Chapter 6
Inflammasome in the Pathogenesis of Pulmonary Diseases

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Contents

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Abstract Lung diseases are common and significant causes of illness and death around the world. Inflammasomes have emerged as an important regulator of lung diseases. The important role of IL-1 beta and IL-18 in the inflammatory response of many lung diseases has been elucidated. The cleavage to turn IL-1 beta and IL-18 from their precursors into the active forms is tightly regulated by inflammasomes. In this chapter, we structurally review current evidence of inflammasome-related components in the pathogenesis of acute and chronic lung diseases, focusing on the "inflammasome-caspase-1-IL-1 beta/IL-18" axis.

Keywords Inflammasomes · Infectious pulmonary diseases · Lung injury · Smoking · Chronic obstructive pulmonary disease

6.1 Introduction

In serving its primary function in gas exchange, the lung is constantly exposed to the outside world and is highly susceptible to all kinds of foreign matters. Lung diseases are common and significant causes of illness and death around the world. According to the World Health Organization (WHO) (http://www.who.int/mediacentre/factsheets/fs310/en/), lower respiratory infections, chronic obstructive pulmonary disease (COPD), and tuberculosis are among the top 10 causes of death worldwide. Up to 7.73 million people died of these three diseases, accounting for nearly 14% of all death in 2015, not to mention other pulmonary diseases. In addition, lower respiratory infection is the leading cause of death in low-income economies.

The lack of effective treatment for many pulmonary diseases is at least partly due to our limited understanding of the pathobiology of these diseases. The lung has a defense mechanism consisting of physical barriers and immune cells against infection and injury. Upon insult, such as infection or tissue injury, the innate and adaptive immune system in the lung initiate a series of responses, followed by a period of normalization to restore homeostasis in the lung. Inflammation is one of the immediate responses of the innate immune system, in which cytokines constitute a significant part (Shaikh 2011). Interleukin (IL)-1 beta and its isoform IL-1 alpha are proinflammatory cytokines that exert pleiotropic effects on a variety of cells and play a vital role in acute and chronic inflammatory processes (Ren and Torres 2009). IL-1 signal acting through the type 1 receptor IL-1R1, with the help of IL-1 receptor accessory protein, activates transcription factor nuclear factor-kappa B (NF-kappaB) and activator protein 1 (AP-1). Binding of IL-1 to type 2 receptor IL-1Ra does not lead to downstream signaling, and IL-1Ra is therefore considered a decoy receptor. IL-1 beta has important homeostatic functions under normal circumstances, while its overproduction is implicated in the pathophysiological changes in diverse disease states. IL-18 is another member of the IL-1 family. The IL-18 receptor (IL-18R) is a

heterodimer consisting of IL-18R alpha and beta chains. IL-18 also mediates responses and activates NF-kappa B and AP-1, resulting in the production of IFN-gamma, essential for immunity against invading pathogens. In addition, IL-18 can act as a Th2 response inducer in some allergic diseases (Sedimbi et al. 2013).

The important role of IL-1 beta and IL-18 in the inflammatory response of many diseases has been elucidated. The cleavage to turn IL-1 beta and IL-18 from their precursors into the active forms is tightly regulated. Over the past decade, researchers have found that inflammasome is the key component for this process, therefore, critical for the induction of a proper inflammatory response. The core sensor protein of inflammasome comes from the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) family. All NLR family members are classified into subfamilies based on the N-terminal domain they contain: NLRAs have transactivator activation domains (ADs); NLRBs have BIR (baculoviral inhibitor of apoptosis repeat) domains; NLRCs have CARD (caspase activation/recruitment domains); and NLRPs have PYD (pyrin domains) (Leissinger et al. 2014). Of these, at least four NLR members (NLRP1, NLRP3, NLRC4, NLRB1) and absent in melanoma 2 (AIM2) can form inflammasome complexes with the adaptor protein apoptosis-associated speck-like protein containing caspase-recruitment domain (ASC) and pro-caspase-1. Inflammasome formation results in the catalysis and activation of caspase-1, which in turn catalyzes the cytokine precursors (Lee et al. 2016).

The detailed description of inflammasomes can be found elsewhere in this book. Normally, inflammasome formation requires a canonical two-step mechanism. Taking the NLRP3 inflammasome as an example: the first signal (e.g., TLR4 or other pattern recognition receptors) stimulates NF-kappa B and enhanced the expression and synthesis of NLRP3. The second signal induced NLRP3 inflammasome assembly. Common signal is provided by P2X purinoreceptor 7 (P2X7R) bond by adenosine triphosphate (ATP), K^+ efflux, lysosome destabilization caused by urate crystals, DNA and reactive oxygen species (ROS) generated in mitochondria, etc.

The discovery of inflammasome has changed our understanding of the pathogenesis of many diseases. Here we structurally summarize current evidence for the involvement of inflammasome in the pathogenesis of acute and chronic lung diseases, focusing on the "inflammasome-caspase-1-IL-1 beta/IL-18" axis.

6.2 Acute Lung Diseases

6.2.1 Infectious Pulmonary Diseases

Despite sophisticated advances in antibiotics, lung infection remains a significant cause of morbidity and mortality. As multidrug-resistant bacteria are emerging, it is a priority to better understand the mechanisms how our immune system combat pathogens. Researches involving the discussion of inflammasome in infectious pulmonary diseases are summarized and listed in Table 6.1 according to publish date. The term "conflicting" in the column of "Contribution" means that not all the element studied was reported to take effect in a particular article. These terms are consistent throughout this chapter.

Table 6.1 Articles containing discussions of inflammasomes in infectious pulmonary disease

ID	Species	Pathogen	Design	Element	Contribution
Bhakdi 1989	*Homo sapiens*	*Staphylococcus aureus*	In vitro, monocyte	IL-1 beta	Yes
Shimokata 1991	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, pleural fluid	IL-1	Yes
Chensue 1992	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, granulomas	IL-1 beta	Yes
Hennet 1992	*Mus musculus*	Influenza A virus	In vivo, BALF	IL-1 alpha, IL-1 beta	Yes
Jonas 1994	*Homo sapiens*	*Staphylococcus aureus*	In vitro, T lymphocyte	K^+ efflux	Yes
Law 1996	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, cells in BALF	IL-1 beta	Yes
Kaukoranta-Tolvanen 1996	*Homo sapiens*	*Chlamydia pneumoniae*	In vitro, macrophage	IL-1 beta	Yes
Kawakami 1997	*Mus musculus*	*Cryptococcus neoformans*	In vivo, lung	IL-18	Yes
Bellamy 1998	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, blood	IL-1R1, IL-1 alpha, IL-1 beta	Conflicting
Sareneva 1998	*Homo sapiens*	Influenza A virus	In vitro, macrophage	IL-1 beta, IL-18	Yes
Pirhonen 1999	*Homo sapiens*	Influenza A virus	In vitro, monocyte, macrophage	IL-1 beta, IL-18	Yes
Qureshi 1999	*Mus musculus*	*Cryptococcus neoformans*	In vivo, lung	IL-18	Yes
Sugawara 1999	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-18	Yes
Wilkinson 1999	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, blood	IL-1Ra, IL-1 beta	No
Juffermans 2000	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-1R1	Yes
Kawakami 2000a, b	*Mus musculus*	*Cryptococcus neoformans*	In vivo, lung	IL-18	Yes
Netea 2000	*Homo sapiens*	*Chlamydia pneumoniae*	In vitro, macrophage	IL-1 beta	Yes
Tsao 2000	*Homo sapiens*	*Mycobacterium tuberculosis*	Ex vivo, BALF	IL-1 beta	Yes
Yamada 2000	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-1 alpha, IL-1 beta	Yes
Giacomini 2001	*Homo sapiens*	*Mycobacterium tuberculosis*	In vitro, macrophage, dendritic cell	IL-1	Yes

