Chapter 4
Lung Diseases

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Abstract Inflammasomes are large innate cytoplasmic complexes that play a major role in promoting inflammation in the lung in response to a range of environmental and infectious stimuli. Inflammasomes are critical for driving acute innate immune responses that resolve infection and maintain tissue homeostasis. However, dysregulated or excessive inflammasome activation can be detrimental. Here, we discuss the plethora of recent data from clinical studies and small animal disease models that implicate excessive inflammasome responses in the pathogenesis of a

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number of acute and chronic respiratory inflammatory diseases. Understanding of the role of inflammasomes in lung disease is of great therapeutic interest.

Keywords Inflammasomes · Lung disease · Inflammation · Disease pathogenesis

4.1 Introduction

The innate immune system plays a pivotal role in restoring homeostasis in the lung following an insult such as infection, cellular stress or injury. However, excessive or chronic activation of the immune system can contribute to the development of a number of inflammatory diseases such as acute respiratory distress syndrome (ARDS), asthma, cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). Current treatments for such diseases are limited and ineffective, and new treatments are required to reduce morbidity and mortality. It is of great therapeutic interest that the mechanisms involved in the progression and persistence of immunopathology in the lung be delineated in greater detail.

Inflammasomes are large innate cytoplasmic complexes that play a major role in promoting inflammation in the lung, by enzymatically maturating the inactive pro-inflammatory cytokine precursors, pro-IL-1β and pro-IL-18 into bioactive IL-1β and IL-18, respectively. Inflammasomes are critical for driving acute innate immune responses that resolve infection and maintain tissue homeostasis. However, as discussed in this chapter, there is increasing evidence that excessive inflammasome activation can lead to lung disease.

4.1.1 Inflammasome Activation in the Lung

The lung is continuously exposed to potentially noxious stimuli, which include exogenous signals such as microbial (bacteria, viruses) and environmental antigens (smoke, silica, asbestos, allergens), as well as a plethora of host-derived endogenous danger signals. Innate immune responses produced within the host recognise these noxious stimuli through the tightly coordinated activation of a series of extracellular and cytosolic receptors called pattern recognition receptors (PRRs), which are widely expressed in both immune (e.g. alveolar macrophage, neutrophils) and non-immune (e.g. epithelial) cells in the lung (Bals and Hiemstra 2004). PRRs are classified into several families such as Toll-like receptors (TLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs) and nucleotide-binding oligomerisation domain-containing (NOD)-like receptors (NLRs) (Kawai and Akira 2010; Kersse 2011; Ratsimandresey et al. 2013) (Fig. 4.1). Collectively, PRRs trigger inflammatory responses following recognition of a diverse range of ligands comprising microbial motifs called pathogen-associated molecular patterns (PAMPs), or danger-associated molecular patterns (DAMPs), which can involve endogenous host-derived signals or exogenous stimulants, such as smoke or silica, as above.

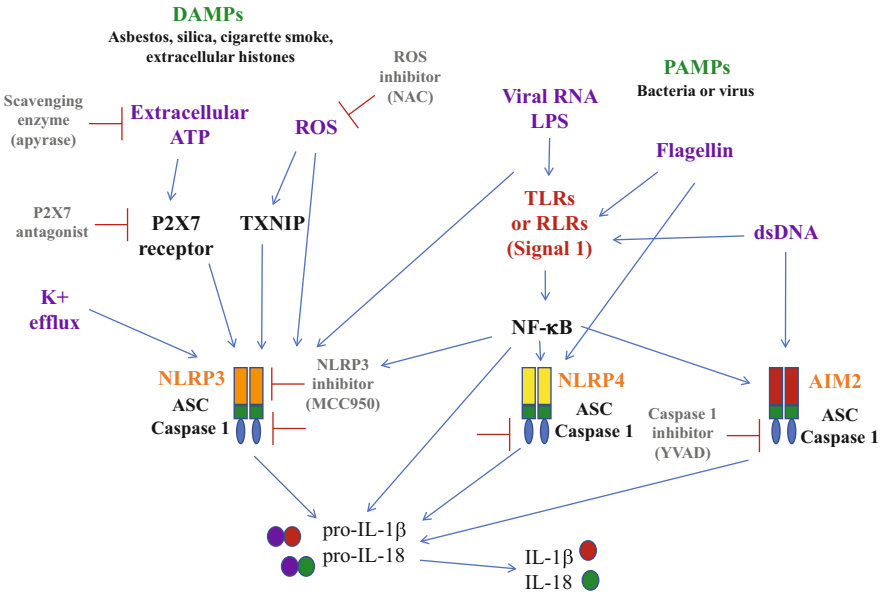

Fig. 4.1 Schematic of inflammasome responses in the lung. The lung is continuously exposed to exogenous signals such as microbial (bacteria, viruses) and environmental (smoke, silica, asbestos, allergens), as well as a plethora of host-derived danger signals. Activation of inflammasomes NLRP3, NLRC4 and AIM2 requires two signals. Signal 1 involves recognition of PAMPs (e.g. viral RNA or bacterial LPS) by PRRs such as TLRs and RLRs, inducing the expression of inflammasome components and pro-IL-1β/18. The second signal activates the inflammasome complexes NLRP3, NLRC4 or AIM2 in response to DAMPS (e.g. extracellular adenosine triphosphate (ATP) and reactive oxygen species (ROS)) or specific PAMPs (e.g. NLRP3, viral RNA/proteins; NLRC4, bacterial flagellin; AIM2, dsDNA). Inflammasome activation initiates the processing of pro-IL-1β and pro-IL-18 into their bioactive forms IL-1β and IL-18, by caspase-1

