further analyzed as part of the Third National Health and Nutrition Examination Survey (NHANES III) (Hnizdo et al. 2002). This study has found that not only workers in the 'traditional' COPD-related industries listed above but those in rubber, plastics, and leather manufacturing, utilities, office building services, textile mill products manufacturing, the armed forces, food products manufacturing, automotive repair services and gas stations, sales clerks, transportation and trucking, personal services (like hairdressers and cosmetologists), health care workers, record processing and distribution clerks, machine operators, and waitresses all have a higher than the average population prevalence of COPD. In fact the attributable portion of COPD among these workers was 19 % for the general population and 31 % for those who have never smoked (Hnizdo et al. 2002). It appears that workplace exposure to vapors, gas, dust, and fumes (VGDF) in common has the potential to induce and maintain the pathological process associated with COPD in susceptible individuals. In effect workplace exposure to VGDF more than doubled the odds of developing COPD later in life and accounted for almost a third of all cases in a population-based study (Blanc et al. 2009a). The interaction between occupational exposure and cigarette smoking on the development of COPD remains poorly understood. Studies observing a super additive increased risk (Blanc et al. 2009b) or a less than additive effect (Blanc et al. 2009a) have been published by the same group of investigators analyzing data collected from similar populations. This and other studies available suggest that factors beyond simple co-exposure to VGDF and cigarette smoke have to be dissected before we will have a clear understanding of their role in COPD.

5.6 Anatomical Considerations

COPD is a disease of the small airways and respiratory parenchyma. To better understand the underlying mechanisms, we first review the role of these constituents of the respiratory system. Air moves between the atmosphere and the alveoli via the upper (the nasal and oral cavity, the pharynx, the larynx) and lower (the trachea and the bronchi) airways. The flow of air depends on a variety of factors, most important of which is the diameter of the conductive pathway. The critical, flow-limiting elements in COPD are the small bronchi and bronchioli, the diameter of which are in the range of less than 1 mm to about 3.5 mm. Normal small bronchi with the size over 1 mm contain cartilaginous rings; these rings are replaced by smooth muscle fibers and connective tissue elements below the diameter of 1 mm (after about 11 divisions of the tracheobronchial tree). This feature results in an

important change in the response of the small airways to the alternating increase and decrease in intrathoracic pressure with the respiratory cycle. During inspiration the pressure in the thoracic cavity is reduced resulting in traction via elastic components on the alveolar walls and the airways. While this has negligible effect on airways containing cartilaginous rings (they are rigid in nature), those airways without cartilage get expanded and their diameter increases. During exhalation the reverse happens: these same airways get compressed. Under normal circumstances the air flow throughout these small airways when breathing at rest, and even during exercise is unrestricted. The total diameter of the airways is very large and the velocity of the flow is such that it remains laminar (Lumb 2000). However, with the pathological alterations present in patients with COPD this situation changes dramatically, resulting in critically reduced diameter and turbulent flow. There are three major underlying pathological mechanisms for air flow limitation due to decreased luminal diameter and increased airway resistance in the small airways:

1. *Accumulated material* within the lumen as a result of increased production and reduced clearance of mucus.
2. *Thickening of the wall of the passageway* due to increased deposition of connective tissue in the walls of the small airways resulting in constrictive remodeling.
3. *Increased pressure* (*compression*) *from outside* because the loss of alveoli and elastic matter causes reduced tethering of the small airways during expiration.

All three of these pathological features (the increased production and reduced clearance of mucus, deposition of connective tissue in the walls of the small airways and loss of alveoli and elastic matter) are simultaneously present in COPD. In the clinical manifestation of the disease (***1***) and (***2***) are characteristics of chronic bronchitis while (***3***) is commonly known as emphysema. Patients suffering from COPD present with a mixture of all three. Limited air flow during exhalation results in air trapping in the lung at end-expiration and the consequential alveolar hyperinflation further compresses the small airways (Barnes and Rennard 2009).

The limitation of air flow during exhalation can be quantified in patients by measuring the forced expiratory volume in the first second of expiration (FEV_1) and the Tiffeneau index which is the ratio of FEV_1 to FVC (forced vital capacity). Commonly used flow measurements are the peak expiratory flow rate and the maximum mid-expiratory flow (MMEF) rate which is the forced expiratory flow between the 25th and 75th percentiles of the FVC. While peak expiratory flow is effort sensitive, MMEF is effort independent and reflects the maximum flow rate permissible by the small airways. Lung development continues into early adulthood thus lung function steadily increases after birth until the third decade of life. This is important given that outdoor pollution and traffic-related air pollution can have an adverse effect on lung development in children aged 10–18 years (Gauderman et al. 2004; Ko and Hui 2012). In adults there is a constant decline of lung function resulting in reduced physiological reserve in the elderly. However, in a healthy individual even of very advanced age lung function provides adequate gas exchange at rest and during mild or moderate exercise (Sharma and Goodwin 2006). The effects of air pollution on the age-related decline in pulmonary physiology are not well understood but gender

differences have been reported in susceptibility. After controlling for demographic and socioeconomic factors, cigarette smoking and background air pollution, greater traffic density significantly correlated with reduced FEV1 and FVC in women but not men in a cross sectional community based study of 15,792 middle aged men and women (Ko and Hui 2012; Kan et al. 2007). The FEV1/FVC ratio however did not correlate with traffic exposure. While traffic-related air pollution was associated with the development of adult onset asthma among never-smokers (Kunzli et al. 2009), the relationship between air pollution and decline in lung function with subsequent development of COPD needs additional clarifications (Ko and Hui 2012).

The main effect of air pollution on the clinical progress of COPD is induced as chronic airway inflammation manifesting itself with wide variability between affected individuals. The quality, quantity and duration of exposure, the response of the various elements of the innate and adaptive immune systems, the still poorly understood genetic and epigenetic determinants regulating airway remodeling in COPD are focal points of ongoing research.

5.7 Cellular Pathways of Air Pollutant-Induced COPD

A wide variety of structural, immune and inflammatory cells have been implicated in the pathogenesis of COPD. The significance of specific cell types in mediating the effects of air pollution however remains the subject of intense investigations. The effects of acute inhalation of air pollutants are manifested in activation of signaling pathways and proinflammatory mediator release by resident epithelial cells and macrophages leading to recruitment of inflammatory cells, structural damage and exacerbations of the symptoms of COPD (Bates 2000; Barnes and Rennard 2009; Baraldo et al. 2012; Barnes 2004a, b, c; Becker et al. 2005). Chronic, prolonged or intermittent exposure to pollutants evokes more complex pathways including development of "adaptation" (Jakab et al. 1995) and tissue protection and repair (Burgel and Nadel 2004; Crosby and Waters 2010; Hogg et al. 2004; Leikauf et al. 2001; Sunil et al. 2012).

5.7.1 Macrophages

The most commonly found immune cells in the normal lung are the alveolar macrophages contributing to both the innate and acquired immune response. These cells clear inhaled particles, identify and destroy pathogens appearing in the terminal airways. Exposure of human alveolar macrophages to ultrafine carbon particles or diesel exhaust particles (DEP) *in vitro* reduced their binding and phagocytic activity via their scavenger, mannose, and complement receptors while binding and opsonization via the Fc receptor remained unchanged (Lundborg et al. 2006). Macrophage numbers in the lung may increase up to 15-fold in patients with COPD and their

numbers appear to correlate with disease severity (Barnes 2004a; Finkelstein et al. 1995). Macrophages, activated locally or recruited during the disease process can account for most of the known features of the disease (Barnes 2004a, b). In a healthy lung the majority of macrophages are made up by the "alveolar" and "interstitial" types. Under inflammatory conditions, however, these cells become highly heterogeneous and differentiate into several additional phenotypes classified as "migratory (or proinflammatory) vs. residential" or "M1 vs. M2" (Moreira and Hogaboam 2011). During inflammation in COPD, bone marrow derived monocytes migrate through the circulation and differentiate under the effects of macrophage colony stimulating factor (M-CSF) and epithelial derived cytokines, chemokines and other inflammatory mediators such as prostaglandins, leukotrienes and components of the complement cascade. Macrophages from COPD patients have increased levels of the transcription factor nuclear factor κB (NF-κB), that may be responsible for the increased secretion of elastolytic enzymes and inflammatory proteins (Di Stefano et al. 2004). Proinflammatory macrophages release a number of inflammatory mediators and chemokines (CXCL1, CXCL2, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, TNF-α, IL-1-β, IL-6, IL-18) (Barnes 2004a, b), elastolytic enzymes (matrix metalloproteinases (MMP) most important of which is MMP-9, cysteine and serine proteases) (Russell et al. 2002a), and oxidative radicals. Exposure to DEP suppressed CXCL8 expression as well as intracellular lysosomal and mitochondrial activity *in vitro* in monocyte-derived macrophages resulting in a reduced lifespan and impaired ability for translocation, differentiation, and cytokine response to lipopolysaccharide and heat killed bacteria (Chaudhuri et al. 2012). Phagocytosis of DEP by native primary alveolar macrophages induced apoptosis through generation of reactive oxygen species which triggered caspase and stress-activated protein kinase dependent mechanisms. This process was phagocytosis-dependent as non-phagocytic lung cells were not affected (Hiura et al. 1999). Released local factors are also important in the priming and skewing of these cells into the "classically activated" or "alternatively activated" subclasses. "Classically activated" M1 macrophages are present in severe inflammation. In response to LPS activation and exposure to IFN-γ M1 macrophages produce IFN-γ, TNF-α, IL-1β, IL-6, IL-12, IL-23, ROS, NO, GM-CSF, MIP-1α (CCL3), TARC (CCL17) and MCP-1 (CCL2) (Boorsma et al. 2013). The alternatively activated M2 macrophages are composed of several subclasses. M2a (after exposure to IL-4 or IL-13), M2b (in response to immune complexes in combination with IL-1β or LPS) and M2c (IL-10, TGFβ or glucocorticoids) has been described (Martinez et al. 2008). Depending on their differential expression of mediators, M2 cell subclasses support allergic airway inflammation; facilitate resolution of airway changes through a heightened phagocytic capability; contribute to airway remodeling; or provide immunosuppressive activities. M2 cells express CD206 (mannose receptor, MR) and display a unique mediator profile, that can include IL-4, IL-5, IL-10, IL-13 and IL-33, CCL18, CCL22, CCL24, HO-1, Arginase 1, chitinase-like Ym1, and Fizz1 (found in inflammatory zone-1) (Draijer et al. 2013; Martinez et al. 2013).