Sugawara 2001	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-1R1	Yes
Kinjo 2002	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-18	Yes
Rupp 2003	*Homo sapiens*	*Chlamydia pneumoniae*	In vitro, macrophage	IL-1 beta, IL-1Ra	Yes
Liu 2004	*Mus musculus*	Influenza A virus	In vivo, lung	IL-18	Yes
Netea 2004	*Homo sapiens* *Mus musculus*	*Chlamydia pneumoniae*	In vitro, macrophage	IL-18	Yes
Schmitz 2005	*Mus musculus*	Influenza virus	In vivo, lung	IL-1R1	Yes
Stasakova 2005	*Homo sapiens*	Influenza A virus	In vitro, macrophage	IL-1 beta, IL-18, caspase-1	Yes
Amer 2006	*Mus musculus*	*Legionella pneumophila*	In vitro, macrophage	NLRC4, caspase-1	Yes
Denton 2007	*Mus musculus*	Influenza A virus	In vivo, lung	IL-18	Yes
Fremond 2007	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung; in vitro, macrophage, dendritic cell	IL-1R, IL-18	Conflicting
Reiniger 2007	*Mus musculus* *Homo sapiens*	*Pseudomonas aeruginosa*	In vivo; in vitro, *epithelial cell*	IL-1 beta, IL-1R1	Yes
Simitsopoulou 2007	*Homo sapiens*	*Aspergillus fumigatus*	In vitro, THP-1	IL-1 beta	Yes
Sutterwala 2007	*Mus musculus*	*Pseudomonas aeruginosa*	In vitro, macrophage	NLRC4, caspase-1, IL-1	Yes
Koo 2008	*Mus musculus*	*Mycobacterium tuberculosis, Mycobacterium marinum*	In vitro, macrophage	NLRP3, NLRC4, caspase-1, IL-1 beta, IL-18	Conflicting
Master 2008	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung; in vitro, J774A, RAW 264.7	IL-1 beta	No
Miao 2008	*Mus musculus*	*Pseudomonas aeruginosa*	In vitro, macrophage	NLRC4, caspase-1, IL-1 beta	Yes
Wolk 2008	*Mus musculus*	Influenza A virus	In vivo, BALF	ATP	Yes
Allen 2009	*Mus musculus*	Influenza A virus	In vivo, lung; in vitro, BMDM, EC	NLRP3, NLRC4, ROS, caspase-1	Yes
Case 2009	*Mus musculus*	*Legionella pneumophila*	In vivo, lung; in vitro, macrophage	NLRP3, NLRC4, ASC, IL-1 beta, IL-18	Conflicting

(continued)

Table 6.1 (continued)

ID	Species	Pathogen	Design	Element	Contribution
Craven 2009	*Homo sapiens, Mus musculus*	*Staphylococcus aureus*	In vitro, monocyte	NLRP3, caspase-1, IL-1 beta, IL-18	Yes
Harder 2009	*Mus musculus*	*Streptococcus pyogenes*	In vitro, macrophage	NLRP3, ASC, caspase-1, IL-1 beta, ATP, P2X7R	Conflicting
Ichinohe 2009	*Mus musculus*	Influenza virus	In vivo, lung; in vitro, $CD4^+$ and $CD8^+$ T cells	NLRP3, ASC, caspase-1	Conflicting
Kleinnijenhuis 2009	*Homo sapiens*	*Mycobacterium tuberculosis*	In vitro, macrophage	IL-1 beta, caspase-1, ATP, P2X7R	Conflicting
Kurenuma 2009	*Mus musculus*	*Mycobacterium tuberculosis*	In vitro, macrophage	Caspase-1, IL-1 beta, IL-18, K^+ efflux, P2X7R	Conflicting
Munoz-Planillo 2009	*Mus musculus*	*Staphylococcus aureus*	In vitro, macrophage	NLRP3, caspase-1, IL-1 beta, IL-18, ATP, P2X7R	Conflicting
Thomas 2009	*Mus musculus*	Influenza A virus	In vivo, lung	NLRP3, caspase-1	Yes
Willingham 2009	*Mus musculus, Homo sapiens*	*Klebsiella pneumoniae*	In vitro, THP-1; in vivo, lung	NLRP3, ASC, IL-1 beta, IL-18 NLRC4	Conflicting
Carlsson 2010	*Mus musculus*	*Mycobacterium marinum*	In vivo, lung	NLRP3, ASC, IL-1 beta	Yes
Ichinohe 2010	*Mus musculus*	Influenza A virus	In vitro, macrophage	NLRP3	Yes
Mayer-Barber 2010	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung	IL-1 beta, IL-1R1	Yes
McElvania Tekippe 2010	*Mus musculus, Homo sapiens*	*Mycobacterium tuberculosis*	In vivo, lung; in vitro, macrophage	ASC, caspase-1, NLRP3, NLRC4, IL-1 beta	Conflicting
McNeela 2010	*Mus musculus*	*Streptococcus pneumonia*	In vitro, dendritic cell	NLRP3, IL-1 beta	Yes
Mishra 2010	*Mus musculus*	*Mycobacterium tuberculosis*	In vitro, macrophage	NLRP3, IL-1 beta	Yes
Said-Sadier 2010	*Homo sapiens*	*Aspergillus fumigatus*	In vitro, THP-1	NLRP3, caspase-1, IL-1 beta, K^+ efflux, ROS, Dectin-1, Syk	Yes
Arlehamn 2011	*Mus musculus*	*Pseudomonas aeruginosa*	In vitro, macrophage	NLRC4, caspase-1, IL-1 beta	Yes