The most well-characterised PRR families are TLRs, which are transmembrane proteins associated with host cell surfaces and endosomes, and the cytosolic NLRs and ALRs (Fritz et al. 2006; Zuo et al. 2015). Signalling by TLRs, with the exception of TLR3, is dependent on the adaptor MyD88 and downstream activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Schnare et al. 2000) (Fig. 4.1). Members of the NLR family, such as NLRP3, NLRC4 (NLR CARD domain containing) (De Nardo et al. 2014) and AIM2 (a cytosolic DNA sensor in the ALR family) (Hornung et al. 2009), form the core of distinct inflammasomes, which are multiprotein complexes regulating the release of bioactive pro-inflammatory cytokines IL-1β and IL-18, in a two-step process. The first "priming" step involves the induced expression of biologically inactive pro-IL-1β and pro-IL-18 precursors, as well as inflammasome components via a PRR-mediated signal (e.g. lipopolysaccharide (LPS)-induced activation of TLR4/NF-κB). The second step involves the sensing of a specific DAMP or PAMP by each NLR or AIM2, leading to the recruitment and oligomerisation of the key adaptor protein, apoptosis-related speck-like protein

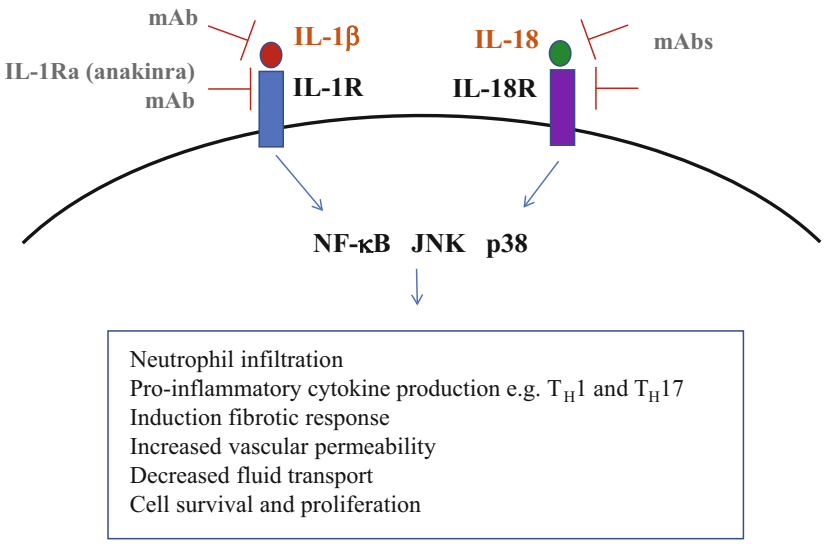

Fig. 4.2 Biological effects of inflammasome-dependent cytokines IL-1β and IL-18. Following inflammasome activation, mature IL-1β and IL-18 are secreted and can then bind their cell surface receptors IL-1R and IL-18R, respectively, which are expressed on a range of cell types. This results in a signalling cascade involving NF-κB, p38 and JNK, leading to a range of biological outcomes, such as pro-inflammatory cytokine secretion, neutrophil infiltration and increased vascular permeability, which have been implicated in a range of respiratory diseases

containing a CARD (ASC, also known as PYCARD), into large filamentous scaffolds called "specks" (De Nardo et al. 2014; Franklin et al. 2014). These ASC speck structures then facilitate the subsequent recruitment and activation of caspase-1, which in turn catalyses the maturation of pro-IL-1β or pro-IL-18 proteins into secreted bioactive cytokines (Vanaja et al. 2015; Franklin et al. 2014), which potently promote inflammatory host responses such as neutrophil infiltration and cytokine production (Latz et al. 2013) (Figs. 4.1 and 4.2). IL-1β and IL-18 mediate their biological effects following binding to cell surface receptors IL-1R and IL-18R, respectively, activating a signalling cascade involving NF-κB, p38 and Jun N-terminal kinase (JNK) (Fig. 4.2).

As described above, inflammasome activation depends on the recognition of PAMPs and DAMPs by PRRs. All cells expressing PRRs immediately identify PAMP-expressing microbes and act as the front line of host defence against infection in the lung. The membrane-bound TLRs scan the extracellular milieu and the endosomal compartment for PAMPs. Bacterial LPS, endotoxins found on the cell membrane of Gram-negative bacteria, and viral RNA are considered to be major PAMPs. LPS is specifically recognised by TLR4. Models of LPS-induced inflammation are widely employed to investigate both host responses in the lung and specific diseases such as acute lung injury (ALI) (Andonegui et al. 2003; Grailer et al. 2014; Jiang et al. 2016), asthma (Kim et al. 2014; Tran et al. 2012) and idiopathic pulmonary fibrosis (IPF) (Lasithiotaki et al. 2016). Mouse models in the above disease settings have shown evidence of neutrophil infiltration, production of IL-1β and IL-18 and most importantly in NLRP3 inflammasome activation in the

lung following LPS stimulation (Andonegui et al. 2003; Grailer et al. 2014; Jiang et al. 2016; Kim et al. 2014; Tran et al. 2012; Lasithiotaki et al. 2016; Tate et al. 2016). In that regard, NLRs located in the cytoplasm of cells are known to directly respond to a variety of PAMPs, including the bacterial wall components peptidoglycan, bacterial flagellin, other bacterial toxins and viral proteins (Kersse et al. 2011; Franchi et al. 2006; Pinar et al. 2017). Studies into lung infections have revealed the important role of NLRP3 as an intracellular sensor for bacterial toxins from *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Chlamydia trachomatis* and *Haemophilus influenzae* in lung diseases such as asthma (Kim et al. 2017) and cystic fibrosis (CF) (Yonker et al. 2015). NLRC4 can directly activate caspase-1 via its own CARD domain (unlike NLRP3) and acts as a cytosolic sensor of bacterial flagellin and type II/IV secretion system bacteria such as *Pseudomonas aeruginosa*. NLRC4 is therefore a key modulator of Gram-negative bacterial infection in the lungs (Cai et al. 2012; Yonker et al. 2015). In addition to these NLR-based inflammasomes, AIM2 forms an inflammasome by binding directly to the double-stranded (ds) DNA from numerous cytosolic bacteria and viruses. However, its role in lung disease is not currently understood (Man et al. 2016).