In patients with emphysema, macrophages accumulate in alveolar septae resulting in structural destruction and loss of breathing surface. This focal inflammation

is dominated by accumulation of macrophages and neutrophil cells in the lung parenchyma resulting in collagen deposition in the airways, goblet cell hyperplasia, and emphysema-like changes as documented in humans suffering of COPD as well as in a mouse model for NO_2-induced COPD (Wegmann et al. 2005). Macrophages derived CXCL1 and CXCL2 recruit circulating monocytes, while CXCL9, CXCL10 and CXCL11 attract T lymphocytes to the distal air spaces in COPD. Inhalation of aerosolized $PM_{2.5–10}$ resulted in macrophage activation, upregulation of inflammatory surface markers, increased phagocytosis and expression of TNF-α mRNA. Some but not all of this effect was mediated by surface bound endotoxin (Alexis et al. 2006). Alveolar macrophages isolated from bronchoalveolar lavage of healthy volunteers have shown proinflammatory response to coarse (PM_{10}) rather than fine ($PM_{2.5}$) particles and minimal oxidative stress response. These effects were mediated via TLR-4 (Becker et al. 2005). It is of note that alveolar macrophages, when exposed briefly to large quantities (20 % of LD50 dose) of PM *in vitro* exhibited reduced phagocytic and opsonizing capacities (Oberdorster et al. 1992; Becker and Soukup 1998). However, this may be attributed to the experimental setting rather than being a reflection of the physiological process in vivo where PM quantities are substantially smaller and exposure times are longer (Miyata and van Eeden 2011). Macrophages isolated from the lungs of patients with COPD exhibited reduced apoptosis and increased survival compared to those found in patients with normal lungs. This increased survival allows for sustained production of inflammatory mediators and increased destruction of lung parenchyma. Increased expression of $Bcl\text{-}X_L$, an antiapoptotic protein has been implicated in the extended survival of alveolar macrophages in COPD (Tomita et al. 2002). Macrophages from patients with COPD show resistance to corticosteroids, the most commonly used medication in obstructive airway diseases. This corticosteroid resistance is likely to be related to the reduced activity of histone deacetyase-2 (HDAC-2) an enzyme responsible the mediation of glucocorticoid effects on inflammatory gene transcription. Impaired suppression of inflammatory genes contributes to the sustained activation of macrophages in COPD (Ito et al. 2005). Normal alveolar macrophages have anti-inflammatory capacity expressed by secretion of TGF-β and inhibitors of MMPs. Macrophages in patients with COPD exhibit a limited capacity for anti-inflammatory activity which further shifts the inflammatory response towards tissue destruction (Pons et al. 2005).

5.7.2 Neutrophils

Normal, healthy lung parenchyma contains few if any neutrophil cells. The life span of neutrophils is short and these cells are capable of fast migration. A general acute effect of inhalation of toxic material (including the major pollutants NO_2, SO_2, PM_{10} [and more importantly $PM_{2.5}$] and ozone) is the influx of neutrophils into the distal air spaces. Although the exact mechanism of how such diverse agents can all elicit this rapid neutrophil recruitment is not clear, a shared pathway mediated by

oxidative stress and generation of reactive oxygen species may play an important role (Tao et al. 2003). Recruitment and translocation from the pulmonary circulation via chemotactic signaling from epithelial cells, activated macrophages and T-cells (via CXCL8, CXCL1, and leukotriene B_4) directs migration of neutrophils towards the airways. Adhesion molecules expressed on endothelial and epithelial cells mediate neutrophil migration with the MAC1/ICAM1 interactions being the most crucial. Smoker COPD patients have increased surface expression of MAC1 (CD11+/CD18+) on their neutrophils (reviewed in (Domagala-Kulawik 2008)). In addition to air pollution, the major causal agents in COPD exacerbations are usually considered bacterial or viral infections, or a combination of the two (Papi et al. 2006; Tsoumakidou and Siafakas 2006; Celli and Barnes 2007). Exacerbations represent an increase in the inflammation that is present in the stable state, with increased numbers of neutrophils, cytokines, chemokines and proteases in the airways, and some increased mediators in the blood with no reliable biomarkers to predict exacerbations (Celli and Barnes 2007). How exacerbations should be defined and graded are still debated today and the role of neutrophils in air pollutant-induced exacerbations of COPD remains complex (Tao et al. 2003; Papi et al. 2006; Tsoumakidou and Siafakas 2006; Celli and Barnes 2007; van Eeden et al. 2005; White et al. 2003).

Neutrophils can secrete a variety of proteases (including MMP, serine proteases, and cathepsin-G) and myeloperoxidase resulting in ROS formation. ROS accumulation in turn facilitates further extravasation of neutrophils in the inflamed airways (Rahman 2005). Oxidative stress also causes elevated concentration of cytokines and growth factors capable of activating and preventing apoptosis of neutrophils. This can lead to either increased survival or necrotic death of these cells. An important feature of the COPD lung is an increased number of dead cells due to necrotic cell death and a reduced ability of alveolar macrophages to perform their scavenger function. Neutrophil elastase was shown to cleave the phosphatidyl serine receptor on macrophages thereby disabling their apoptotic cell sensing and phagocytic capabilities (Vandivier et al. 2002).

Normally epithelial mucins serve the purpose of removing inhaled foreign materials by mucociliary transport and by coughing. In COPD however, excessive mucus is produced and is inadequately cleared. Some earlier studies correlated disease severity with sputum neutrophil numbers (Stanescu et al. 1996). It is becoming more accepted now that the main role of neutrophils in COPD is likely limited to goblet cell activation and increased mucus secretion rather than direct destruction of lung parenchyma. Indeed, the increased number of neutrophils in the airways during exacerbations of COPD manifests itself in the purulent nature of the expectorated sputum. Neutrophil proteases can stimulate mucin release by goblet cells. During oxidative stress neutrophils induce mucin production by activation of the epidermal growth factor receptor (EGFR). At present there is no specific treatment for mucus hypersecretion. However, the discovery that an EGFR related pathway is involved in mucin production by a wide variety of stimuli suggests that blockade may provide specific treatment for hypersecretory diseases (Burgel and Nadel 2004).

5.7.3 Dendritic Cells

Similarly to macrophages, dendritic cells are constitutive elements of the lung parenchyma and airways. In normal healthy lungs, dendritic cells are scattered throughout the respiratory mucosal wall. In resting state their primary role is to sample the environment and regulate immune homeostasis through communication with other cell types of the innate and adaptive immune system. Once dendritic cells are activated they will migrate to the regional lymph nodes and assume a T-cell–stimulatory phenotype. In the proximal and distal air spaces these cells are responsible for either initiating immune responses or maintaining immune tolerance. The fact that the respiratory surface of the average normal adult human lungs filters through over 11,000 l of air every day without a perpetual inflammatory state is in large part due to the collaborative action of dendritic cells and alveolar macrophages. The "hyperinflammatory" condition characterizing the COPD lung is associated with activation of different dendritic cell subpopulations, depending on their origins, migratory patterns, role and function (Haczku 2012; Botelho et al. 2012). The majority of the lung resident dendritic cells under resting conditions are made up by the tolerogenic plasmocytoid type (characterized by the cell surface marker profile 120G8^{high}/PDCA-1^{high}/Gr1^{high}/B220^{high}). During inflammation myeloid (CD11c^{high}/CD11b^{high}/MHC-II^{high}) and CD103^{+} cells migrate rapidly to the lung. These cells are mature and possess antigen presenting and CD4^{+} T cell stimulatory capabilities. Activated dendritic cell migration is propelled by the CCL19-CCR7, CXCL1-CXCR2, CCL2-CCR2/4 and CCL20-CCR6 chemokine ligand-receptor pathways (Demoor et al. 2009, 2011; Demedts et al. 2007). This process can amplify the chronicity of inflammation and can lead to destruction of the normal lung parenchyma. In a recent study, dendritic cells stimulated by cigarette smoke in mice, induced development of emphysema through auto-reactive CD8^{+} T cell activation and release of IL-17A (Shan et al. 2012). Unfortunately, there are no studies to date that investigated the role of these cells in mediating the effects of air pollution in COPD. There are however reports that looked at the effects of air pollutants on dendritic cell function and indicated a general tendency of these cells to lose their tolerogenic capabilities. For example, an association was seen between environmental tobacco smoke exposure and reduced dendritic cell interleukin 10 production during infancy (Gentile et al. 2004). Further, exposure to urban air extract, fine and ultrafine particles or DEP all induced dendritic cell activation leading to production of IL-1β or TNF-α (Gentile et al. 2004; Acciani et al. 2013; Bonisch et al. 2012; Kim et al. 2012; Karle et al. 2012; Myatt et al. 2011; Bezemer et al. 2011; Yoshida et al. 2010; Williams et al. 2008; de Haar et al. 2008). A recent study in mice demonstrated that IL-1R, TLR4, and TLR2 predominant receptors on activated dendritic cells, elicited inflammatory effects via MyD88 in response to wood or cow dung smoke derived PM suggesting that biomass fuel exposure elicits a persistent pulmonary inflammation largely through activation of TLR and IL-1R pathways (Sussan et al. 2014).

5.7.4 Lymphocytes

Lymphocyte accumulation in the pulmonary interstitium and peribronchial areas correlate with the severity of the symptoms of COPD and are considered to be part of the mechanism leading to exacerbation of symptoms brought on by air pollution or infections (Papi et al. 2006). Pollutants may have selective effects on lymphocytes. In a recent study lymphocyte redistribution was observed in NO_2 exposed volunteers (NO_2 levels were negatively correlated with peripheral blood lymphocyte count) but this effect was not seen in response to PM exposure (Steenhof et al. 2014). Lymphocytes organized in follicular structures with B lymphocyte containing germinal centers surrounded by $CD4^+$Th1-cells have been observed in clinically advanced cases of chronic bronchitis while increase in the numbers of $CD8^+$ cytotoxic Tc1 lymphocytes in the alveolar wall appears to be proportional with the severity of emphysema (Hogg et al. 2004).

Cytokine and chemokine signaling from epithelial cell injury, activated alveolar macrophages and antigen presenting dendritic cells may all contribute to the migration of $CD8^+$ and $CD4^+$T-lymphocytes to the lung in pollutant-induced COPD exacerbation. Interferon induced chemokines CXCL9, CXCL10, and CXCL11 elicit homing of CXCR3 positive T-cells while chemo-attractants for CCR4 positive Th2 cells (a predominant cell type in the pathogenesis of bronchial asthma) are not expressed in COPD (Grumelli et al. 2004). This feature is the main reason for the presence of T cells with cytotoxic characteristics in COPD with a relative lack of eosinophilic granulocytes (a hallmark of asthma). Th1 cells are $CD4^+$T-cells that express activated STAT-4 leading to interferon-γ (IFN-γ) secretion. Th1-cell help is required for $CD8^+$ cytotoxic Tc1 activation, survival (suppression of apoptosis) and maintenance of their immunological memory (Barnes and Rennard 2009). $CD8^+$ T-cells synthetize, store and release cytokines and cytotoxic substances like tumor necrosis factor-α (TNF-α), granzyme B, and perforins and their numbers inversely correlate with the FEV_1 of patients suffering of COPD (Freeman et al. 2010). It is of interest that patients with severe COPD of non-smoking origin do not have a Th1 cell inflammatory bias in their lung (Grumelli et al. 2004). CD8+ T cell activation and release of the above-mentioned cytotoxic substances however can be achieved by induction of Toll-like receptor (TLR)2 activation (Freeman et al. 2013). Indeed TLR2 was shown to play an important role in mediating the effects of biomass smoke derived PM (Sussan et al. 2014). Degradation of lung parenchyma may produce antigenic peptides (auto-antigens) that in the presence of chronic inflammation could induce a progressive self-perpetuating autoimmune inflammation (Cosio et al. 2002). The significance of lymphocytes and autoimmune pathways in air pollutant induced COPD needs clarification.