Pereira 2011a	*Mus musculus*	*Legionella pneumophila*	In vivo, lung; in vitro, macrophage	NLRC4, caspase-1, IL-1 beta	Yes
Pereira 2011b	*Mus musculus*	*Legionella*	In vivo, lung	NLRC4	Conflicting
Shimada 2011	*Mus musculus*	*Chlamydia pneumoniae*	In vivo, lung	NLRP3, ASC, caspase-1, IL-1 beta, TLR2, MyD88	Yes
Witzenrath 2011	*Mus musculus, Homo sapiens*	*Streptococcus pneumonia*	In vitro, macrophage; in vivo, lung	NLRP3, IL-1 beta	Conflicting
Cai 2012	*Mus musculus, Homo sapiens*	*Klebsiella pneumoniae*	In vitro, macrophage; in vivo, lung	NLRC4, IL-1 beta, IL-1R1	Yes
Chen 2012	*Homo sapiens*	*Mycobacterium kansasii*	In vitro, THP-1	NLRP3, caspase-1, IL-1 beta, K^+ efflux, ROS, lysosome	Yes
Dorhoi 2012	*Mus musculus*	*Mycobacterium tuberculosis*	In vivo, lung; in vitro, macrophage, dendritic cell, neutrophil	NLRP3, IL-1 beta	Conflicting
Lee 2012	*Homo sapiens*	*Mycobacterium abscessus*	In vitro, macrophage	NLRP3, IL-1 beta, Dectin-1, Syk	Yes
Patankar 2013	*Mus musculus*	*Pseudomonas aeruginosa*	In vitro, macrophage, dendritic cell; in vivo	NLRC4, caspase-1, IL-1 beta	Yes
Rotta Detto Loria 2013	*Homo sapiens*	*Nontypeable Haemophilus influenzae*	In vitro, RAW 264.7, human lung tissue	NLRP3, caspase-1, IL-1 beta, IL-18	Yes
Rimessi 2015	*Homo sapiens*	*Pseudomonas aeruginosa*	In vitro, epithelial cell	NLRP3, caspase-1, mitochondrial Ca^{2+}, IL-1 beta, IL-18,	Yes

Abbreviations in the table are the same as those in the text

6.2.1.1 Influenza Virus

IL-1 Signaling Hennet et al. found an early increase of IL-1 alpha and IL-1 beta peaked between 36 h and 3 days after influenza A virus (IAV) infection in mice (Hennet et al. 1992). Also, IAV-infected human peripheral macrophages secreted IL-1 beta and IL-18 (Sareneva et al. 1998). Similar results were found by Pirhonen et al. with primary human monocytes and differentiated macrophages. Besides, virus-induced IL-1 beta and IL-18 production was significantly blocked by a specific caspase-1 inhibitor (Pirhonen et al. 1999).

The role of IL-1 was further manifested. Schmitz et al. investigated the role of the IL-1R1 signaling during pulmonary antiviral immune responses in $Il1r1^{-/-}$ mice. They demonstrated reduced inflammatory pathology, decreased activation and migration of $CD4^+$ T cells, and greatly diminished immunoglobulin (Ig) M responses in $Il1r1^{-/-}$ mice after influenza virus infection. In contrast, the activation of cytotoxic T lymphocytes and the IgG and IgA antibody responses was intact. Notably, the authors found significantly increased mortality in $Il1r1^{-/-}$ mice after infection (Schmitz et al. 2005).

IL-18 Signaling The role of IL-18 has also been studied in gene knockout mice. $Il18^{-/-}$ mice inoculated with IAV showed increased mortality with the occurrence of pathogenic changes including enhanced virus growth, massive inflammatory infiltration, and elevated nitric oxide production over the first 3 days after respiratory challenge (Liu et al. 2004). Thereafter, Denton et al. found that IL-18 deficiency was associated with delayed virus clearance from the lung and decreased cytokine production by $CD8^+$ T lymphocytes (Denton et al. 2007).

Inflammasome Activation Thomas et al. showed that in vivo activation of the NLRP3 inflammasome by IAV RNA controlled the release of IL-1 beta and IL-18 and modulated the extent of lung pathology. Furthermore $Nlrp3^{-/-}$ and $Casp1^{-/-}$ mice were found more susceptible after IAV infection correlated with decreased cell recruitment and cytokine/chemokine production (Thomas et al. 2009). The in vivo role of NLRP3 inflammasome during influenza virus infection was verified around the same time. Mice lacking Nlrp3, ASC, or caspase-1, but not Nlrc4, exhibited increased mortality and a reduced immune response after influenza virus infection. Using poly I:C and ssRNA40 to analogize virus RNA, the authors concluded that NLRP3 inflammasome could be activated by RNA species dependent on lysosomal maturation and ROS (Allen et al. 2009).

In contrast to studies in certain cell types, like macrophages and epithelial cells, Ichinohe et al. found that ASC and caspase-1, but not NLRP3, were required for $CD4^+$ and $CD8^+$ T cell responses, as well as mucosal IgA secretion and systemic IgG responses to influenza virus infection. This study provided evidence of the requirement for the components of inflammasomes in adaptive immunity to virus infection in vivo (Ichinohe et al. 2009).

The mechanisms by which influenza virus activates the inflammasome have also been studied. Ichinohe et al. showed that the influenza virus M2 protein localized to

the Golgi apparatus dependent on the pH gradient to stimulate the NLRP3 inflammasome in primed macrophages and dendritic cells (Ichinohe et al. 2010). Increased ATP has been observed in the bronchoalveolar lavage fluid (BALF) of mice infected with IAV (Wolk et al. 2008), which is usually believed to be a secondary signal in inflammasome activation and assembly.

Interaction Between Host and Microorganism On the other hand, pathogens have also evolved strategies to take advantage of inflammasome-related mechanisms to evade the host immune system. For example, Stasakova et al. reported that several NS1 mutant viruses induced much more biologically active IL-1 beta and IL-18 than wild-type viruses, therefore inducing rapid apoptosis in infected macrophages, which correlated with the enhanced activity of caspase-1 (Stasakova et al. 2005).

6.2.1.2 Mycobacterium

Mycobacterium is a genus of over 150 recognized species, including pathogens known to cause serious diseases in mammals, like tuberculosis (King et al. 2017). Mycobacteria are aerobic and normally known as acid fast. The studies about infection with mycobacteria, in which inflammasome may take a part in were summarized.

IL-1 Signaling Studies in humans have shown that IL-1 was elevated in monocyte-derived macrophages stimulated in vitro (Giacomini et al. 2001), in pleural fluid (Shimokata et al. 1991), in cells obtained from BALF (Law et al. 1996; Tsao et al. 2000), and in granulomas of patients with tuberculosis (Chensue et al. 1992). It was reported that IL-1 beta production was induced by *M. tuberculosis* through pathways involving ERK, p38, and Rip2 after recognition by TLR2/TLR6 and NOD2 receptors (Kleinnijenhuis et al. 2009).