DAMPs are host-derived biomolecules that alert the immune system to a loss of homeostasis by activation of PRRs (Matzinger 1994) (Fig. 4.1). DAMPs/danger molecules can have an endogenous or exogenous origin. Noxious exogenous signals from infectious (bacteria, viruses) and environmental antigens (smoke, silica, asbestos, allergens such as house dust mite (HDM)) can damage resident airway epithelial cells in the lung, which can induce several modes of cell death such as apoptosis (programmed) and necrosis (unprogrammed), resulting in the release of DAMPs into the extracellular space (Messner et al. 2012; Kaczmarek et al. 2013). Programmed cell death, apoptosis, is caspase-dependent, and most of the released DAMPs are retained within apoptotic bodies for phagocytosis by macrophages (Krysko et al. 2010). However, when these apoptotic bodies are not adequately cleared, their presence leads to secondary necrosis resulting from the release of DAMPs (Krysko et al. 2010; Kono and Rock 2008). Necrotic cell death is the most immunogenic form of cell death and leads to a further massive release of DAMPs (Rubartelli and Lotze 2007). In recent years, it has been reported that exogenous stimuli can induce an inflammatory mode of airway epithelial cell death independent of executioner caspase activity in a manner akin to necrosis, and this process has been termed pyroptosis (Dos Santos et al. 2012). Pyroptosis, in contrast to the immunologically silent programmed cell death of apoptosis, is dependent on the inflammatory caspase-1 and is characterised by the rapid loss of plasma membrane integrity, leading to the release of DAMPs. In addition to release of DAMPs, cell death can also lead to release of several cytokines and chemokines such as interleukin (IL)-6 and IL-33, which can also act as DAMPs or danger signals (Hirsiger et al. 2012; Krysko et al. 2012). DAMPs include dsDNA, ROS, heat shock proteins, ATP and extracellular matrix fragments, which can potentiate pro-inflammatory reactions in innate immune (e.g. macrophage) and epithelial cells (Kaczmarek et al. 2013; Kono and Rock 2008; Pouwels et al. 2014). Upon release of ATP into the extracellular space, ATP triggers inflammasome activation by signalling through P2X7 (purinergic receptors) (Lucattelli et al. 2011) or changes in ion influx/efflux from cells (such as K^+) (Latz 2010). Several experimental

models have shown that ROS can cause the development of many acute and chronic airway diseases, including fibrosis, asthma, emphysema, ARDS and bronchial carcinogenesis (Birrell and Eltom 2011).

4.1.2 Current Therapies

There are a limited number of specific drugs to block inflammasome activities under development currently. However, there are numerous preclinical inhibitors/antibodies tested in mouse studies, which show promise against up- and downstream key activators of inflammasomes in the lung (Figs. 4.1 and 4.2). Here, we will examine some of these key activators and the efficacy of corresponding preclinical therapeutics that have been tested against them.

The production of ROS has been suggested to act as an upstream modulator of the NLRP3 inflammasome. However, ROS inhibitors block the priming step of NLRP3 inflammasome activation by preventing pro-IL-1β synthesis (Bauernfeind et al. 2011), suggesting ROS inhibitors act at the synthesis level, rather than activation level, of NLRP3. The ROS scavenger *N*-acetyl cysteine (NAC) is one of the widely used antioxidants in vitro (Dostert et al. 2008) or in COPD and pulmonary fibrosis patients (Salve and Atram 2016; Tarrant et al. 2017) to block inflammasome activation. However NAC must be used at high concentrations to be able to block inflammasome activities (Bauernfeind et al. 2011). NecroX-5 is a mitochondrial inhibitor which displays excellent efficacy as an antioxidant focusing on the relationship between mitochondrial ROS and NLRP3 activation in allergic airway diseases such as asthma in mouse models (Kim et al. 2014). NLRP3 inflammasome activation via extracellular ATP acting on the P2X7 receptor signalling has been seen in lung inflammation and lung diseases (Wang et al. 2015). The P2X7 receptor antagonist has successfully blocked P2X7/NLRP3 inflammasome pathway resulting in a significant amelioration of lung injury in mouse models (Wang et al. 2015). Thus far no P2X7R antagonists are used for treating lung diseases in clinic; however, the P2X7 receptor antagonist CE-224-535 is currently in clinical trials to treat arthritis (Arulkumaran et al. 2011). ATP represents a suitable pharmacological target for the development of new effective therapeutic options in the treatment of inflammasome-related lung diseases. In that regard, glyburide, a blocker of K+ channels associated with ATP, has shown to inhibit NLRP3 inflammasome activation and lung inflammation in mouse models of bronchopulmonary dysplasia and cystic fibrosis (Liao et al. 2015; Buchanan et al. 2013). Modulation of ATP levels using the ATP-degrading enzyme apyrase is employed as another method to inhibit ATP-regulated inflammasome activities such as production of IL-1β in pulmonary fibrosis (Riteau et al. 2010).

Caspase-1 activation is important for NLRs and AIM2 inflammasome activities. The administration of caspase-1 inhibitors such as Ac-YVAD-CHO and z-WEHD-fmk has shown to effectively inhibit inflammasome activity by reducing IL-1β in vivo (Churg et al. 2009, Kim et al. 2017). The caspase-1 inhibitor VX-765 is an