5.7.5 Epithelial Cells

Epithelial cells in the lung are highly specialized and form the first line of defense against inhaled air pollutants. The major role of type-1 alveolar cells is gas exchange: facilitation of the uptake of oxygen and release of carbon dioxide. Type-2 alveolar cells produce surfactant that reduces surface tension and allows alveoli of different diameters to remain open even at low lung volumes. The bronchial epithelium is composed of pseudostratified columnar cells that include basal, ciliated or secretory (Clara or goblet) cells. Ciliated bronchial epithelial cells transport foreign matter towards the larynx along the surface of the tracheobronchial tree. Goblet cells in the bronchi secret mucus, which enhances expulsion via cilial activity (Lumb 2000). In patients with COPD epithelial cells express high levels of inflammatory mediators (CXCL-8, IL-1-β, and GM-CSF) (Hellermann et al. 2002) and adhesion molecules (sICAM-1 (Hellermann et al. 2002) and E-selectin (Di Stefano et al. 1994)) thereby facilitating recruitment and translocation of inflammatory cells.

Cultured bronchial epithelial cells when exposed to airborne particulate matter respond with increased expression of CXCL8 and to a lesser and irritant specific extent by upregulation of a variety of chemokines (CXCL1, 3, 10, 11, CCL20) and proinflammatory factors (TNF-α, IL-6, LTβ) (Øvrevik et al. 2009). It is of note that expression of CXCL8, a chemokine mostly associated with neutrophilic granulocyte recruitment is associated with pollutants as diverse as fine carbon particles, 1-nitropyrene, aerosolized bacterial lipopolysaccharide and $ZnCl_2$ (Øvrevik et al. 2009). This common feature perhaps explains the epidemiological finding that exposure to a wide variety of inhaled airborne pollutants results in common clinical outcomes and disease progression (Schwarze et al. 2006). On the other hand, relatively similar chemical substances like various nitro-polycyclic aromatic hydrocarbons (nitro-PAHs) may elicit either increased cytokine and chemokine expression or epithelial cell apoptosis (Øvrevik et al. 2010). Furthermore, seasonal variability in particulate matter composition produces distinct effects as shown from samples taken in Milan, Italy. The winter PM had higher levels of PAHs while in the summer, mineral dust elements have dominated. When cultured human epithelial cells were exposed to these PM samples the winter samples were more cytotoxic while the summer samples exhibited a higher proinflammatory potential (Gualtieri et al. 2010).

The mechanisms of interaction between airborne pollutants and epithelial cells, inflammatory cells and mesenchymal cells in the development of COPD are complex and remain to be fully elucidated. This complexity is increased by the fact that in addition to its pro-inflammatory function, the airway epithelium is also responsible for maintaining immune homeostasis and protecting against chronic inflammatory changes in the lung. The protective function of airway epithelial cells has been attributed to a constitutive production of the immune modulators, lung collectins: surfactant protein A and D. The majority of these molecules are produced by type II alveolar epithelial cells in the distal air spaces but Clara cells and goblet cells can also release collectins. SP-A and SP-D belong to a small family of structurally related Ca^{2+} dependent lectins that share collagen-like and lectin domains. Collectins are involved in pathogen binding (opsonization) and direct inhibition of

immune and inflammatory cell function (Rosseau et al. 1997). Collectin-specific interactions with lung cells can be mediated through CD14 (Sano et al. 2000), TLR2 (Ohya et al. 2006) and TLR4 (Ohya et al. 2006; Guillot et al. 2002) as well as through the signal inhibitory regulatory protein (SIRPα) (Gardai et al. 2003). This signal regulatory membrane protein uniquely carries an ITIM containing intracellular domain which is responsible for inhibiting functions of myeloid derived cells, particularly, macrophages and dendritic cells (Matozaki et al. 2009). Lung collectins regulate antigen presentation, T-cell stimulation (Brinker et al. 2003; Brinker et al. 2001; Hansen et al. 2007) and TNFα expression by antigen presenting cells (Hortobagyi et al. 2008).

Under normal conditions SP-A–/– mice display no overt pathological features. SP-D–/– mice on the other hand showed serious constitutive inflammatory alterations (Botas et al. 1998; Hawgood et al. 2002) resembling pathological characteristics of COPD indicating special importance of this molecule in regulating immune homeostasis and function of the innate immune cells (Crouch et al. 2000; Crouch 2000; Wright 2005; Haczku 2006, 2008). Studies on airway responses to allergen (Takeda et al. 2001) or O_3 (Kierstein et al. 2006) exposure showed that C57BL/6 mice were significantly more protected against developing inflammation than Balb/c mice and this protection was associated with a greater amount of SP-D in their airways (Kierstein et al. 2006; Atochina et al. 2003). Mice lacking this molecule due to genetic deletion were highly susceptible to allergen or O_3-induced airway inflammation and showed a prolonged recovery period (Haczku 2006; Kierstein et al. 2006). O_3-induced changes in sputum dendritic cell phenotype were associated with changes in serum SP-D levels in healthy volunteers (Alexis et al. 2008). Further, low SP-D levels in the lung correlated with disease severity in COPD patients (Sims et al. 2008).

Mouse models of low or no SP-D expression in different mouse strains and gene-manipulated mice mimic patients who have low SP-D levels in the lung due to genetic reasons or as a consequence of chronic inflammation. Locally administered SP-D has been protective in mouse models of airway inflammation. It is possible therefore that it will work in patients, too. SP-D is not only an anti-inflammatory agent but also an important opsonin that binds a wide range of common respiratory pathogens. Thus, unlike the traditional immunosuppressive therapies, an SP-D-based anti-inflammatory approach could have an advantage of a preserved host defense function.

5.8 Molecular Mechanisms of Air Pollutant-Induced Lung Damage in COPD

COPD is characterized by a progressive destruction of the alveolar structure of the lung parenchyma with associated fibrotic narrowing of small airways by the underlying inflammatory processes. In addition to cytokines and chemokines many inflammatory mediators were described and characterized in this process. The major

players include arachidonic acid derivatives, molecular products of oxidative stress, players of cell death, extracellular matrix destruction and repair (Barnes 2004c).

5.8.1 Arachidonic Acid Metabolites

Ozone exposure of human nasal mucosa *in vitro* induced heightened eicosanoid metabolism with the release of cyclooxygenase and lipoxygenase products into the culture supernatant including prostaglandin (PG)$F_2\alpha$, thromboxane B2 and leukotriene B4 (LTB4) (Schierhorn et al. 1997). In COPD however arachidonic acid metabolism follows a typical pattern in the lungs: There is an increase in prostaglandins PGE_2, $PGF_2\alpha$, and LTB_4 but not of thromboxane or cysteinyl leukotrienes (increase of which is characteristic for bronchial asthma) (Barnes and Rennard 2009). Increased expression of cyclooxygenase-2 (COX2) is responsible for increased production of these prostanoids.

Urban air collected in different zones in Mexico City, containing PM_{10} induced PGE_2 in cultured rat fibroblasts in a dose-dependent manner *in vitro* (Alfaro-Moreno et al. 2002). Further, nickel (Ni), a common component of urban PM enhanced IL-8 production by fibroblasts in the presence of PGE_2, suggesting a synergistic action (Brant and Fabisiak 2013).

Alveolar macrophages in patients with COPD express pro-inflammatory BLT_1-receptors and LTB_4 inactivating PPAR-α receptors. LTB_4 also recruits circulating $CD8^+$ T-cells and neutrophils to the lung parenchyma through high affinity BLT_1-receptors expressed on these cells (Marian et al. 2006). Investigation of exhaled breath condensate from ozone-exposed subjects (in comparison with air exposed ones) revealed elevated levels of 8-isoprostane and LTB4. These levels were significantly greater in subjects sensitive to ozone suggesting that sensitive subjects have elevated arachidonic acid metabolites in their exhaled breath condensates (Alfaro et al. 2007).

5.8.2 Role of Oxidative Stress

Reactive oxygen species (ROS) are generated in the pulmonary parenchyma as part of the first line defense mechanism by the innate immune system. Exogenous irritants and inflammatory mediators induce ROS production by epithelial cells, alveolar macrophages, and neutrophil cells in the lungs (Yao and Rahman 2011). These ROS overwhelm and destroy invading bacteria, fungi, and viruses in a non-specific manner. ROS are also produced, in smaller quantities, as by-products of signaling and energy generating intracellular processes. ROS also have a role in inducing and maintaining local inflammation (Rahman 2005). The enzyme NADPH oxidase generates superoxide anions (O_2^-) from molecular oxygen. This superoxide anion is relatively unstable and highly reactive and is converted by superoxide dismutase

(SOD) to hydrogen peroxide (H_2O_2). H_2O_2 can diffuse to farther distances than superoxide anion allowing for a larger radius of effect. In the extracellular space reaction of O_2^- with free iron or nitric oxide (NO) produces highly reactive hydroxyl radicals (OH^-) and peroxynitrite ($ONOO^-$), respectively. ROS interacting with lipids generate lipid radicals (lipid peroxides) leading to a redox chain reaction in lipid bilayers damaging cellular membranes or oxidize arachidonic acid leading to the formation of isoprostanes, a class of prostanoids; mediators implicated in bronchoconstriction and increased alveolar and capillary permeability. Both isoprostane levels (Garcia-Rio et al. 2011) and lipid peroxidation markers (Rahman et al. 2002) positively correlate with disease severity in patients with COPD. There is increased synthesis of NO in lung parenchyma and small airways due to chronic inflammation-induced increase in the expression of inducible NO synthase in epithelial cells and macrophages in COPD (Ricciardolo et al. 2005). Peroxynitrite reacts with tyrosine residues in proteins producing 3-nitrotyrosine. As tyrosine moieties often have a significant role in protein activation or inhibition these changes may result in significant alterations in the function of the given proteins. Reactive aldehydes or carbonylate proteins form aldehyde-protein adducts that alter or suspend protein function. Aldehyde-protein adducts may also induce immunogenicity and serve as targets for the adaptive immune system (Yao and Rahman 2011). ROS when reaching the cell nucleus may inflict direct damage on the DNA or interact with regulatory enzymes like histone deacetylase (HDAC and sirtuins) or histone methylation (HMT)/demethylation (HDM) enzymes leading to alterations in inflammatory gene expression (Sundar et al. 2013).