Genetic studies conducted by Bellamy et al. suggested that polymorphisms in IL-1R1 and possibly IL-1 alpha (but not IL-1 beta) significantly associated with tuberculosis (Bellamy et al. 1998). However, Wilkinson et al. reported no allele or genotype in IL-1Ra and IL-1 beta, single or in combination, was associated with an increased risk of tuberculosis (Wilkinson et al. 1999).

In vivo animal studies using Il1r1$^{-/-}$ and IL-1 beta$^{-/-}$ mice displayed acute mortality with increased bacterial burden in the lungs, suggesting an important role for IL-1 beta/IL-1R1 signaling response to *Mycobacterium tuberculosis* (Mayer-Barber et al. 2010). Il1r1$^{-/-}$ mice showed defective granuloma formation containing fewer macrophages and lymphocytes, defective migration of immune cells, and a decrease in IFN-gamma production in the spleen. These changes were associated with increased mortality and an enhanced mycobacterial outgrowth in the lungs and distant organs (Juffermans et al. 2000). IL-l alpha/beta double knockout mice developed significantly larger granulomas in lungs than wild-type mice after infection with *M. tuberculosis*, suggesting a protective role of IL-1 (Yamada et al. 2000). More precisely, *M. tuberculosis* infection in Il1r1$^{-/-}$ mice led to a profound defect of early control of infection with higher bacterial load in the lung and necrotic pneumonia. While pulmonary CD4^{+} and CD8^{+} T cell responses were unaffected

(Fremond et al. 2007). However, in contrast, Master et al. showed that *M. tuberculosis* prevented inflammasome activation and subsequent IL-1 beta release and zmp1, which encoded a Zn^{2+} metalloprotease, was responsible (Master et al. 2008). Besides, Sugawara reported that $Il1r1^{-/-}$ mice developed significantly larger granulomatous lesions with neutrophil infiltration in the lungs than wild-type mice did, and IFN-gamma production in spleen cells was lower in $Il1r1^{-/-}$ mice (Sugawara et al. 2001).

IL-18 Signaling $Il18^{-/-}$ mice developed marked granulomas compared with wild-type ones after *M. tuberculosis* infection. The granulomatous lesions could be inhibited significantly by exogenous recombinant IL-18. The splenic IFN-gamma levels were also lower in $Il18^{-/-}$ mice (Sugawara et al. 1999). Similarly, $Il18^{-/-}$ mice were more prone to this infection than wild-type mice, and IFN-gamma production was significantly attenuated. Consistently, IL-18 transgenic mice were more resistant to the infection than their littermate mice, and IFN-gamma levels were increased (Kinjo et al. 2002). However, Fremond et al. reported that unlike IL-1 beta, IL-18-dependent pathways seemed to be dispensable in response to *M. tuberculosis* infection (Fremond et al. 2007).

Inflammasome Activation *Mycobacterium tuberculosis* activated the NLRP3 inflammasome and induced a strong IL-1 beta response. The mechanism is not yet fully understood, but it was believed that *M. tuberculosis* induced inflammasome activation involving the export of the 6 kDa early secreted antigenic target (ESAT-6) through a functional protein secretion system ESX-1 (Mishra et al. 2010). The function of ESX-1 in NLRP3 activation was further confirmed by Dorhoi et al. They also concluded that although NLRP3 inflammasome was critical for IL-1 beta secretion in macrophages, $Nlrp3^{-/-}$ mice were not susceptible to *M. tuberculosis* infection, due to NLRP3-independent compensatory IL-1 beta production in lung parenchyma (Dorhoi et al. 2012). Kleinnijenhuis et al. showed that the secretion of IL-1 beta in macrophage depended on the activation of P2X7R by endogenously ATP. However, they also suggested that constitutively expressed caspase-1 in monocyte need not be activated by *M. tuberculosis* (Kleinnijenhuis et al. 2009). Kurenuma et al. found that a genomic locus called "region of difference 1" (RD1) in *Mycobacterium tuberculosis* was essential for the activation of caspase-1 and subsequent secretion of IL-1 beta and IL-18 in macrophages. The activation was induced via RD1-dependent K^+ efflux independent of P2X7R (Kurenuma et al. 2009). While the above experiments were performed in an acute settings, McElvania et al. showed that *M. tuberculosis* induced IL-1 beta secretion in human and mouse macrophages in vitro, depending on ASC, caspase-1, and NLRP3, but not NLCR4. In addition, murine ASC protected the host during chronic *M. tuberculosis* infection, but the effects of caspase-1 and NLRP3 were dispensible (McElvania Tekippe et al. 2010).

Mycobacterium marinum *Mycobacterium marinum* possesses virtually all of the virulence factors associated with *M. tuberculosis*, including the ESX-1 secretion system. Koo et al. identified that NLRP3, caspase-1, ASC, but not NLRC4, were

required for the release of IL-1 beta and IL-18 after *M. marinum* or *M. tuberculosis* infection. Mostly important, they showed that mycobacteria-induced ESX-1-dependent lysosome secretion was essential to release, but not to synthesize IL-1 beta and IL-18 in vitro (Koo et al. 2008). In vivo study confirmed the function of ESX-1 secretion system in activating NLRP3 inflammasome. However, the activation of NLRP3 inflammasome did not restrict bacterial growth, indicating a host-detrimental role of this inflammatory pathway in mycobacterial infection (Carlsson et al. 2010).

Mycobacterium abscessus *Mycobacterium abscessus* is one of the common species that causes disseminated infections in patients with cystic fibrosis. It has been reported that NLRP3 inflammasome activation contributed to the antimicrobial responses against *M. abscessus* in human macrophages, and its activation was dependent on dectin-1/Syk signaling (Lee et al. 2012).

Mycobacterium kansasii Live intracellular *Mycobacterium kansasii* has been reported to trigger the activation of the NLRP3 inflammasome, leading to caspase-1 activation and IL-1 beta secretion. Furthermore, K^+ efflux, lysosomal acidification, ROS production, and cathepsin B release played a role in this activation process (Chen et al. 2012).

6.2.1.3 Other Pathogens

Some other pathogens that are common cause of respiratory tract and pulmonary infections are included in this part.