orally available prodrug, and it reduces the release of IL-1β and IL-18 in patients with cryopyrin-associated periodic syndromes (Wannamaker et al. 2007), but it is not used in lung diseases. IL-1β is one of the main downstream modulators of inflammasome, exerting its inflammatory action by binding to its receptor (IL-1R). The IL-1R antagonist (IL-1RA) prevents IL-1β binding and signalling through IL-1R. Anakinra is the recombinant form of naturally found IL-1RA and is widely used in clinic. However, anakinra is rapidly excreted by the kidney and therefore has a very short half-life, requiring frequent administration by subcutaneous injections (daily) which is associated with hepatotoxicity (Dinarello 2010). This antagonist has been widely used in animal models of asthma, ALI, bronchopulmonary dysplasia and cystic fibrosis (Jones et al. 2014; Kim et al. 2014; Rimessi et al. 2015; Rudloff et al. 2017). The fully humanised monoclonal antibodies against IL-1β (IL-1β mAb) such as canakinumab are also used in an animal model of asthma (Kim et al. 2017) and small clinical trials of asthma and COPD (Rogliani et al. 2015). However, the use of IL-1β mAb in lung diseases needs further investigation. There are also monoclonal antibodies against IL-1R and IL-18 receptor (IL-18R) which block their IL-1-mediated signal transduction. Even though those have exhibited excellent safety for patients (Dinarello 2010), those are not as effective in relieving the symptoms as anakinra in disease settings. However these antibodies have not thus applied for lung diseases.

Despite the emerging role for the inflammasomes in immunity, no drugs directly targeting specific inflammasomes, or with pan-inflammasome activity, have yet been described. MCC950 is a potent selective inhibitor of the NLRP3 inflammasome and has been successfully used in in vivo models of asthma to block NLRP3 activation.

4.2 Role of Inflammasomes in Respiratory Diseases

4.2.1 Role in Acute Lung Diseases

Acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), are major causes of fatal respiratory failure. These diseases often occur as a result of severe viral and bacterial pneumonia, sepsis, burns or even oxygen and mechanical ventilator therapy (reviewed in Umbrello et al. 2016). Increased vascular permeability is a hallmark feature leading to lung oedema and poor arterial oxygenation. These conditions are characterised by the infiltration of neutrophils into the lung and the production of inflammatory mediators including complement activation products, cytokines and chemokines, proteases and oxidants. Currently, the mortality rate for patients who develop ALI is as high as 60%, and current treatments involve mechanical ventilatory support and anti-inflammatory drugs such as corticosteroids.

It is becoming evident that inflammasomes play a role in ALI and ARDS. IL-1β has been shown to be elevated and biologically active in the lungs of patients early after the onset of ALI (Olman et al. 2002; Pugin et al. 1996). Elevated levels of

plasma IL-18 protein (Dolinay et al. 2012; Makabe et al. 2012) were shown to be associated with long-term poor prognosis in ALI (Makabe et al. 2012). At the mRNA level, *CASP1* and *IL-1B* and *IL-18* were increased in PBMCs from patients with ARDS (Dolinay et al. 2012). Furthermore, direct effects of IL-1β and IL-18 on lung vascular permeability and fluid transport, which are altered in ALI, have been shown. Treating rats with IL-1β and IL-18 and adenoviral overexpression of IL-1β in mice has been shown to increase vascular permeability in vivo (Ganter et al. 2008; Leff et al. 1994; Jordan et al. 2001). IL-1β has also been shown to inhibit fluid transport across the lung epithelium by decreasing the expression of the epithelial sodium channel alpha subunit (Roux et al. 2005). Collectively, inflammasome activation and the overproduction of IL-1β and IL-18 may play an important role in the pathogenesis of ALI/ARDS.

In the mouse model, instillation of LPS into the lung results in pulmonary oedema, injury, neutrophil infiltration and the production of pro-inflammatory cytokines including IL-1β and IL-18 (Grailer et al. 2014; Jiang et al. 2016). However, NLRP3 and caspase-1 knockout mice are protected from LPS-induced ALI (Grailer et al. 2014; Dolinay et al. 2012; Frank et al. 2008). Grailer et al. also demonstrated that neutrophil and macrophage depletion reduced IL-1β production in the lung following LPS instillation (Grailer et al. 2014), indicating these cells are a major source of this cytokine. Genetic deletion of caspase-1, IL-18 or the IL-1β receptor (IL-1R1) was also shown to reduce ALI in a mechanical ventilation model (Frank et al. 2008). Similar results have been seen with anti-IL-1β, anti-IL-18 antibody treatment or administration of recombinant IL-1R antagonist (IL1-Ra) in an attenuating ventilator model of ALI (Frank et al. 2008; Kuipers et al. 2012; Wu et al. 2013; Jordan et al. 2001). Furthermore, in a two-hit LPS and mechanical ventilation model, NLRP3- and caspase-1-deficient mice or those mice treated with IL-1R antagonist (anakinra) were shown to have diminished IL-1β levels and to be protected from ALI (Jones et al. 2014). Overall, these studies highlight a role for the NLRP3 inflammasome, as well as IL-1β and IL-18 in the pathogenesis of LPS and ventilator-induced ALI mouse models.

The role of inflammasomes in ALI induced by hypoxia or burns is less clear. Hypoxia-induced ALI is a serious complication of prolonged oxygen therapy, and mice lacking NLRP3 have been reported to display decreased (Mizushina et al. 2015) as well as increased (Fukumoto et al. 2013) susceptibility to ALI. The latter study identified that deletion of NLRP3 did not alter IL-1β levels, yet STAT3 responses were abrogated. While increased levels of IL-1β and IL-18 have been observed following burn injury (Ipaktchi et al. 2006; Rana et al. 2005; Han et al. 2015), studies have not directly examined the role of inflammasomes. In one study, the NF-κB inhibitor, BAY11-7082, was shown to dampen NLRP3 activation and to attenuate histological changes and inflammation in burn-induced ALI (Han et al. 2015).