Inhalation of nitro-PAHs (a component of diesel exhaust particles) can lead to the generation of electrophilic metabolites including epoxides (Yamazaki et al. 2000; Andersson et al. 2009) or nitro-reductions [this later is catalyzed by enzymes like NOS, xanthine oxidase, aldehyde oxidase (Arlt et al. 2003) or NADPH:quinone oxidoreductase (Arlt et al. 2005)] resulting in generation of ROS (Øvrevik et al. 2010). On the other hand, sulfate conjugation or acetylation generates reactive nitrenium ions which then create protein and DNA adducts (Arlt et al. 2005). DNA damaging potential of various nitro-PAHs appears to be specific to their chemical structure. The most abundant 1-nitropyrene appears to have very mild DNA toxicity while 3-nitrobenzanthrone has considerable DNA damaging potential resulting in accumulation of cells in S-phase and marked increase in apoptosis in cultured bronchial epithelial cells (Øvrevik et al. 2010). Furthermore, the generation of ROS by nitro-PAHs is paralleled by a decrease in intracellular GSH suggesting depletion of protective antioxidant mechanisms (Park and Park 2009).

Bronchial epithelial cells obtained from airway mucosal biopsies of healthy volunteers show significant increase in hemoxygenase-1 expression, a marker of oxidative stress when exposed to coarse or fine PM. This response involves the TLR-2 signaling pathway (Becker et al. 2005). The body counters the effects of ROS on the self by producing antioxidants. These substances (glutathione, ascorbic acid [vitamin C], tocopherol [vitamin E], lactoferrin, and uric acid) protect the self against the action of ROS. Enzyme systems geared towards removing reactive aldehydes including aldehyde dehydrogenase and aldo-keto reductase are present in the lung

parenchyma in COPD (Pastor et al. 2013). When these antioxidant mechanisms are exhausted, cellular damage ensues (Repine et al. 1997). In the lung parenchyma the majority of antioxidants are found in the extracellular matrix while intracellular antioxidants are expressed at a low level (Rahman 2005). While oxidative stress has little effect on intracellular antioxidant levels extracellular antioxidant enzymes like glutathione peroxidase, glutathione-S-transferase M_1, and SOD3 markedly increase. Activation of the transcription factor Nrf2 (nuclear erythroid-related factor 2) has a key role in gene activation and transcription of protective antioxidant enzymes in lungs when exposed to oxidative stress (Ishii et al. 2005). Nrf2 levels are decreased in lungs of patients with emphysema and COPD (Goven et al. 2008). Posttranslational modification of Nrf2 results in decreased activity and limited nuclear translocation. A stabilizer of Nrf2, DJ-1 has been found to be downregulated in patients with COPD but not in unaffected smokers (Malhotra et al. 2008). Activation of Nrf2 and stabilizing DJ-1 can open potential protective pathways in patients susceptible to airborne-inhalant induced COPD (Sundar et al. 2013). The Nrf2 pathway is also one of the outlets of the UPR (unfolded protein response) an intracellular mechanism protective among others against oxidative stress (Kelsen et al. 2008).

Increased oxidative stress in the lung epithelium and parenchyma may play a significant role in disease progression in COPD by amplifying and perpetuating the inflammatory response and increasing tissue destruction. ROS upregulate transcription factors NF-κB and AP-1 in alveolar macrophages and structural cells inducing inflammatory mediator and cytokine production as described above. Oxidative stress also decreases corticosteroid responsiveness in patients with COPD. This is attributed to reduced activity and expression of histone deacetylase (HDAC). Histone acetylation by histone acetyltransferase leads to transcription of pro-inflammatory genes encoding IL-8 and TNF-α through NF-κB. HDAC2 activated by corticosteroid activated-glucocorticoid receptor inhibits this process in normal lungs. However, in COPD increased peroxynitrite production inactivates HDAC2 leading to glucocorticoid resistance (Ito et al. 2005). ROS also directly impair protease inhibitors like α_1-antitrypsine and SLPI contributing to the destruction of elastic elements of the lung parenchyma in COPD. Ozone-induced NF-κB activation correlated with expression of monocyte chemotactic protein-1, inducible NO synthase and cyclooxygenase-2 in alveolar macrophages (Sunil et al. 2012). Similarly, oxidative stress secondary to free radicals generated by PM_{10} exposure resulted in calcium mediated nuclear translocation and activation of NF-κB leading to decreased expression of HDAC2 (MacNee and Donaldson 2003). The ensuing increase in acetylation of histone residues could then allow for increased transcription factor binding and expression of proinflammatory genes (Gilmour et al. 2003).

5.8.3 Mechanisms and Mediators of Apoptosis and Autophagy

Mounting evidence suggests an imbalance between apoptotic cell loss and cell proliferation in lung tissue of patients suffering of COPD as well as in animal models of emphysema (Demedts et al. 2006). This imbalance affects alveolar epithelial

cells (Imai et al. 2005), alveolar endothelial cells (Segura-Valdez et al. 2000), and lung T-cells (Hodge et al. 2005) suggesting a complex interaction between vascular growth regulation (Kasahara et al. 2000; Kanazawa and Yoshikawa 2005), inflammation, oxidative stress (Aoshiba and Nagai 2003) and epithelial cell wellbeing (Calabrese et al. 2005) in the lungs of patients with COPD. It is also of note that increased apoptosis continues after cessation of exposure to noxious inhalants (Hodge et al. 2005). Disturbance in the regulation of cell proliferation and programmed cell loss extends beyond the lungs in patients with advanced emphysema and examples of this are found in skeletal muscle atrophy resulting in peripheral muscle weakness (Agusti et al. 2002) and loss of peripheral T-cells resulting in inability to mount an adequate defensive response to infections (Hodge et al. 2003a). Suggested mechanisms of increased apoptosis include depletion or inhibition of VEGF (Kasahara et al. 2000), elevated levels of IFN-γ (Ma et al. 2005), activation of caspase-3 (Aoshiba et al. 2003) and accumulation of ceramide in the lung parenchyma (Scarpa et al. 2013). Inflammatory cells (Saetta et al. 1999) and mediators present in COPD have also been associated with pulmonary epithelial and endothelial cell apoptosis (Hodge et al. 2003b). On the other hand the decreased ability of alveolar macrophages in eliminating apoptotic cells contributes to the sustained inflammation (Vandivier et al. 2002). Elastolytic activity resulting in loss of structural basal membrane depletes alveolar epithelial cells of vital cell-matrix contacts for survival signaling and promotes apoptosis (Aoshiba et al. 1997).

Cellular organelles, old and damaged mitochondria, structural cellular proteins are removed and recycled in a dynamic process called autophagy (Ryter et al. 2012). This is an inducible mechanism originally developed to recycle cellular material thus reducing need for nutrients in starvation. Oxidative stress accelerates autophagy as there is increased number of damaged cellular components to recycle. However, excessive autophagy is harmful and may lead to death of the cell. Lung tissue from patients with COPD show accelerated autophagy, which is attributed to reduction of SIRT1, a sirtuin class histone deacetylase. Decrease in SIRT1 levels allows transcription of the early growth response protein-1 (Egr-1) gene, an important transcription factor in autophagy (Chen et al. 2008). Increased extracellular levels of superoxide dismutase (SOD) attenuate intracellular Egr-1 levels (Nozik-Grayck et al. 2008) further illustrating the complex interaction between oxidative stress and cell organelle recycling. Ozone exposure increased levels of biomarkers representative of apoptosis and autophagy like cleaved capsase-9 and beclin-1 in alveolar macrophages. This air pollutant effect was associated with presence of matrix metalloproteinases (MMP)-2, MMP-9 and cellular debris in the bronchoalveolar lavage fluid (Sunil et al. 2012).

5.8.4 Proteinases and Extracellular Matrix (ECM) Interactions

Proteinases released from macrophages, cytotoxic T-cells and to a lesser extent, neutrophilic granulocytes contribute to degrading of pulmonary parenchymal connective tissue (Segura-Valdez et al. 2000). MMPs especially MMP-9 released from

alveolar macrophages have been implicated in elastin destruction and development of emphysema (Russell et al. 2002b). Macrophages isolated from patients with COPD contain higher amounts of MMP-9 and are resistant to suppression by glucocorticoids (Chana et al. 2014). Alveolar macrophages also synthetize and secrete proteinase inhibitors (tissue inhibitors of MP, TIMP). However, the amount and activity of these inhibitors is reduced in patients with COPD and is insufficient to neutralize the MMP activity (Russell et al. 2002b).

MMPs have also been implicated in regulation of programmed cell death in COPD. MMP-7 sheds and activates Fas ligand, an apoptosis signaling molecule, from alveolar epithelial cells (Powell et al. 1999). Chronic exposure of mice to ozone mimicked the inflammatory and pathological changes of COPD and increased caspase-3 mediated apoptosis and activity of MMPs (Triantaphyllopoulos et al. 2011). The imbalance between levels and activity of MMPs and proteinase inhibitors has been associated with histone deacetylation and deficiency of sirtuin 1 (SIRT1, a member of class III histone deacetylases). The protective role of SIRT1 was also supported in a study using exposure to ambient PM and gene deficient mice in which lack of SIRT1 resulted in aggravated lung vascular leakage and inflammation after PM exposure, which was correlated with increased NF-κB acetylation and activation (Wu et al. 2012). Pertinent to air pollution induced COPD, increasing expression of SIRT1 was shown to reestablish the balance between proteinases and inhibitors. This strategy may become a pharmacological approach against inhaled irritant induced COPD (Yao et al. 2013).

5.8.5 Repair Mechanisms

Post inflammatory repair markers (arginase-1, galectin-3, Ym-1) representing alveolar macrophage contribution to wound healing were expressed in the lung 24–72 h after exposure to ozone (Sunil et al. 2012). Transforming growth factor-α (TGF-α) is secreted by alveolar macrophages and is a potent stimulator alveolar epithelial cell proliferation and repair (Crosby and Waters 2010). In goblet cells, TGF-α increases mucus production thereby worsening the disease (Burgel and Nadel 2004). Interestingly, transgenic mice expressing TGF-α were rescued from $NiSO_4$ injury (they had diminished SP-B loss and increased survival time) (Leikauf et al. 2001).

TGF-β is a potent anti-inflammatory molecule in the lung (Yang et al. 2012) expressed in both airway epithelial cells and alveolar macrophages. TGF-β is a key factor in the development of peribronchial fibrosis in COPD. A complex interaction between mediators regulating production and destruction of the ECM is highlighted by the fact that the action of MMP-9 is necessary to activate TGF-β contributing to fibrotic remodeling of lung parenchyma in COPD (Chung 2005). Exposure to various dust particles was shown to increase gene expression of procollagen, TGF-β, and platelet-derived growth factor, and increased hydroxyproline in lung explants. Addition of TNF-α increased dust adhesion to, and ozone exposure increased dust

uptake by tracheal epithelial cells (Churg and Wright 2002). Further, Katre and colleagues demonstrated in a mouse model that O_3 exposure increased TGF-β expression and activated TGF-β signaling pathways leading to O_3-induced lung fibrotic responses *in vivo* (Katre et al. 2011).