Streptococcus pneumonia *Streptococcus pneumonia* is a frequent colonizer in the upper respiratory tract and a leading cause of infections like pneumonia. McNeela et al. demonstrated that the activation of NLRP3 inflammasome was required for *S. pneumonia* or its virulence factor pneumolysin-mediated enhancement of IL-1 beta secretion in dendritic cells. Furthermore, NLRP3 was required for protective immunity against respiratory infection with *S. pneumonia* (McNeela et al. 2010). Similarly, Witzenrath et al. reported that *S. pneumonia* expressing hemolytic pneumolysin also induced NLRP3-dependent IL-1 beta production in human and murine mononuclear cells. The inflammasome pathway was protective maintaining the pulmonary microvascular barrier. Additionally, the results showed that inflammasome was not activated by bacterial mutants lacking pneumolysin, which could cause invasive disease clinically (Witzenrath et al. 2011).

Staphylococcus aureus Staphylococcal α-hemolysin, an essential virulence factor of *Staphylococcus aureus*, has been shown to be required for the promotion of pneumonia in mouse models. It has long been proven that α-hemolysin could induce IL-1 beta secretion from human monocytes (Bhakdi et al. 1989). Furthermore, α-hemolysin can induce K^+ efflux in host cells (Jonas et al. 1994). Craven et al. demonstrated that α-hemolysin activated the NLRP3 inflammasome resulting in the activation of caspase-1 and secretion of cytokines IL-1 beta and IL-18 in monocyte-

derived cells from humans and mice. They also reported that α-hemolysin induced NLRP3-dependent cellular necrosis resulting in the release of endogenous danger-associated molecular patterns (DAMPs) (Craven et al. 2009). Munoz-Planillo et al. further concluded that bacterial lipoproteins released by *S. aureus* were required for NLRP3 and caspase-1 activation triggered by α- and β-hemolysins. Notably, caspase-1 activation was independent of ATP and P2X7R (Munoz-Planillo et al. 2009).

Streptococcus pyogenes Harder et al. found that caspase-1 activation and IL-1 beta secretion were induced by live *Streptococcus pyogenes*. The toxin streptolysin O, NLRP3, and ASC were crucial for the process, while exogenous ATP or the P2X7R was not required (Harder et al. 2009).

Klebsiella pneumoniae NLRP3 inflammasome protected host during infection with *Klebsiella pneumoniae*, as inflammatory response decreased and mortality increased in Nlrp3$^{-/-}$ and Asc$^{-/-}$, but not Nlrc4$^{-/-}$ mice. NLRP3 activated necrosis and triggered HMGB1 release in addition to IL-1 beta as well as IL-18 secretion in macrophages (Willingham et al. 2009). However, NLRC4 has also been found to be of importance for host survival, bacterial clearance, production of IL-1 beta, as well as neutrophil-mediated inflammation following pulmonary *K. pneumoniae* infection. Exogenous IL-1 beta partially rescued survival and restored neutrophil accumulation and cytokine/chemokine expression in the lungs of Nlrc4$^{-/-}$ mice. Furthermore, Il1r1$^{-/-}$ mice displayed a decrease in neutrophilic inflammation after infection (Cai et al. 2012).

Legionella pneumophila NLRC4 is shown to be important in the recognition, response, and resolution of infection with flagellated pathogens. *Legionella pneumophila* is a flagellated, Gram-negative, facultative intracellular pathogen. Amer et al. found that *Legionella*-induced NLRC4-dependent caspase-1 activation to restrict replication in macrophages (Amer et al. 2006). ASC was found to be important for caspase-1 activation during *L. pneumophila* infection. Activation of caspase-1 via ASC did not require sense of flagellin by NLRC4. Besides, activation of caspase-1 in macrophages occurred independently of NLRP3 (Case et al. 2009). Slightly different, Pereira et al. found that NLRC4-dependent growth restriction of *L. pneumophila* was fully due to flagellin. In addition, *L. pneumophila* multiplied better in Nlrc4$^{-/-}$ mice, and macrophages compared with that in caspase-1 deficient ones, suggesting a caspase-1-independent downstream of NLRC4 (Pereira et al. 2011b). The importance of flagellin in activating NLRC4 was further tested, as nonflagellated *Legionella* bypassed the NLRC4 inflammasome-mediated growth restriction (Pereira et al. 2011a). The type 4 secretion system was also suggested to be important for NLRC4- and caspase-1-dependent host response (Silveira and Zamboni 2010).

Chlamydia pneumonia Studies have shown that in vitro *Chlamydia pneumoniae* infection could elicit IL-1 beta and IL-18 secretion (Netea et al. 2000; Kaukoranta-Tolvanen et al. 1996; Netea et al. 2004; Rupp et al. 2003). Shimada et al. demonstrated that *C. pneumoniae* infection in the lung induced NLRP3 inflammasome

activation, leading to caspase-1-dependent IL-1 beta secretion. This inflammatory response was critical for host defense against infection, manifested by delayed bacterial clearance and increased mortality in caspase1$^{-/-}$ mice, which could be rescued by recombinant IL-1 beta (Shimada et al. 2011).

Nontypeable Haemophilus influenzae *Nontypeable Haemophilus influenzae* (NTHi) is the most common cause for bacterial exacerbations in COPD. Higher expression of NLRP3 and caspase-1 and a significant induction of IL-1 beta after NTHi stimulation were detected in a murine macrophage cell line. In addition, inhibition of caspase-1 in human lung tissue led to a significant reduction of IL-1 beta and IL-18 (Rotta Detto Loria et al. 2013).

Pseudomonas aeruginosa Reiniger et al. found rapid release of IL-1 beta in response to *Pseudomonas aeruginosa*. And Il1r$^{-/-}$ mice were susceptible to chronic *P. aeruginosa* lung infection (Reiniger et al. 2007). NLRC4 inflammasome was identified critical for optimal bacterial clearance in an in vivo model of lung infection with *P. aeruginosa*. The activation of caspase-1 and secretion of IL-1 beta were triggered by bacterial flagellin and type 3 secretion system (T3SS) (Franchi et al. 2007). The importance of NLRC4 and T3SS was further manifested by Sutterwala et al. and Miao et al. (Miao et al. 2008). Sutterwala et al. also reported that the *P. aeruginosa* strain expressing the exoenzyme U (ExoU, a T3SS effector) phospholipase was able to suppress caspase-1-mediated cytokine production via NLRC4, associated with more severe disease (Sutterwala et al. 2007). Pilin, a major component of the type 4 bacterial pilus, has also been reported to activate NLRC4 inflammasome via the T3SS in *P. aeruginosa* infection (Arlehamn and Evans 2011). Activation of NLRC4 may depend not only on T3SS or flagellin but also on bacterial motility, as caspase-1 activation and IL-1 beta production were reduced when exposed to nonmotile *P. aeruginosa* in macrophages and dendritic cells (Patankar et al. 2013). As an example, the temporal loss of *P. aeruginosa* motility has been described during chronic infections in patients with cystic fibrosis (Luzar et al. 1985; Mahenthiralingam et al. 1994). Recently, Rimessi et al. demonstrated that flagellin of *P. aeruginosa* caused mitochondrial perturbation, which regulated NLRP3 activation and IL-1β and IL-18 processing by mitochondrial Ca2+ in human bronchial epithelial cells (Rimessi et al. 2015).