The mechanisms of inflammasome activation during ALI have been examined. In the LPS instillation model, neutrophils were shown to be a source of extracellular histones in vivo, which were shown to activate NLRP3 in a caspase-1- and K+ efflux-dependent manner (Grailer et al. 2014). The P2X7 membrane receptor is activated in response to binding of extracellular ATP, resulting in NLRP3

inflammasome responses (Moncao-Ribeiro et al. 2011; Kolliputi et al. 2010). A role for P2X7 in hypoxia- and LPS-induced ALI was identified by genetic deletion of P2X7 or inhibition of P2X7 with antagonist A438079 treatment, resulting in reduced IL-1β production and inflammation (Galam et al. 2016; Wang et al. 2015). Reactive oxygen metabolites are also thought to play a key role in the pathogenesis of ALI/ARDS. In the presence of ROS, thioredoxin-interacting protein (TXNIP) has been shown to dissociate from thioredoxin (TRX) and bind to NLRP3, leading to its activation (Zhou et al. 2010).

4.2.2 Role in Chronic Lung Diseases

4.2.2.1 Asthma

Asthma is a chronic inflammatory respiratory disease characterised by the infiltration of inflammatory cells (e.g. eosinophils and neutrophils); elevated cytokine levels, including IL-1β and IL-33; production of immunoglobulin E (IgE); airway hyperresponsiveness; and mucus hypersecretion (Madouri et al. 2015; Kim et al. 2014; Tran et al. 2012; Leaker et al. 2017). Mild asthma due to allergic airway inflammation (AAI), typically caused by allergens such as house dust mites (HDM) or grass pollen, involves $CD4^+$ T helper type 2 (T_H2) cells and eosinophils. Severe steroid-resistant asthma due to nonallergic airway inflammation (NAAI), such as microbial (viral or bacterial) invasion, is largely neutrophilic and T_H1/T_H17-dependent (Madouri et al. 2015; Kim et al. 2014, 2017; Tran et al. 2012; McKinley et al. 2008).

IL-1β treatment of mast cells has been shown to increase IgE-mediated T_H2 cytokine secretion, suggesting the NLRP3 may play a role in the manifestation of AAI (Lee et al. 2004; Hultner et al. 2000). In addition, increased levels of NLRP3 and caspase-1 in BAL fluid from asthmatic patients have been observed in comparison with healthy individuals (Kim et al. 2014). These human studies are supported by similar findings in mouse models of neutrophilic asthma (LPS and ovalbumin (OVA) treatment) and AAI (OVA treatment alone) (Kim et al. 2014; Tran et al. 2012). Activation of NLRP3 has been observed in airway epithelial cells and eosinophils in tissue sections from OVA-treated mice, which was shown to be accompanied by the presence of IL-1β and IL-18 (Tran et al. 2012). LPS-/OVA-treated mice deficient in NLRP3 and ASC display reduced levels of pro-inflammatory cytokines IL-1β, IL-5 and IFN-γ, as well as decreased eosinophil numbers in bronchoalveolar lavage (BAL) following OVA challenge (Kim et al. 2014). Furthermore, genetic absence of IL-1R1 or administration of IL-1R antagonist anakinra also reduced eosinophil numbers, suggesting that IL-1β could be the main contributor to the recruitment of tissue eosinophils in asthma (Kim et al. 2014). Of note, treatment of mice with the mitochondrial ROS inhibitor NecroX-5 ablated IL-1β as well as NLRP3 and caspase-1, suggesting that mitochondrial ROS plays a vital role in the activation of NLRP3 and production of functional IL-1β in allergic

asthma (Kim et al. 2014). These studies suggest NLRP3 and IL-1β play a multifactorial role in the development of asthma.

On the contrary, in the HDM-induced allergic asthma model, the levels of eosinophils and T_H2 pro-inflammatory cytokines IL-1β, IL-33, IL-4 and IL-5 were increased in BAL fluid of NLRP3-, caspase-1- and ASC-deficient mice following challenge (Madouri et al. 2015). With the use of gene-deficient mice, NLRP4 was shown to play no major role. IL-33 is a strong inducer of T_H2 cytokines, and IL-33 antagonist treatment was found to reverse the enhanced allergic response in caspase-1 knockout mice, suggesting a link between IL-33 and caspase-1. The role of caspase-11 in the HDM model is unclear and warrants further investigation with regard to the possible involvement of a noncanonical inflammasome pathway.

Alarmingly, steroid treatment is largely ineffective in severe asthma, possibly due to an impairment in nuclear translocation of glucocorticoid receptor (GR)α, as evidenced by a reduction of GR staining in the nucleus of PBMCs isolated from steroid-resistant asthmatic patients (Kim et al. 2017; Matthews et al. 2004). Clinically, mRNA expression of *NLRP3*, *ASC*, *CASP1* and *IL-1B* genes in sputum was found to be increased in neutrophilic compared with eosinophilic asthma (Simpson et al. 2014). However, increased levels of IL-1β protein in the sputum were also detected. Recently, Kim et al. demonstrated that increased mRNA expression of *NLRP3* and *IL-1B* is linked to increased neutrophilic inflammation and decreased lung function, as well as severe asthma, despite high-dose steroid treatment (Kim et al. 2017). Using experimental models of *Chlamydia trachomatis* and *Haemophilus influenzae* infection-induced severe steroid-resistant asthma, it was shown that anti-IL-1β antibody, caspase-1 inhibitor (Ac-YVAD-cho) or NLRP3 inhibitor (MCC950) treatment in vivo suppresses IL-1β production and airway hyperresponsiveness. Of note, IL-1β has been shown to promote T_H17 differentiation and IL-17 production (Chung et al. 2009), which is involved in the development of steroid-resistant asthma (McKinley et al. 2008). These studies suggest that regulating NLRP3 responses may be a potential therapy for severe asthma (Kim et al. 2017).

4.2.2.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory lung disease that encompasses conditions such as chronic bronchitis and emphysema and is the third leading cause of death worldwide (Barnes et al. 2003). The main cause of COPD is cigarette smoke, which triggers potent immune responses leading to chronic inflammation and then to clinically significant COPD in up to 20% of smokers (Lokke et al. 2006). Exposure to cigarette smoke, which contains over 4000 toxins, including LPS, can cause damage to the lung epithelium resulting in recruitment of macrophages and neutrophils and the release of many inflammatory mediators involved in COPD, such as ROS, ATP, chemokines and other growth factors (Valenca et al. 2006; Barbu et al. 2011; Yoshida and Tuder 2007). In this regard, a growing body of evidence implicates inflammasomes and their associated mediators (such as IL-1β, IL-33) in alveolar destruction and small airway obstruction in COPD. Therefore, understanding the

pathways and mediators of COPD development will lead to better therapeutic approaches for this debilitating disease, which has no current treatment options.