5.9 Summary and Future Projections

The evidence for epidemiological association between occupational and environmental (outdoor and indoor) exposure to air pollutants and COPD is well established but it is also clear, that individuals respond differently to the same noxious stimuli. Although various inflammatory pathways have been implicated, the mechanisms by which air pollution affects development of COPD in susceptible individuals are not well understood. Recent investigations on subjects participating in the Normative Aging Study (a prospective cohort of aging established in 1963, enrolling men from the Greater Boston area), applied a novel genetic approach to investigate interactions between pathways relevant to chronic inflammation and air pollution. The authors found that among participants with higher genetic scores (i.e. a higher allelic risk profile) within the oxidative stress and metal processing pathways, there were significant associations between pollutant particle number and variants of the fibrinogen, C-reactive protein and ICAM-1 genes (Bind et al. 2014a). These data supported that in addition to the extent of exposure, disease development in exposed subjects is related to genetic predisposition affecting specific, inflammatory genes.

Further investigations by Lepeule et al. (2014) showed that sub-chronic (3-to 28-days, cumulated) but not acute exposure to black carbon, total and non-traffic $PM_{2.5}$, CO and NO_2 was associated with a 1–5 % decrease in FVC and FEV_1 in elderly, Normative Aging Study participants. These data suggested the importance of duration of exposure to air pollutants. Interestingly, in participants with a greater exposure (28-days cumulated), low methylation in the TLR2 and high methylation in the glucocorticoid receptor genes were observed. Thus, prolonged exposure to air pollution may lead to epigenetic alterations of genes related to inflammatory and immune regulatory pathways.

Indeed in another well characterized cohort of subjects from the Normative Aging Study (1999–2009) (Bind et al. 2014b) increase in air pollutant (ozone and components of fine particle mass) concentrations was significantly associated with hypomethylation of tissue factor-3, ICAM-1, and TLR-2 genes and hypermethylation of the IFN-γ and IL-6 genes. While these studies suggested that altered DNA methylation could reflect biological impact of air pollution, the significance and mechanisms of such epigenetic pathways need further clarifications.

In summary, today we have epidemiological evidence that supports a pathogenetic role of air pollutants in the development and course of COPD. We also understand that there is a great degree of heterogeneity in the air pollution effects: disease development involves only a lesser but significant proportion of the population where in addition to genetic factors, the extent and duration of exposure also play a

deterministic role. Thus, the physician and policy maker are both in quandary when the question is asked: who are the vulnerable and who are those not affected by the pollutants. Protecting all including those who are not affected would consume large financial resources, oftentimes not available for the individual or the society. Further research is needed to determine the most vulnerable populations and what actions might be successful in preventing or slowing the progress of disease. Emerging work in genetics (Bind et al. 2014a; Zhou et al. 2013) and epigenetics (Lepeule et al. 2014; Bind et al. 2014b; Sakao and Tatsumi 2011) of COPD provides hope in this direction of prevention and cure.

References

Acciani TH, Brandt EB, Khurana Hershey GK, Le Cras TD (2013) Diesel exhaust particle exposure increases severity of allergic asthma in young mice. Clin Exp Allergy 43:1406–1418

Agusti AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E, Batle S, Busquets X (2002) Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:485–489

Alexis NE, Lay JC, Zeman K, Bennett WE, Peden DB, Soukup JM, Devlin RB, Becker S (2006) Biological material on inhaled coarse fraction particulate matter activates airway phagocytes in vivo in healthy volunteers. J Allergy Clin Immunol 117:1396–1403

Alexis NE, Lay JC, Haczku A, Gong H, Linn W, Hazucha MJ, Harris B, Tal-Singer R, Peden DB (2008) Fluticasone propionate protects against ozone-induced airway inflammation and modified immune cell activation markers in healthy volunteers. Environ Health Perspect 116:799–805

Alfaro MF, Walby WF, Adams WC, Schelegle ES (2007) Breath condensate levels of 8-isoprostane and leukotriene B4 after ozone inhalation are greater in sensitive versus nonsensitive subjects. Exp Lung Res 33:115–133

Alfaro-Moreno E, Martinez L, Garcia-Cuellar C, Bonner JC, Murray JC, Rosas I, Rosales SP, Osornio-Vargas AR (2002) Biologic effects induced in vitro by PM10 from three different zones of Mexico City. Environ Health Perspect 110:715–720

Anderson HR, Limb ES, Bland JM, Ponce de Leon A, Strachan DP, Bower JS (1995) Health effects of an air pollution episode in London, December 1991. Thorax 50:1188–1193

Andersson H, Piras E, Demma J, Hellman B, Brittebo E (2009) Low levels of the air pollutant 1-nitropyrene induce DNA damage, increased levels of reactive oxygen species and endoplasmic reticulum stress in human endothelial cells. Toxicology 262:57–64

Aoshiba K, Nagai A (2003) Oxidative stress, cell death, and other damage to alveolar epithelial cells induced by cigarette smoke. Tob Induc Dis 1:219–226

Aoshiba K, Rennard SI, Spurzem JR (1997) Cell-matrix and cell-cell interactions modulate apoptosis of bronchial epithelial cells. Am J Physiol 272:L28–L37

Aoshiba K, Yokohori N, Nagai A (2003) Alveolar wall apoptosis causes lung destruction and emphysematous changes. Am J Respir Cell Mol Biol 28:555–562

Arbex MA, de Souza Conceicao GM, Cendon SP, Arbex FF, Lopes AC, Moyses EP, Santiago SL, Saldiva PH, Pereira LA, Braga AL (2009) Urban air pollution and chronic obstructive pulmonary disease-related emergency department visits. J Epidemiol Community Health 63:777–783

Arbex MA, Santos Ude P, Martins LC, Saldiva PH, Pereira LA, Braga AL (2012) Air pollution and the respiratory system. J Bras Pneumol 38:643–655

Arlt VM, Glatt H, Muckel E, Pabel U, Sorg BL, Seidel A, Frank H, Schmeiser HH, Phillips DH (2003) Activation of 3-nitrobenzanthrone and its metabolites by human acetyltransferases,

sulfotransferases and cytochrome P450 expressed in Chinese hamster V79 cells. Int J Cancer 105:583–592

Arlt VM, Stiborova M, Henderson CJ, Osborne MR, Bieler CA, Frei E, Martinek V, Sopko B, Wolf CR, Schmeiser HH, Phillips DH (2005) Environmental pollutant and potent mutagen 3-nitrobenzanthrone forms DNA adducts after reduction by NAD(P)H:quinone oxidoreductase and conjugation by acetyltransferases and sulfotransferases in human hepatic cytosols. Cancer Res 65:2644–2652

Atochina EN, Beers MF, Tomer Y, Scanlon ST, Russo SJ, Panettieri RA Jr, Haczku A (2003) Attenuated allergic airway hyperresponsiveness in C57BL/6 mice is associated with enhanced surfactant protein (SP)-D production following allergic sensitization. Respir Res 4:15

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G, Environmental and Occupational Health Assembly, American Thoracic Society (2003) American Thoracic Society Statement: occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 167:787–797

Baraldo S, Turato G, Saetta M (2012) Pathophysiology of the small airways in chronic obstructive pulmonary disease. Respiration 84:89–97

Barnes PJ (2004a) Alveolar macrophages as orchestrators of COPD. COPD 1:59–70

Barnes PJ (2004b) Alveolar macrophages in chronic obstructive pulmonary disease (COPD). Cell Mol Biol 50:OL627–OL637, Online Pub

Barnes PJ (2004c) Mediators of chronic obstructive pulmonary disease. Pharmacol Rev 56:515–548

Barnes PJ, Rennard SI (2009) Pathophysiology of COPD. In: Barnes PJ, Drazen JM, Rennard SI, Thomson NC (eds) Asthma and COPD: basic mechanisms and clinical management, 2nd edn. Elsevier, Amsterdam

Bates DV (2000) Revisiting "respiratory function in emphysema in relation to prognosis". Can Respir J 7:271–279

Becker S, Soukup JM (1998) Decreased CD11b expression, phagocytosis, and oxidative burst in urban particulate pollution-exposed human monocytes and alveolar macrophages. J Toxicol Environ Health A 55:455–477

Becker S, Mundandhara S, Devlin RB, Madden M (2005) Regulation of cytokine production in human alveolar macrophages and airway epithelial cells in response to ambient air pollution particles: further mechanistic studies. Toxicol Appl Pharmacol 207:269–275

Becklake MR (1989) Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 140:S85–S91

Bell ML, Davis DL (2001) Reassessment of the lethal London fog of 1952: novel indicators of acute and chronic consequences of acute exposure to air pollution. Environ Health Perspect 109(Suppl 3):389–394

Bezemer GF, Bauer SM, Oberdorster G, Breysse PN, Pieters RH, Georas SN, Williams MA (2011) Activation of pulmonary dendritic cells and Th2-type inflammatory responses on instillation of engineered, environmental diesel emission source or ambient air pollutant particles in vivo. J Innate Immun 3:150–166

Bind MA, Coull B, Suh H, Wright R, Baccarelli A, Vokonas P, Schwartz J (2014a) A novel genetic score approach using instruments to investigate interactions between pathways and environment: application to air pollution. PLoS One 9:e96000

Bind MA, Lepeule J, Zanobetti A, Gasparrini A, Baccarelli A, Coull BA, Tarantini L, Vokonas PS, Koutrakis P, Schwartz J (2014b) Air pollution and gene-specific methylation in the Normative Aging Study: association, effect modification, and mediation analysis. Epigenetics 9:448–458

Blanc PD, Eisner MD, Earnest G, Trupin L, Balmes JR, Yelin EH, Gregorich SE, Katz PP (2009a) Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. J Occup Environ Med 51:804–810

Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, Sidney S, Eisner MD (2009b) Occupational exposures and the risk of COPD: dusty trades revisited. Thorax 64:6–12

Bonisch U, Bohme A, Kohajda T, Mogel I, Schutze N, von Bergen M, Simon JC, Lehmann I, Polte T (2012) Volatile organic compounds enhance allergic airway inflammation in an experimental mouse model. PLoS One 7:e39817

Boorsma CE, Draijer C, Melgert BN (2013) Macrophage heterogeneity in respiratory diseases. Mediators Inflamm 2013:769214

Botas C, Poulain F, Akiyama J, Brown C, Allen L, Goerke J, Clements J, Carlson E, Gillespie AM, Epstein C, Hawgood S (1998) Altered surfactant homeostasis and alveolar type II cell morphology in mice lacking surfactant protein D. Proc Natl Acad Sci U S A 95:11869–11874

Botelho FM, Nikota JK, Bauer CM, Morissette MC, Iwakura Y, Kolbeck R, Finch D, Humbles AA, Stampfli MR (2012) Cigarette smoke-induced accumulation of lung dendritic cells is interleukin-1alpha-dependent in mice. Respir Res 13:81