Cryptococcus neoformans Recombinant IL-18 enhanced the elimination of live *Cryptococcus neoformans* from the lungs, prevented its dissemination to the brain, and increased the survival rate of infected mice. In addition, administration of neutralizing anti-IL-18 antibody exacerbated the infection (Kawakami et al. 1997). They further reported that fungal clearance in the lung was reduced and the levels of IL-12 and IFN-gamma in the sera were significantly lower in Il18$^{-/-}$ mice (Kawakami et al. 2000a). IL-12 and IL-18 have been shown to synergistically increase the fungicidal activity against *C. neoformans*. A single administration of either IL-12 or IL-18 was not effective, while their combination significantly prolonged survival time of infected mice and reduced the fungal growth in lungs (Qureshi et al. 1999). To discriminate the activity of IL-18 from that of counterpart

cytokines like IL-12, Kawakami et al. conducted the experiment in IL-12p40$^{-/-}$ mice. Neutralizing anti-IL-18 antibody almost completely abrogated IFN-gamma production, and host response in IL-12p40 and IL-18 double knockout mice was more profoundly impaired than in IL-12p40$^{-/-}$ mice. Moreover, administration of IL-12 as well as IL-18 significantly restored the host resistance (Kawakami et al. 2000b).

Aspergillus fumigatus The release of IL-1 beta was significantly increased from monocytes stimulated with hyphal fragments of *Aspergillus fumigatus* (Simitsopoulou et al. 2007). Further study found that hyphal fragments induced NLRP3 inflammasome assembly, caspase-1 activation, and IL-1 beta release from THP-1 cell line. The activation of NLRP3 required dectin-1/Syk signaling, K^+ efflux, and ROS production (Said-Sadier et al. 2010).

6.2.2 Acute Lung Injury (ALI)

Acute respiratory distress syndrome (ARDS) is the acute onset of hypoxemia with bilateral infiltrates, in the absence of left atrial hypertension. In the 2012 Berlin definition, ALI was reassigned to be a mild type of ARDS. As it is not a single disease, we listed in Table 6.2 the studies on ALI of different causes.

IL-1 Signaling IL-1 beta has been found in BALF from patients with ARDS (Pugin et al. 1996). And it has been previously shown in rats that lung vascular permeability increases after short-term exposure to IL-1 alpha and IL-1 beta (Leff et al. 1994). Ganter et al. demonstrated a role for the alphavbeta5 and alphavbeta6 integrins in mediating IL-1 beta-induced ALI (Ganter et al. 2008).

Inflammasome Activation Our group demonstrated that lipopolysaccharides (LPS) activated NLRP3, enhanced the release of IL-1 beta, and promoted pyroptosis in alveolar macrophages. Meanwhile, IL-1 beta upregulated IL-1R1 through an autocrine mechanism (He et al. 2016). Our group examined the role of the NLRP3 inflammasome in response to hemorrhagic shock in a mouse model of ALI. In our study, pulmonary endothelial cells were the primary source of IL-1 beta secretion after hemorrhagic shock. DAMPs (especially HMGB1) activated NADPH oxidase and caused thioredoxin-interacting protein to associate with NLRP3, leading to inflammasome activation. Notably, endothelial cells were also targets of IL-1 beta, which might cause a range of inflammatory molecules and an amplification of inflammation leading to ALI (Xiang et al. 2011). We further showed that there existed a negative-feedback regulating the activation of inflammasome. While activating NLRP3 inflammasome, LPS also induced pyrin expression, which in turn suppressed the activation of inflammasome in mouse lungs. However, hemorrhagic shock suppressed IL-10 and pyrin expression, therefore significantly enhancing inflammasome activation and IL-1 beta secretion in macrophages and endothelial cells (Xu et al. 2013).

Table 6.2 Articles containing discussion of inflammasomes in ALI

ID	Species	Diseases	Design	Element	Contribution
Leff 1994	*Rattus norvegicus*	ALI	In vivo, lung	IL-1 alpha, IL-1 beta	Yes
Narimanbekov 1995	*Oryctolagus cuniculus*	ALI (mechanical ventilation)	In vivo, lung	IL-1Ra	Yes
Pugin 1996	*Homo sapiens*	ARDS	Ex vivo, BALF	IL-1 beta	Yes
Tremblay 1997	*Rattus norvegicus*	ALI (mechanical ventilation)	Ex vivo, lung	IL-1 beta	Yes
Ranieri 1999	*Homo sapiens*	ARDS (mechanical ventilation)	Ex vivo, BALF	IL-1 beta, IL-1Ra	Yes
Wrigge 2000	*Homo sapiens*	Mechanical ventilation	Ex vivo, blood	IL-1Ra	No
Ricard 2001	*Rattus norvegicus*	ALI (mechanical ventilation)	Ex vivo, lung; in vivo, lung	IL-1 beta	No
Rich 2003	*Rattus norvegicus*	ALI (mechanical ventilation)	Ex vivo, BALF	ATP	Yes
Ma 2005	*Rattus norvegicus* *Mus musculus*	ALI (mechanical ventilation)	Microarray, lung tissue	IL-1 beta	Yes
Lin 2007	*Rattus norvegicus*	LPS + mechanical ventilation	In vivo, lung	IL-1 beta	Yes
Frank 2008	*Rattus norvegicus* *Mus musculus*	ALI (mechanical ventilation)	In vivo, lung	IL-1R1, IL-1Ra	Yes
Ganter 2008	*Mus musculus*	ALI	In vivo, lung	IL-1 beta	Yes
Kolliputi 2010	*Mus musculus*	ALI (hyperoxia)	In vivo, lung, BALF; in vitro, macrophage	NLRP3, K^+ efflux, P2X7R	Yes
Xiang 2011	*Mus musculus*	ALI (hemorrhagic shock)	In vivo, lung; in vitro, endothelial cells	NLRP3, IL-1 beta, ROS	Yes
Dolinay 2012	*Homo sapiens* *Mus musculus*	ALI (mechanical ventilation)	In vivo, lung; in vitro, blood, BALF	IL-1 beta, IL-18, caspase-1	Yes
Kuipers 2012	*Homo sapiens* *Mus musculus*	ALI (mechanical ventilation)	In vivo, lung; in vitro, BALF	NLRP3, ASC, caspase-1, IL-1 beta, uric acid	Yes
Fukumoto 2013	*Mus musculus*	ALI (hyperoxia)	In vivo, lung; in vitro, BALF	NLRP3, IL-1 beta	Yes
Wu 2013	*Mus musculus*	ALI (mechanical ventilation)	In vitro, macrophage	NLRP3, IL-1 beta, IL-18, uric acid, ROS	Yes

(continued)

Table 6.2 (continued)

ID	Species	Diseases	Design	Element	Contribution
Xu 2013	*Mus musculus*	ALI (hemorrhagic shock)	In vivo, lung; in vitro, endothelial cells, macrophage	NLRP3, IL-1 beta	Yes
Mizushina 2015	*Mus musculus*	ALI (hyperoxia)	In vivo, lung, BALF	NLRP3, IL-1 beta	Yes
He 2016	*Mus musculus*	ALI (infection)	In vivo, lung; in vitro, macrophage	NLRP3, IL-1 beta, IL-1R1	Yes

Ventilation-induced lung injury (VILI) is a special type of ALI. Ventilation alone for a short period does not seem sufficient for mediator release and major lung injury in normal lungs (Wrigge et al. 2000). However, mechanical ventilation may augment preexisting lung injury.