As discussed above, there is significant crosstalk between the TLR and inflammasome activation pathways, particularly in the first "priming" step required for inflammasome activation. While the role of TLRs in COPD development appear to be protective. This is best evidenced for TLR4, whereby $TLR4^{-/-}$ mice spontaneously develop emphysema as a result of excessive oxidant activity (Zhang et al. 2006; Ruwanpura et al. 2013). Furthermore, TLR4 polymorphisms and downregulated TLR4 expression are observed in lung tissues from emphysematous smokers (Pace et al. 2011; Ruwanpura et al. 2013). It has shown that the bronchial epithelial cells express mRNA of TLRs and release CXCL8 and IL-1β in response to cigarette smoke via TLR9 (Hoppstadter et al. 2010; Akira et al. 2001). Furthermore, cigarette smoke-induced CXCL8 levels are inhibited by TLR4 antibody, and exposure of bronchial epithelial cells to TLR4 or TLR9 ligands resulted in release of CXCL8 and IL-1β through ROS and P2X7 activation (Hoppstadter et al. 2010). Despite these observations, critical functions for TLRs in promoting cigarette smoke-induced lung inflammation leading to COPD have not been investigated.

Even though a role for inflammasome activation in COPD development is not well known, there are emerging lines of evidence that inflammasome-associated mediators (such as ASC, caspase-1, IL-1β and IL-18) are induced in COPD. Extracellular ATP is upregulated in the airways of COPD (Lommatzsch et al. 2010) and correlates with the decline in lung function (Cicko et al. 2010) and increased airway infiltration of inflammatory cells. Expression of P2X7 receptor is also elevated in inflammatory cells (macrophages and neutrophils) in blood from COPD patients (Lommatzsch et al. 2010) and in a cigarette smoke-induced lung inflammation mouse model (Lucattelli et al. 2011). ATP activates the NLRP3 inflammasome through the P2X7 receptor (Lucattelli et al. 2011): however, the role of NLRP3 in the development of COPD is not fully investigated. Despite this observation, caspase-1 is increased in lung tissues of mice following acute cigarette smoke exposure (Churg et al. 2009) and COPD patients who are smokers compared to non-smokers (Eltom et al. 2011). In addition, selective inhibition of caspase-1 using z-WEHD-fmk, a caspase-1 (IL-1-converting enzyme) inhibitor, significantly reduced inflammatory cells and serum IL-1β in an acute cigarette smoke-induced model (Churg et al. 2009). Furthermore, inflammasome-associated cytokines IL-1β and IL-18 are increased in the lungs of COPD patients and cigarette smoke-induced mouse models of COPD (Kang et al. 2007; Hoshino et al. 2007). Cigarette smoke induces caspase-1 activity, as well as IL-1β and IL-18 production, both in vitro (lung epithelial cells) and in vivo (Botelho et al. 2011; Churg et al. 2009; Kang et al. 2007; Hoshino et al. 2007). Moreover, experimentally induced (i.e. cigarette smoke, elastase) emphysema mouse models involving mice either lacking the receptors for IL-1β and IL-18 or treated with an IL-1R antagonist are protected against emphysema (Couillin et al. 2009). Despite these observations, further studies have suggested that even though P2X7 receptor activation, IL-1R signalling and caspase-1 are upregulated in cigarette smoke-induced mouse models of COPD, NLRP3/caspase-1 cleavage of IL-1β is not required for disease phenotype (Eltom et al. 2011; Pauwels et al. 2011). In contrast, a study shows that $NLRP3^{-/-}$ mice are protected

against a cigarette smoke-induced COPD-like phenotype in the lung (Yang et al. 2015).

Collectively, these observations highlight the pressing need for informative animal models of COPD, in parallel with complementary human studies to elucidate a causal role for specific inflammasomes in promoting COPD, the identification of which will not only shed new light on the complex molecular and cellular pathogenesis of COPD but also pave the way forward for novel therapeutic approaches.

4.2.2.3 Fibrotic Lung Diseases

Idiopathic Pulmonary Fibrosis (IPF)

Pulmonary fibrosis is involved in a broad range of lung disorders characterised by irreversible destruction of normal lung architecture as well as scarring. This leads to a progressive decline in lung function and impaired gas exchange causing morbidity and mortality. The recruitment of fibroblasts and their activation/proliferation lead to the formation of fibrotic foci and the release of components of the extracellular matrix. The causes of the majority of cases of pulmonary fibrosis are unknown. Innate immune responses are known to be impaired in IPF; however, TLR9 activation is thought to contribute to progression through the differentiation of pulmonary fibroblasts into myofibroblasts (Kirillov et al. 2015).

Increased levels of IL-1β have been observed in the BAL fluid of IPF patients (Kitasato et al. 2004; Pan et al. 1996; Zhang et al. 1993; Lasithiotaki et al. 2016). However, macrophages isolated from the BAL have been shown to have impaired IL-1β production following LPS/ATP treatment ex vivo (Lasithiotaki et al. 2016). In line with these results, transcriptome analysis identified expression of *ASC*, *CASP1*, as well as *IL-1R1* genes as being significantly downregulated in cultured lung fibroblasts from IPF patients, in comparison with healthy controls (Plantier et al. 2016). The impact of IL-1β on fibroblasts in vitro is unclear with both pro- and anti-fibrotic effects being reported (Borthwick 2016; Mia et al. 2014; Furuyama et al. 2008). Alveolar macrophage-derived IL-1β has been shown to play a key role in the initiation of a fibrotic response by upregulating platelet-derived growth factor receptor (PDGF-R) (Lindroos et al. 1997). A number of studies have demonstrated a role for IL-1β in lung fibrosis in vivo in overexpression models or by recombinant delivery of IL-1β (Kolb et al. 2001; Gasse et al. 2007; Lappalainen et al. 2005). The role of IL-1β in IPF may be therefore cell type specific.