Brant KA, Fabisiak JP (2013) Role of hypoxia-inducible factor 1, alpha subunit and cAMP-response element binding protein 1 in synergistic release of interleukin 8 by prostaglandin E2 and nickel in lung fibroblasts. Am J Respir Cell Mol Biol 49:105–113

Brinker KG, Martin E, Borron P, Mostaghel E, Doyle C, Harding CV, Wright JR (2001) Surfactant protein D enhances bacterial antigen presentation by bone marrow-derived dendritic cells. Am J Physiol Lung Cell Mol Physiol 281:L1453–L1463

Brinker KG, Garner H, Wright JR (2003) Surfactant protein A modulates the differentiation of murine bone marrow-derived dendritic cells. Am J Physiol Lung Cell Mol Physiol 284:L232–L241

Burgel PR, Nadel JA (2004) Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. Thorax 59:992–996

Calabrese F, Giacometti C, Beghe B, Rea F, Loy M, Zuin R, Marulli G, Baraldo S, Saetta M, Valente M (2005) Marked alveolar apoptosis/proliferation imbalance in end-stage emphysema. Respir Res 6:14

Cazzola M, Donner CF, Hanania NA (2007) One hundred years of chronic obstructive pulmonary disease (COPD). Respir Med 101:1049–1065

Celli BR, Barnes PJ (2007) Exacerbations of chronic obstructive pulmonary disease. Eur Respir J 29:1224–1238

Chana KK, Fenwick PS, Nicholson AG, Barnes PJ, Donnelly LE (2014) Identification of a distinct glucocorticosteroid-insensitive pulmonary macrophage phenotype in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 133:207–216.e211

Chaudhuri N, Jary H, Lea S, Khan N, Piddock KC, Dockrell DH, Donaldson K, Duffin R, Singh D, Parker LC, Sabroe I (2012) Diesel exhaust particle exposure in vitro alters monocyte differentiation and function. PLoS One 7:e51107

Chen ZH, Kim HP, Sciurba FC, Lee SJ, Feghali-Bostwick C, Stolz DB, Dhir R, Landreneau RJ, Schuchert MJ, Yousem SA, Nakahira K, Pilewski JM, Lee JS, Zhang Y, Ryter SW, Choi AM (2008) Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. PLoS One 3:e3316

Chung KF (2005) Inflammatory mediators in chronic obstructive pulmonary disease. Curr Drug Targets Inflamm Allergy 4:619–625

Churg A, Wright JL (2002) Airway wall remodeling induced by occupational mineral dusts and air pollutant particles. Chest 122:306S–309S

Cosio MG, Majo J, Cosio MG (2002) Inflammation of the airways and lung parenchyma in COPD: role of T cells. Chest 121:160S–165S

Crosby LM, Waters CM (2010) Epithelial repair mechanisms in the lung. Am J Physiol Lung Cell Mol Physiol 298:L715–L731

Crouch EC (2000) Surfactant protein-D and pulmonary host defense. Respir Res 1:93–108

Crouch E, Hartshorn K, Ofek I (2000) Collectins and pulmonary innate immunity. Immunol Rev 173:52–65

Davis DL, Bell ML, Fletcher T (2002) A look back at the London smog of 1952 and the half century since. Environ Health Perspect 110:A734–A735

de Haar C, Kool M, Hassing I, Bol M, Lambrecht BN, Pieters R (2008) Lung dendritic cells are stimulated by ultrafine particles and play a key role in particle adjuvant activity. J Allergy Clin Immunol 121:1246–1254

Demedts IK, Demoor T, Bracke KR, Joos GF, Brusselle GG (2006) Role of apoptosis in the pathogenesis of COPD and pulmonary emphysema. Respir Res 7:53

Demedts IK, Bracke KR, Van Pottelberge G, Testelmans D, Verleden GM, Vermassen FE, Joos GF, Brusselle GG (2007) Accumulation of dendritic cells and increased CCL20 levels in the airways of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175:998–1005

Demoor T, Bracke KR, Vermaelen KY, Dupont L, Joos GF, Brusselle GG (2009) CCR7 modulates pulmonary and lymph node inflammatory responses in cigarette smoke-exposed mice. J Immunol 183:8186–8194

Demoor T, Bracke KR, Dupont LL, Plantinga M, Bondue B, Roy MO, Lannoy V, Lambrecht BN, Brusselle GG, Joos GF (2011) The role of ChemR23 in the induction and resolution of cigarette smoke-induced inflammation. J Immunol 186:5457–5467

Di Stefano A, Maestrelli P, Roggeri A, Turato G, Calabro S, Potena A, Mapp CE, Ciaccia A, Covacev L, Fabbri LM, Saetta M (1994) Upregulation of adhesion molecules in the bronchial mucosa of subjects with chronic obstructive bronchitis. Am J Respir Crit Care Med 149:803–810

Di Stefano A, Caramori G, Ricciardolo FL, Capelli A, Adcock IM, Donner CF (2004) Cellular and molecular mechanisms in chronic obstructive pulmonary disease: an overview. Clin Exp Allergy 34:1156–1167

Domagala-Kulawik J (2008) Effects of cigarette smoke on the lung and systemic immunity. J Physiol Pharmacol 59(Suppl 6):19–34

Draijer C, Robbe P, Boorsma CE, Hylkema MN, Melgert BN (2013) Characterization of macrophage phenotypes in three murine models of house-dust-mite-induced asthma. Mediators Inflamm 2013:632049

Ezzati M, Kammen DM (2002) The health impacts of exposure to indoor air pollution from solid fuels in developing countries: knowledge, gaps, and data needs. Environ Health Perspect 110:1057–1068

Fairbairn AS, Reid DD (1958) Air pollution and other local factors in respiratory disease. Br J Prev Soc Med 12:94–103

Finkelstein R, Fraser RS, Ghezzo H, Cosio MG (1995) Alveolar inflammation and its relation to emphysema in smokers. Am J Respir Crit Care Med 152:1666–1672

Freeman CM, Han MK, Martinez FJ, Murray S, Liu LX, Chensue SW, Polak TJ, Sonstein J, Todt JC, Ames TM, Arenberg DA, Meldrum CA, Getty C, McCloskey L, Curtis JL (2010) Cytotoxic potential of lung CD8(+) T cells increases with chronic obstructive pulmonary disease severity and with in vitro stimulation by IL-18 or IL-15. J Immunol 184:6504–6513

Freeman CM, Martinez FJ, Han MK, Washko GR Jr, McCubbrey AL, Chensue SW, Arenberg DA, Meldrum CA, McCloskey L, Curtis JL (2013) Lung CD8+ T cells in COPD have increased expression of bacterial TLRs. Respir Res 14:13

Garcia-Rio F, Romero D, Lores V, Casitas R, Hernanz A, Galera R, Alvarez-Sala R, Torres I (2011) Dynamic hyperinflation, arterial blood oxygen, and airway oxidative stress in stable patients with COPD. Chest 140:961–969

Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, Henson PM (2003) By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 115:13–23

Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J (2004) The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 351:1057–1067

Gentile D, Howe-Adams J, Trecki J, Patel A, Angelini B, Skoner D (2004) Association between environmental tobacco smoke and diminished dendritic cell interleukin 10 production during infancy. Ann Allergy Asthma Immunol 92:433–437

Gilmour PS, Rahman I, Donaldson K, MacNee W (2003) Histone acetylation regulates epithelial IL-8 release mediated by oxidative stress from environmental particles. Am J Physiol Lung Cell Mol Physiol 284:L533–L540

Götschi T, Heinrich J, Sunyer J, Kunzli N (2008) Long-term effects of ambient air pollution on lung function: a review. Epidemiology 19:690–701

Goven D, Boutten A, Lecon-Malas V, Marchal-Somme J, Amara N, Crestani B, Fournier M, Leseche G, Soler P, Boczkowski J, Bonay M (2008) Altered Nrf2/Keap1-Bach1 equilibrium in pulmonary emphysema. Thorax 63:916–924

Grumelli S, Corry DB, Song LZ, Song L, Green L, Huh J, Hacken J, Espada R, Bag R, Lewis DE, Kheradmand F (2004) An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. PLoS Med 1:e8

Gualtieri M, Øvrevik J, Holme JA, Perrone MG, Bolzacchini E, Schwarze PE, Camatini M (2010) Differences in cytotoxicity versus pro-inflammatory potency of different PM fractions in human epithelial lung cells. Toxicol In Vitro 24:29–39

Guillot L, Balloy V, McCormack FX, Golenbock DT, Chignard M, Si-Tahar M (2002) Cutting edge: the immunostimulatory activity of the lung surfactant protein-A involves Toll-like receptor 4. J Immunol 168:5989–5992

Haczku A (2006) Role and regulation of lung collectins in allergic airway sensitization. Pharmacol Ther 110:14–34

Haczku A (2008) Protective role of the lung collectins surfactant protein A and surfactant protein D in airway inflammation. J Allergy Clin Immunol 122:861–879, quiz 880–881

Haczku A (2012) The dendritic cell niche in chronic obstructive pulmonary disease. Respir Res 13:80

Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J (2008) Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 63:635–641

Hansen S, Lo B, Evans K, Neophytou P, Holmskov U, Wright JR (2007) Surfactant protein D augments bacterial association but attenuates major histocompatibility complex class II presentation of bacterial antigens. Am J Respir Cell Mol Biol 36:94–102

Hawgood S, Ochs M, Jung A, Akiyama J, Allen L, Brown C, Edmondson J, Levitt S, Carlson E, Gillespie AM, Villar A, Epstein CJ, Poulain FR (2002) Sequential targeted deficiency of SP-A and -D leads to progressive alveolar lipoproteinosis and emphysema. Am J Physiol Lung Cell Mol Physiol 283:L1002–L1010

Hellermann GR, Nagy SB, Kong X, Lockey RF, Mohapatra SS (2002) Mechanism of cigarette smoke condensate-induced acute inflammatory response in human bronchial epithelial cells. Respir Res 3:22

Hiura TS, Kaszubowski MP, Li N, Nel AE (1999) Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages. J Immunol 163:5582–5591

Hnizdo E, Sullivan PA, Bang KM, Wagner G (2002) Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 156:738–746

Hodge SJ, Hodge GL, Reynolds PN, Scicchitano R, Holmes M (2003a) Increased production of TGF-beta and apoptosis of T lymphocytes isolated from peripheral blood in COPD. Am J Physiol Lung Cell Mol Physiol 285:L492–L499

Hodge S, Hodge G, Scicchitano R, Reynolds PN, Holmes M (2003b) Alveolar macrophages from subjects with chronic obstructive pulmonary disease are deficient in their ability to phagocytose apoptotic airway epithelial cells. Immunol Cell Biol 81:289–296

Hodge S, Hodge G, Holmes M, Reynolds PN (2005) Increased airway epithelial and T-cell apoptosis in COPD remains despite smoking cessation. Eur Respir J 25:447–454

Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Pare PD (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350:2645–2653

Hortobagyi L, Kierstein S, Krytska K, Zhu X, Das AM, Poulain F, Haczku A (2008) Surfactant protein D inhibits TNF-alpha production by macrophages and dendritic cells in mice. J Allergy Clin Immunol 122:521–528

Hunt A, Abraham JL, Judson B, Berry CL (2003) Toxicologic and epidemiologic clues from the characterization of the 1952 London smog fine particulate matter in archival autopsy lung tissues. Environ Health Perspect 111:1209–1214

Imai K, Mercer BA, Schulman LL, Sonett JR, D'Armiento JM (2005) Correlation of lung surface area to apoptosis and proliferation in human emphysema. Eur Respir J 25:250–258

Ishii Y, Itoh K, Morishima Y, Kimura T, Kiwamoto T, Iizuka T, Hegab AE, Hosoya T, Nomura A, Sakamoto T, Yamamoto M, Sekizawa K (2005) Transcription factor Nrf2 plays a pivotal role in protection against elastase-induced pulmonary inflammation and emphysema. J Immunol 175:6968–6975

Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM, Barczyk A, Hayashi S, Adcock IM, Hogg JC, Barnes PJ (2005) Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 352:1967–1976

Jakab GJ, Spannhake EW, Canning BJ, Kleeberger SR, Gilmour MI (1995) The effects of ozone on immune function. Environ Health Perspect 103(Suppl 2):77–89

Jerrett M, Burnett RT, Pope CA 3rd, Ito K, Thurston G, Krewski D, Shi Y, Calle E, Thun M (2009) Long-term ozone exposure and mortality. N Engl J Med 360:1085–1095

Kan H, Heiss G, Rose KM, Whitsel E, Lurmann F, London SJ (2007) Traffic exposure and lung function in adults: the Atherosclerosis Risk in Communities study. Thorax 62:873–879

Kanazawa H, Yoshikawa J (2005) Elevated oxidative stress and reciprocal reduction of vascular endothelial growth factor levels with severity of COPD. Chest 128:3191–3197

Karle AC, Oostingh GJ, Mutschlechner S, Ferreira F, Lackner P, Bohle B, Fischer GF, Vogt AB, Duschl A (2012) Nitration of the pollen allergen bet v 1.0101 enhances the presentation of bet v 1-derived peptides by HLA-DR on human dendritic cells. PLoS One 7:e31483

Kasahara Y, Tuder RM, Taraseviciene-Stewart L, Le Cras TD, Abman S, Hirth PK, Waltenberger J, Voelkel NF (2000) Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J Clin Invest 106:1311–1319

Katre A, Ballinger C, Akhter H, Fanucchi M, Kim DK, Postlethwait E, Liu RM (2011) Increased transforming growth factor beta 1 expression mediates ozone-induced airway fibrosis in mice. Inhal Toxicol 23:486–494

Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, Samoli E, Touloumi G, Burnett RT, Krewski D, Ramsay T, Dominici F, Peng RD, Schwartz J, Zanobetti A, Committee HEIHR (2009) Air pollution and health: a European and North American approach (APHENA). Res Rep Health Eff Inst 142:5–90

Kelsen SG, Duan X, Ji R, Perez O, Liu C, Merali S (2008) Cigarette smoke induces an unfolded protein response in the human lung: a proteomic approach. Am J Respir Cell Mol Biol 38:541–550

Kierstein S, Poulain FR, Cao Y, Grous M, Mathias R, Kierstein G, Beers MF, Salmon M, Panettieri RA Jr, Haczku A (2006) Susceptibility to ozone-induced airway inflammation is associated with decreased levels of surfactant protein D. Respir Res 7:85

Kim H, Tse K, Levin L, Bernstein D, Reponen T, LeMasters G, Lummus Z, Horner AA (2012) House dust bioactivities predict skin prick test reactivity for children with high risk of allergy. J Allergy Clin Immunol 129:1529–1537.e1522

Ko FW, Hui DS (2012) Air pollution and chronic obstructive pulmonary disease. Respirology 17:395–401

Krewski D (2009) Evaluating the effects of ambient air pollution on life expectancy. N Engl J Med 360:413–415

Kunzli N, Bridevaux PO, Liu LJ, Garcia-Esteban R, Schindler C, Gerbase MW, Sunyer J, Keidel D, Rochat T (2009) Traffic-related air pollution correlates with adult-onset asthma among never-smokers. Thorax 64:664–670

Leigh JP, Romano PS, Schenker MB, Kreiss K (2002) Costs of occupational COPD and asthma. Chest 121:264–272

Leikauf GD, McDowell SA, Wesselkamper SC, Miller CR, Hardie WD, Gammon K, Biswas PP, Korfhagen TR, Bachurski CJ, Wiest JS, Willeke K, Bingham E, Leikauf JE, Aronow BJ, Prows DR (2001) Pathogenomic mechanisms for particulate matter induction of acute lung injury and inflammation in mice. Res Rep Health Eff Inst 105:5–58; discussion 59–71

Lepeule J, Bind MA, Baccarelli AA, Koutrakis P, Tarantini L, Litonjua A, Sparrow D, Vokonas P, Schwartz JD (2014) Epigenetic influences on associations between air pollutants and lung function in elderly men: the normative aging study. Environ Health Perspect

Lumb AB (2000) Nunn's applied respiratory physiology. Reed Educational and Professional Publishing Ltd., London

Lundborg M, Dahlen SE, Johard U, Gerde P, Jarstrand C, Camner P, Lastbom L (2006) Aggregates of ultrafine particles impair phagocytosis of microorganisms by human alveolar macrophages. Environ Res 100:197–204

Ma B, Kang MJ, Lee CG, Chapoval S, Liu W, Chen Q, Coyle AJ, Lora JM, Picarella D, Homer RJ, Elias JA (2005) Role of CCR5 in IFN-gamma-induced and cigarette smoke-induced emphysema. J Clin Invest 115:3460–3472

MacNee W, Donaldson K (2003) Mechanism of lung injury caused by PM10 and ultrafine particles with special reference to COPD. Eur Respir J 40 Suppl:47s–51s

Malhotra D, Thimmulappa R, Navas-Acien A, Sandford A, Elliott M, Singh A, Chen L, Zhuang X, Hogg J, Pare P, Tuder RM, Biswal S (2008) Decline in NRF2-regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1. Am J Respir Crit Care Med 178:592–604

Marian E, Baraldo S, Visentin A, Papi A, Saetta M, Fabbri LM, Maestrelli P (2006) Up-regulated membrane and nuclear leukotriene B4 receptors in COPD. Chest 129:1523–1530

Martinez FO, Sica A, Mantovani A, Locati M (2008) Macrophage activation and polarization. Front Biosci 13:453–461

Martinez FO, Helming L, Milde R, Varin A, Melgert BN, Draijer C, Thomas B, Fabbri M, Crawshaw A, Ho LP, Ten Hacken NH, Cobos Jimenez V, Kootstra NA, Hamann J, Greaves DR, Locati M, Mantovani A, Gordon S (2013) Genetic programs expressed in resting and IL-4 alternatively activated mouse and human macrophages: similarities and differences. Blood 121:e57–e69

Matozaki T, Murata Y, Okazawa H, Ohnishi H (2009) Functions and molecular mechanisms of the CD47-SIRPalpha signalling pathway. Trends Cell Biol 19:72–80

Miyata R, van Eeden SF (2011) The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. Toxicol Appl Pharmacol 257:209–226

Moran-Mendoza O, Perez-Padilla JR, Salazar-Flores M, Vazquez-Alfaro F (2008) Wood smoke-associated lung disease: a clinical, functional, radiological and pathological description. Int J Tuberc Lung Dis 12:1092–1098

Moreira AP, Hogaboam CM (2011) Macrophages in allergic asthma: fine-tuning their pro- and anti-inflammatory actions for disease resolution. J Interferon Cytokine Res 31:485–491

Myatt TA, Vincent MS, Kobzik L, Naeher LP, MacIntosh DL, Suh H (2011) Markers of inflammation in alveolar cells exposed to fine particulate matter from prescribed fires and urban air. J Occup Environ Med 53:1110–1114

Nozik-Grayck E, Suliman HB, Majka S, Albietz J, Van Rheen Z, Roush K, Stenmark KR (2008) Lung EC-SOD overexpression attenuates hypoxic induction of Egr-1 and chronic hypoxic pulmonary vascular remodeling. Am J Physiol Lung Cell Mol Physiol 295:L422–L430

Oberdorster G, Ferin J, Morrow PE (1992) Volumetric loading of alveolar macrophages (AM): a possible basis for diminished AM-mediated particle clearance. Exp Lung Res 18:87–104

Ohya M, Nishitani C, Sano H, Yamada C, Mitsuzawa H, Shimizu T, Saito T, Smith K, Crouch E, Kuroki Y (2006) Human pulmonary surfactant protein D binds the extracellular domains of Toll-like receptors 2 and 4 through the carbohydrate recognition domain by a mechanism different from its binding to phosphatidylinositol and lipopolysaccharide. Biochemistry 45:8657–8664

Øvrevik J, Låg M, Holme JA, Schwarze PE, Refsnes M (2009) Cytokine and chemokine expression patterns in lung epithelial cells exposed to components characteristic of particulate air pollution. Toxicology 259:46–53

Øvrevik J, Arlt VM, Øya E, Nagy E, Mollerup S, Phillips DH, Låg M, Holme JA (2010) Differential effects of nitro-PAHs and amino-PAHs on cytokine and chemokine responses in human bronchial epithelial BEAS-2B cells. Toxicol Appl Pharmacol 242:270–280

Papi A, Luppi F, Franco F, Fabbri LM (2006) Pathophysiology of exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:245–251

Park EJ, Park K (2009) Induction of pro-inflammatory signals by 1-nitropyrene in cultured BEAS-2B cells. Toxicol Lett 184:126–133

Pastor MD, Nogal A, Molina-Pinelo S, Melendez R, Salinas A, Gonzalez De la Pena M, Martin-Juan J, Corral J, Garcia-Carbonero R, Carnero A, Paz-Ares L (2013) Identification of proteomic signatures associated with lung cancer and COPD. J Proteomics 89:227–237

Po JY, FitzGerald JM, Carlsten C (2011) Respiratory disease associated with solid biomass fuel exposure in rural women and children: systematic review and meta-analysis. Thorax 66:232–239

Pons AR, Sauleda J, Noguera A, Pons J, Barcelo B, Fuster A, Agusti AG (2005) Decreased macrophage release of TGF-beta and TIMP-1 in chronic obstructive pulmonary disease. Eur Respir J 26:60–66

Powell WC, Fingleton B, Wilson CL, Boothby M, Matrisian LM (1999) The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. Curr Biol 9:1441–1447

Rahman I (2005) Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms. Cell Biochem Biophys 43:167–188