IL-1 Signaling A RCT showed that mechanical ventilation caused increased concentrations of IL-1 beta and IL-1Ra in BALF of ARDS patients (Ranieri et al. 1999). In basic research, combined LPS instillation and ventilation synergistically unregulated the production of IL-1 beta in rat lung tissues (Lin et al. 2007). Ventilation with a large tidal volume for 2 h induced the released of IL-1 beta in isolated, unperfused rat lungs with or without LPS injection (Tremblay et al. 1997). However, Ricard et al. reappraised the cytokine production in both in vivo and ex vivo ventilated rat lungs and were unable to detect the release of IL-1 beta (Ricard et al. 2001). In gene expression microarray studies, IL-1 beta has been identified as a candidate gene in rodent (mouse and rat) VILI models (Ma et al. 2005).

Furthermore, recombinant IL-1Ra significantly lowered the concentration of albumin and elastase and decreased neutrophil infiltration in a rabbit model of VILI (Narimanbekov and Rozycki 1995). Similarly, mice deficient in IL1R1 and rats treated with IL-1Ra showed preserved alveolar barrier function, reduced neutrophil recruitment, and decreased epithelial injury and permeability after mechanically ventilation (Frank et al. 2008).

IL-18 Signaling Dolinay et al. reported a critical role of caspase-1 and IL-18 in VILI. A comprehensive gene expression analysis on peripheral blood from patients with ARDS and polymerase chain reaction and ELISA were performed. IL-1 beta and IL-18 transcripts were increased. And human plasma IL-18 levels were correlated with disease severity and mortality in critically ill patients. Besides, mechanical ventilation enhanced IL-18 levels in the lung, serum, and BALF in mice.

Genetic deletion of IL-18 or caspase-1 or treatment with IL-18 neutralizing antibody reduced lung injury and inflammation in response to ventilation (Dolinay et al. 2012).

Inflammasome Activation More directly, Kuipers et al. showed that mRNA levels of ASC were higher in lung brush samples from patients after 5 h of ventilation. Also, ventilation increased relative expression of NLRP3 in alveolar macrophages. Besides,

mechanical ventilation increased the expression of NLRP3 and ASC, activated caspase-1, and promoted the release of IL-1 beta in mouse lung. In this process, uric acid was also released and may serve as the ligand for NLRP3. Additionally, mice deficient in NLRP3 or treatment with IL-1 receptor antagonist or glibenclamide displayed less VILI (Kuipers et al. 2012). Using an in vitro model, Wu et al. also demonstrated that alveolar macrophages subjected to cyclic stretch released uric acid, which activated the NLRP3 inflammasome, and induced the release of IL-1 beta and IL-18. They determined that mitochondrial ROS generation was required for NLRP3 activation (Wu et al. 2013). It has long been reported that high-pressure mechanical ventilation significantly increased ATP release in BALF (Rich et al. 2003).

Another form of ALI associated with ventilation is hyperoxic acute lung injury (HALI). Kolliputi et al. reported that hyperoxia-induced K^+ efflux activated the NLRP3 inflammasome via the purinergic P2X7R to cause inflammation and HALI (Kolliputi et al. 2010). Further, they demonstrated that $Nlrp3^{-/-}$ mice had suppressed inflammatory response in BALF and lung tissue and blunted epithelial cell apoptosis to HALI (Fukumoto et al. 2013). Notably, Mizushina et al. found that deficiency in NLRP3 shortened survival under hyperoxic conditions regardless of diminished inflammatory responses. And this lethality was due to Stat3 signaling (Mizushina et al. 2015).

6.3 Chronic Lung Diseases

6.3.1 Smoke and Particles Inhalation

6.3.1.1 Cigarette Smoking (CS)

Table 6.3 lists the studies containing discussion of inflammasomes in smoking.

IL-1 Signaling Cytokine regulation in the lung may be altered by smoke exposure. CS inhalation in smokers (healthy and COPD patients) induced IL-1 beta release in BALF (Kuschner et al. 1996) and in lung tissue and induced sputum (Pauwels et al. 2011). However, there are also studies reporting a lower level of IL-1 beta in macrophage from smokers before and after LPS stimulation (Sauty et al. 1994; Brown et al. 1989). Pauwels et al. demonstrated that pulmonary inflammation after subacute CS exposure could be significantly attenuated by IL-1R1 knockout or neutralizing IL-1 alpha or IL-1 beta (Pauwels et al. 2011). TLR4, MyD88, and IL-1R1 were reported to be involved in the inflammatory response to CS both in vitro and in vivo. Besides, CS-activated macrophages released IL-1 beta only in presence of ATP (Doz et al. 2008).

IL-18 Signaling IL-18 signaling has also been demonstrated to be critical in the response to CS. CS was a potent stimulator of IL-18 and caspases-1. In addition, CS-induced inflammation was significantly decreased in $Il18ra^{-/-}$ mice (Kang et al. 2007).