In the bleomycin-induced mouse model, lung fibrosis and inflammation were shown to be mediated through IL-1β and IL-1R1/MyD88 signalling (Gasse et al. 2007). It was subsequently identified that this pathway involved IL-17A and IL-23, which are necessary for TGF-β1 production, collagen deposition and evolution to fibrosis (Wilson et al. 2010; Gasse et al. 2011). Currently, the role of NLRP3 or other inflammasome components in IPF is not well understood; however, extracellular ATP activation of NLRP3 may act as a danger signal during IPF. Riteau et al. detected significantly elevated levels of ATP in BAL fluid from patients with both stable and exacerbated IPF (Riteau et al. 2010). Furthermore, instillation of

bleomycin was found to rapidly increase levels of ATP in the airways of mice. Local depletion of ATP in wild-type mice with apyrase in treatment or genetic deletion of the ATP receptor P2X7 was shown to reduce neutrophil infiltration, IL-1β production and pulmonary fibrosis in vivo.

Inhibition of NLRP3 and/or IL-1β may therefore provide a therapeutic option for dampening lung fibrosis. Two drugs approved by the United States FDA, pirfenidone (Esbriet by Roche) and nintedanib (Ofev by Boehringer Ingelheim), slow progression of IPF, having been shown to inhibit lung fibrosis in murine models, with these effects being associated with a reduction in IL-1β levels in lung tissue (Oku et al. 2008; Wollin et al. 2014).

Cystic Fibrosis (CF)

CF is an autosomal recessive disorder due to mutations in the CFTR gene leading to an abnormality of chloride channels in mucus and sweat-producing cells. CF patients experience a vicious cycle of infection, inflammation and tissue damage, which progressively impacts on pulmonary function with respiratory failure the primary cause of death (reviewed in Yonker et al. 2015). Pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae* and *Aspergillus fumigatus* are commonly observed in cystic fibrosis patients. Macrophages and epithelial cells in the lung recognise such pathogens leading to neutrophil recruitment and production of pro-inflammatory cytokines. A number of inflammatory pathways have been shown to be dysregulated in CF (reviewed in Cantin et al. 2015; Yonker et al. 2015). For example, CF bronchial epithelial cells display aberrant PRR signalling and constitutively elevated NF-κB activity (Venkatakrishnan et al. 2000).

Pathogens such as those associated with CF patients can activate NLRP3 and NLRC4 inflammasomes. Mice lacking NLRC4 have been shown to be less susceptible to *P. aeruginosa* infection (Cohen and Prince 2013), suggesting that dysregulation of the response may be detrimental and there is increasing evidence that this occurs in CF. Increased levels of IL-1β in the BAL fluid of CF patients (Bonfield et al. 1995) and polymorphisms in the *IL-1B* gene are reported to be associated with disease severity (Levy et al. 2009). Bronchial epithelial cells and haematopoietic cells have been shown to be a source of IL-1β in CF. Of note, IL-1R signalling activates pathogenic IL-17A-secreting T cells and thereby modulates the T_H17/regulatory T (Treg) cell balance (Basu et al. 2015), important for the control of *Aspergillus fumigatus* colonisation and disease in CF (Iannitti et al. 2013).

In line with the results seen in patients with CF, $CFTR^{-/-}$ mice, which represent a murine model of CF, have been shown to have increased caspase-1 activity and production of IL-1β in the lung following *A. fumigatus* or *P. aeruginosa* infection (Iannitti et al. 2016). NLRP3 expression in lung epithelial cells was found to be higher, while NLRC4 was lower in $CFTR^{-/-}$ mice compared to wild-type controls, suggesting the latter may be defective. These results lead Iannitti et al. to postulate that NLRP3 may play a detrimental role in the absence of NLRC4. NLRC4 was found to induce IL-1RA, which dampens NLRP3 activity and therefore may act as a negative regulator. Lastly, treatment of $CFTR^{-/-}$ mice with IL-1R antagonist

anakinra was found to increase survival following *P. aeruginosa* infection and reduce bacterial burden. In an additional study, *P. aeruginosa* infection in CF epithelial cells was found to induce mitochondrial dysfunction and increase mitochondrial Ca^{2+} uptake, leading to increased NLRP3 responses, which could be ameliorated with anakinra treatment (Rimessi et al. 2015). These studies suggest a complex role for NLRP3 and NLRC4 in the pathogenesis of CF that requires further delineation.

Bronchopulmonary Dysplasia (BPD)

BPD is a chronic lung disease of preterm infants with long-term impact (reviewed in Davidson and Berkelhamer 2017). BPD is more common in infants of low birth weight and those who receive mechanical ventilation and oxygen therapy to treat respiratory distress syndrome. There are currently limited therapeutic options available for prevention and treatment of this disease, but one such treatment involves IL-1 receptor antagonist (IL-1RA). The development of BPD is associated with an inflammatory response, including increased numbers of neutrophils and macrophages and elevated levels of IL-1β (Rindfleisch et al. 1996; Watterberg et al. 1994; Kotecha et al. 1996); however, the pathogenic pathways involved are not well defined.