Rahman I, van Schadewijk AA, Crowther AJ, Hiemstra PS, Stolk J, MacNee W, De Boer WI (2002) 4-Hydroxy-2-nonenal, a specific lipid peroxidation product, is elevated in lungs of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:490–495

Repine JE, Bast A, Lankhorst I (1997) Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. Am J Respir Crit Care Med 156:341–357

Ricciardolo FL, Caramori G, Ito K, Capelli A, Brun P, Abatangelo G, Papi A, Chung KF, Adcock I, Barnes PJ, Donner CF, Rossi A, Di Stefano A (2005) Nitrosative stress in the bronchial mucosa of severe chronic obstructive pulmonary disease. J Allergy Clin Immunol 116:1028–1035

Rosseau S, Guenther A, Seeger W, Lohmeyer J (1997) Phagocytosis of viable Candida albicans by alveolar macrophages: lack of opsonin function of surfactant protein A. J Infect Dis 175:421–428

Russell RE, Thorley A, Culpitt SV, Dodd S, Donnelly LE, Demattos C, Fitzgerald M, Barnes PJ (2002a) Alveolar macrophage-mediated elastolysis: roles of matrix metalloproteinases, cysteine, and serine proteases. Am J Physiol Lung Cell Mol Physiol 283:L867–L873

Russell RE, Culpitt SV, DeMatos C, Donnelly L, Smith M, Wiggins J, Barnes PJ (2002b) Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 26:602–609

Ryter SW, Nakahira K, Haspel JA, Choi AM (2012) Autophagy in pulmonary diseases. Annu Rev Physiol 74:377–401

Saetta M, Baraldo S, Corbino L, Turato G, Braccioni F, Rea F, Cavallesco G, Tropeano G, Mapp CE, Maestrelli P, Ciaccia A, Fabbri LM (1999) CD8+ ve cells in the lungs of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:711–717

Sakao S, Tatsumi K (2011) The importance of epigenetics in the development of chronic obstructive pulmonary disease. Respirology 16:1056–1063

Sano H, Chiba H, Iwaki D, Sohma H, Voelker DR, Kuroki Y (2000) Surfactant proteins A and D bind CD14 by different mechanisms. J Biol Chem 275:22442–22451

Scarpa MC, Baraldo S, Marian E, Turato G, Calabrese F, Saetta M, Maestrelli P (2013) Ceramide expression and cell homeostasis in chronic obstructive pulmonary disease. Respiration 85:342–349

Schierhorn K, Zhang M, Kacy M, Kunkel G (1997) Ozone-induced augmentation of eicosanoid metabolism in human nasal mucosa in vitro. Int Arch Allergy Immunol 113:312–315

Schikowski T, Mills IC, Anderson HR, Cohen A, Hansell A, Kauffmann F, Kramer U, Marcon A, Perez L, Sunyer J, Probst-Hensch N, Kunzli N (2014) Ambient air pollution – a cause for COPD? Eur Respir J 43(1):250–263

Schwarze PE, Øvrevik J, Låg M, Refsnes M, Nafstad P, Hetland RB, Dybing E (2006) Particulate matter properties and health effects: consistency of epidemiological and toxicological studies. Hum Exp Toxicol 25:559–579

Segura-Valdez L, Pardo A, Gaxiola M, Uhal BD, Becerril C, Selman M (2000) Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD. Chest 117:684–694

Sezer H, Akkurt I, Guler N, Marakoglu K, Berk S (2006) A case–control study on the effect of exposure to different substances on the development of COPD. Ann Epidemiol 16:59–62

Shan M, Yuan X, Song LZ, Roberts L, Zarinkamar N, Seryshev A, Zhang Y, Hilsenbeck S, Chang SH, Dong C, Corry DB, Kheradmand F (2012) Cigarette smoke induction of osteopontin (SPP1) mediates T(H)17 inflammation in human and experimental emphysema. Sci Transl Med 4:117ra119

Sharma G, Goodwin J (2006) Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 1:253–260

Sims MW, Tal-Singer RM, Kierstein S, Musani AI, Beers MF, Panettieri RA, Haczku A (2008) Chronic obstructive pulmonary disease and inhaled steroids alter surfactant protein D (SP-D) levels: a cross-sectional study. Respir Res 9:13

Sint T, Donohue JF, Ghio AJ (2008) Ambient air pollution particles and the acute exacerbation of chronic obstructive pulmonary disease. Inhal Toxicol 20:25–29

Stanescu D, Sanna A, Veriter C, Kostianev S, Calcagni PG, Fabbri LM, Maestrelli P (1996) Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. Thorax 51:267–271

Steenhof M, Janssen NA, Strak M, Hoek G, Gosens I, Mudway IS, Kelly FJ, Harrison RM, Pieters RH, Cassee FR, Brunekreef B (2014) Air pollution exposure affects circulating white blood cell counts in healthy subjects: the role of particle composition, oxidative potential and gaseous pollutants – the RAPTES project. Inhal Toxicol 26:141–165

Stieb DM, Judek S, Burnett RT (2002) Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. J Air Waste Manage Assoc 52:470–484

Sundar IK, Yao H, Rahman I (2013) Oxidative stress and chromatin remodeling in chronic obstructive pulmonary disease and smoking-related diseases. Antioxid Redox Signal 18:1956–1971

Sunil VR, Patel-Vayas K, Shen J, Laskin JD, Laskin DL (2012) Classical and alternative macrophage activation in the lung following ozone-induced oxidative stress. Toxicol Appl Pharmacol 263:195–202

Sunyer J (2001) Urban air pollution and chronic obstructive pulmonary disease: a review. Eur Respir J 17:1024–1033

Sussan TE, Ingole V, Kim JH, McCormick S, Negherbon J, Fallica J, Akulian J, Yarmus L, Feller-Kopman D, Wills-Karp M, Horton MR, Breysse PN, Agrawal A, Juvekar S, Salvi S, Biswal S (2014) Source of biomass cooking fuel determines pulmonary response to household air pollution. Am J Respir Cell Mol Biol 50:538–548

Takeda K, Haczku A, Lee JJ, Irvin CG, Gelfand EW (2001) Strain dependence of airway hyperresponsiveness reflects differences in eosinophil localization in the lung. Am J Physiol Lung Cell Mol Physiol 281:L394–L402

Tao F, Gonzalez-Flecha B, Kobzik L (2003) Reactive oxygen species in pulmonary inflammation by ambient particulates. Free Radic Biol Med 35:327–340

Tomita K, Caramori G, Lim S, Ito K, Hanazawa T, Oates T, Chiselita I, Jazrawi E, Chung KF, Barnes PJ, Adcock IM (2002) Increased p21(CIP1/WAF1) and B cell lymphoma leukemia-x(L) expression and reduced apoptosis in alveolar macrophages from smokers. Am J Respir Crit Care Med 166:724–731

Torres-Duque C, Maldonado D, Perez-Padilla R, Ezzati M, Viegi G, E. Forum of International Respiratory Studies Task Force on Health Effects of Biomass (2008) Biomass fuels and respiratory diseases: a review of the evidence. Proc Am Thorac Soc 5:577–590

Triantaphyllopoulos K, Hussain F, Pinart M, Zhang M, Li F, Adcock I, Kirkham P, Zhu J, Chung KF (2011) A model of chronic inflammation and pulmonary emphysema after multiple ozone exposures in mice. Am J Physiol Lung Cell Mol Physiol 300:L691–L700

Tsoumakidou M, Siafakas NM (2006) Novel insights into the aetiology and pathophysiology of increased airway inflammation during COPD exacerbations. Respir Res 7:80

van Eeden SF, Yeung A, Quinlam K, Hogg JC (2005) Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. Proc Am Thorac Soc 2:61–67
Vandivier RW, Fadok VA, Hoffmann PR, Bratton DL, Penvari C, Brown KK, Brain JD, Accurso FJ, Henson PM (2002) Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic cell clearance in cystic fibrosis and bronchiectasis. J Clin Invest 109:661–670
Wegmann M, Fehrenbach A, Heimann S, Fehrenbach H, Renz H, Garn H, Herz U (2005) NO2-induced airway inflammation is associated with progressive airflow limitation and development of emphysema-like lesions in C57bl/6 mice. Exp Toxicol Pathol 56:341–350
White AJ, Gompertz S, Stockley RA (2003) Chronic obstructive pulmonary disease. 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. Thorax 58:73–80
Williams MA, Rangasamy T, Bauer SM, Killedar S, Karp M, Kensler TW, Yamamoto M, Breysse P, Biswal S, Georas SN (2008) Disruption of the transcription factor Nrf2 promotes pro-oxidative dendritic cells that stimulate Th2-like immunoresponsiveness upon activation by ambient particulate matter. J Immunol 181:4545–4559
Wright JR (2005) Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 5:58–68
Wu Z, Liu MC, Liang M, Fu J (2012) Sirt1 protects against thrombomodulin down-regulation and lung coagulation after particulate matter exposure. Blood 119:2422–2429
Yamazaki H, Hatanaka N, Kizu R, Hayakawa K, Shimada N, Guengerich FP, Nakajima M, Yokoi T (2000) Bioactivation of diesel exhaust particle extracts and their major nitrated polycyclic aromatic hydrocarbon components, 1-nitropyrene and dinitropyrenes, by human cytochromes P450 1A1, 1A2, and 1B1. Mutat Res 472:129–138
Yang YC, Zhang N, Van Crombruggen K, Hu GH, Hong SL, Bachert C (2012) Transforming growth factor-beta1 in inflammatory airway disease: a key for understanding inflammation and remodeling. Allergy 67:1193–1202
Yao H, Rahman I (2011) Current concepts on oxidative/carbonyl stress, inflammation and epigenetics in pathogenesis of chronic obstructive pulmonary disease. Toxicol Appl Pharmacol 254:72–85
Yao H, Hwang JW, Sundar IK, Friedman AE, McBurney MW, Guarente L, Gu W, Kinnula VL, Rahman I (2013) SIRT1 redresses the imbalance of tissue inhibitor of matrix metalloproteinase-1 and matrix metalloproteinase-9 in the development of mouse emphysema and human COPD. Am J Physiol Lung Cell Mol Physiol 305:L615–L624
Yoshida T, Yoshioka Y, Fujimura M, Yamashita K, Higashisaka K, Nakanishi R, Morishita Y, Kayamuro H, Nabeshi H, Nagano K, Abe Y, Kamada H, Tsunoda S, Yoshikawa T, Itoh N, Tsutsumi Y (2010) Potential adjuvant effect of intranasal urban aerosols in mice through induction of dendritic cell maturation. Toxicol Lett 199:383–388
Zanobetti A, Bind MA, Schwartz J (2008) Particulate air pollution and survival in a COPD cohort. Environ Health 7:48
Zhou H, Wu Y, Jin Y, Zhou J, Zhang C, Che L, Jing J, Chen Z, Li W, Shen H (2013) Genetic polymorphism of matrix metalloproteinase family and chronic obstructive pulmonary disease susceptibility: a meta-analysis. Sci Rep 3:2818