NLRP3 has been implicated in the development of hypoxia-induced lung injury. Using a neonatal model, Liao et al. demonstrated that NLRP3 activation is associated with the development of BPD in murine and primate models (Liao et al. 2015). Neonatal mice exposed to 85% oxygen were shown to have increased caspase-1 activation and apoptotic cells in the lung, IL-1β secretion and airway inflammation. Decreased alveolarisation was also a feature, which was not observed in mice lacking NLRP3. In addition, treatment of hypoxia-exposed neonatal mice with recombinant IL-1RA reduces inflammation and improves alveolarisation, suggesting the NLRP3/IL-1R pathway promotes the disease (Nold et al. 2013; Liao et al. 2015; Rudloff et al. 2017). In line with these results, ventilated preterm baboons were also found to have increased NLRP3 inflammasome activation and IL-1β/IL-1RA ratio in tracheal aspirates. Increased levels of IL-1β have also been observed in amniotic and BAL fluid from infants with BPD (Kotecha et al. 1996; Yoon et al. 1997). Importantly, overexpression of IL-1β in alveolar epithelial cells has been shown to result in respiratory insufficiency and postnatal growth abnormality, associated with increased postnatal mortality of mice (Bry et al. 2007). Overall, the NLRP3/IL-1β pathway appears to promote inflammation in the development of BPD, and inhibition of this pathway has been shown to be of therapeutic benefit in preclinical models.

Inhalation of Pathogenic Pollutants: Asbestosis and Silicosis

Inhalation of pathogenic pollutants such as asbestos and crystalline silica can lead to the development of chronic lung disease (reviewed in Maeda et al. 2010). For

example, inhalation of silica and asbestos results in the progressive pulmonary fibrotic disorders silicosis and asbestosis, respectively. Airborne silica particles are commonly encountered occupationally in mining, construction, manufacturing and farming. Asbestosis does not normally manifest for more than 15 years after the initial exposure. There are currently no effective treatments available. Once inhaled, silica particles and asbestos fibres are engulfed by macrophages in the lung, which leads to the induction of inflammation and the development of fibrosis after repeated exposure.

The NLRP3 inflammasome and IL-1β have been implicated in the development of asbestosis and silicosis. Alveolar macrophages from patients with asbestosis have been shown to secrete elevated amounts of IL-1β compared with healthy controls (Kline et al. 1993). Treatment of LPS-primed macrophages with silica or asbestos induces ROS production and K^+ efflux, leading to caspase-1-dependent NLRP3 activation, as well as IL-1β and IL-18 secretion in vitro (Cassel et al. 2008; Hornung et al. 2008; Dostert et al. 2008). Silica has also been reported to activate NLRP3 in human bronchial epithelial cells (Peeters et al. 2013, 2014), and treatment of mice and rats induces caspase-1 activity and IL-1β production in vivo (Cassel et al. 2008; Sarih et al. 1993; Peeters et al. 2014). In the murine model of silicosis, inflammation and collagen deposition was observed in wild-type mice 3 months after treatment: however, this was reduced in mice lacking NLRP3, ASC or IL-1β (Cassel et al. 2008; Sarih et al. 1993). The infiltration of eosinophils and neutrophils into the airways, as well as IL-1β, has also been shown to be NLRP3-dependent 9 days following asbestos treatment (Dostert et al. 2008).

4.2.2.4 Lung Cancer

Lung cancer is strongly associated with chronic lung inflammation triggered by cigarette smoke, and 80% of all lung cancers occur in patients with a history of smoking. Investigations into the role of inflammasomes in lung cancer are in their relatively infancy, with a small volume of literature on the contradictory pro- and anti-tumorigenic roles for inflammasomes largely limited to in vivo studies on other cancers. Therefore, there is a clear and urgent need to elucidate a causal role for inflammasomes in lung cancer development.

While the role of TLRs in lung cancer has been controversial with reports of opposing pro- and anti-tumorigenic functions (e.g. TLR4) (Wang et al. 2017), the role of NLR- and AIM2-containing inflammasomes in lung adenocarcinoma development is ill-defined. The incidence of tumour development is reduced in mice lacking NLRP3; caspase-$1^{-/-}$ and IL-$1R1^{-/-}$ mice were also resistant to tumour development (Chaix et al. 2008). Furthermore, NLRP3 is required for NK-mediated experimentally induced lung cancer and primary tumour growth, with NK cells having an indirect effect as they do not express NLRP3 (Chow et al. 2012). Further indirect evidence for the potential involvement of inflammasomes in lung adenocarcinoma has come from observations that the NLRP3 inflammasome can promote the proliferation and migration of human lung adenocarcinoma cells (e.g. A549) in vitro

following ATP and LPS stimulation (Wang et al. 2016; Kong et al. 2015). Also, clinical data have shown that increased mRNA expression of specific inflammasome components (i.e. AIM2) and production of the inflammasome effector cytokines IL-1β and IL-18 are associated with disease grading, invasion and chemoresistance of lung cancer (Kong et al. 2015). However, in light of this paucity of information, the role of inflammasomes in lung tumorigenesis needs comprehensive and urgent study.

4.3 Conclusion/Future Directions

Inflammasomes play an important role in mediating inflammation in the lung and are activated in response to a range of microbial and cellular stress responses. In turn, inflammasome responses need to be tightly regulated, and excessive activation has been implicated in the development of a number of respiratory diseases. Here, we have discussed the recent findings and evidence for a role for inflammasomes, as well as the potent pro-inflammatory cytokines IL-1β and IL-18, in a number of lung pathologies. The activation and regulation of inflammasome responses in the lung is complex. A greater understanding of the molecular subtleties of inflammasome responses in the context of specific lung diseases is imperative to design improved and better-targeted treatments. There is also increasing evidence that inflammasome responses not only occur in myeloid cells, such as alveolar macrophages, but also in epithelial cells and the contribution of each cell type to the pathogenesis of respiratory diseases is not clear. In addition to secretion of IL-1β and IL-18, inflammasome activation results in pyroptosis, an inflammatory form of cell death, and, currently, little is known regarding about the role of pyroptosis in lung diseases. A number of broad-acting antagonists and inhibitors that block different aspects of the inflammasome pathway (Fig. 4.1) or downstream cytokine signalling (Fig. 4.2) have been utilised in small animal models of respiratory disease. The development of cell-targeted therapies that inhibit or blunt pathogenic responses could offer improved efficacy.

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