Table 6.3 Articles containing discussion of inflammasomes in relation to smoking

ID	Species	Design	Element	Contribution
Brown et al. 1989	*Homo sapiens*	In vitro, macrophage	IL-1 beta	No
Sauty 1994	*Homo sapiens*	Ex vivo, BALF	IL-1 beta	No
Kuschner 1996	*Homo sapiens*	Ex vivo, BALF	IL-1 beta	Yes
Kang 2007	*Mus musculus, Homo sapiens*	In vivo, lung; in vitro, macrophage	IL-18, IL-18R	Yes
Doz 2008	*Mus musculus*	In vivo, lung; ex vivo, BALF; in vitro, macrophage	TLR4, MyD88, IL-1R1, IL-1 beta, ATP	Yes
Eltom 2011	*Mus musculus, Homo sapiens*	In vivo, lung; ex vivo, lung	P2X7R, caspase-1, IL-1 beta	Yes
Pauwels 2011	*Mus musculus, Homo sapiens*	In vivo, lung; ex vivo, sputum	IL-1 alpha, IL-1 beta, IL-1R1, NLRP3, caspase-1	Conflicting
Eltom 2014	*Mus musculus*	In vivo, lung	IL-1 beta, IL-18, NLRP3, ASC, NLRC4, AIM2, caspase-1	Yes

CS is closely related to COPD, which will be discussed in Sect. 6.3.2

Inflammasome Activation Direct evidence of inflammasome involvement came from Eltom et al. They demonstrated that NLRP3 and ASC, but not NLRC4 or AIM2, were required for CS-induced IL-1 beta and IL-18 release. Besides, mice deficient in caspase 1/11 had markedly attenuated levels of cytokines and neutrophil infiltration (Eltom et al. 2014). However, CS-induced inflammation and IL-1 alpha production were reported to occur independently of the NLRP3-caspase-1 axis (Pauwels et al. 2011).

Genetic deletion of the P2X7R or using a selective P2X7R inhibitor reduced CS-induced caspase-1 activation and IL-1 beta release during acute CS exposure in vivo. They reported that caspase-1 activity were higher in lung tissue from smokers (Eltom et al. 2011).

6.3.1.2 Inhalation of Particles

Articles containing discussion of inflammasomes in particle inhalation are summarized in Table 6.4.

There are various kinds of particles in industrial and urban life, which can cause injuries to the lungs and pulmonary diseases.

Carbon black nanoparticles have been reported to cause caspase-1 activation, IL-1 beta release, and pyroptosis in alveolar macrophages (Reisetter et al. 2011).

Inorganic materials can trigger NLRP3 response as well. Nano-TiO_2 activated NLRP3 inflammasome and induced IL-1 alpha and beta release in a phagocytosis-independent manner (Yazdi et al. 2010). Nickel nanoparticles induced transient increase of IL-1 beta in rats (Morimoto et al. 2010). Hamilton et al. demonstrated that nickel contamination in multiwalled carbon nanotubules activated NLRP3 via lysosomal disruption in primary macrophages (Hamilton et al. 2012).

Urban particulate matter has been shown to induce IL-1 beta release in human primary bronchial epithelial cells (Fujii et al. 2001). Furthermore, NLRP3 inflammasome was required for the production of IL-1 beta in vivo (Hirota et al. 2012). Diesel exhaust particles (DEP) are a major component of the ambient particulate matter. It was shown that in vitro DEP stimulated IL-1 beta production in monocytes and macrophages (Pacheco et al. 2001; Yang et al. 1997) and in epithelial cells (Boland et al. 1999). $Il1r1^{-/-}$ mice and mice treated with IL-1Ra had reduced inflammation upon DEP exposure. However, the authors concluded that

Table 6.4 Articles containing discussion of inflammasomes in particle inhalation

ID	Species	Particles	Design	Element	Contribution
Yang 1997	*Rattus norvegicus*	Diesel exhaust particles	In vitro, macrophage	IL-1 beta	Yes
Boland 1999	*Homo sapiens*	Diesel exhaust particles	In vitro, epithelial cell line	IL-1 beta	Yes
Fujii 2001	*Homo sapiens*	Particulate matter	In vitro, epithelial cell	IL-1 beta	Yes
Pacheco 2001	*Homo sapiens*	Diesel exhaust particles	In vitro, PBMC	IL-1 beta	Yes
Morimoto 2010	*Rattus norvegicus*	Nickel nanoparticle	In vivo, lung, BALF	IL-1 beta	Yes
Yazdi 2010	*Homo sapiens, Mus musculus*	Nano-titanium dioxide	In vivo, lung; in vitro, macrophage, dendritic cell, keratinocyte	NLRP3, IL-1 alpha, IL-1 beta, IL-1R1	Yes
Provoost 2011	*Mus musculus*	Diesel exhaust particles	In vivo, lung, BALF	IL-1R1, NLRP3, Caspase-1	Conflicting
Reisetter 2011	*Mus musculus, Homo sapiens*	Carbon black nanoparticle	In vitro, macrophage	Caspase-1, IL-1 beta	Yes
Hamilton 2012	*Mus musculus*	Nickel	In vitro, macrophage	NLRP3, lysosome	Yes
Hirota 2012	*Mus musculus*	Particulate matter	In vivo, lung	NLRP3, IL-1 beta	Yes

DEP-initiated inflammation did not depend on NLRP3-caspase-1 pathway (Provoost et al. 2011).

6.3.2 Chronic Obstructive Pulmonary Disease

Listed in Table 6.5 are the articles containing discussion on inflammasomes in COPD.

COPD is an important lung and airway disease, and is increasing in incidence, especially in developing countries. COPD may affect over 200 million people worldwide (data from WHO). Long-term cigarette smoking is the most important risk factor that may initiate the disease. The evidence for the involvement of inflammasome in cigarette smoking has been discussed in previous section.

IL-1 Signaling Acute exposure to smoke elevated IL-1 beta, while 6 months of exposure did not. Mice deficient in IL-1R or treatment with pan-caspase or caspase-1 inhibitor were protected from inflammatory cell infiltration and matrix breakdown during acute smoke exposure. After 6 months of exposure, $Il1r^{-/-}$ mice were 65% protected against emphysema and completely protected against small airway remodeling (Churg et al. 2009).

IL-18 Signaling Kang et al. demonstrate that IL-18 is present in exaggerated quantities in the lungs and the serum from patients with COPD (Kang et al. 2007). The levels of IL-18 in induced sputum of patients with COPD were also found to be elevated compared with healthy subjects and were inversely correlated with lung function (% predicted FEV_1 and FEV_1/FVC ratio) (Rovina et al. 2009).

Furthermore, targeted overexpression of IL-18 in murine lungs resulted in widespread pulmonary inflammation, emphysema, mucus metaplasia, and airway remodeling through increased pulmonary $CD4^+$, $CD8^+$, $CD19^+$, and $NK1.1^+$ cells

Table 6.5 Articles containing discussion of inflammasomes in COPD

ID	Species	Design	Element	Contribution
Kang 2007	*Mus musculus, Homo sapiens*	In vivo, lung; in vitro, macrophage	IL-18, IL-18R	Yes
Churg 2009	*Mus musculus*	In vivo, lung	IL-1 beta, IL-1R, IL-18	Yes
Rovina 2009	*Homo sapiens*	Ex vivo, sputum	IL-18	Yes
Cicko 2010	*Mus musculus*	In vivo, lung	ATP	Yes
Kang 2012	*Mus musculus*	In vivo, lung	IL-18	Yes
Bartziokas 2014	*Homo sapiens*	Ex vivo, blood	Uric acid	Yes
Di Stefano 2014	*Homo sapiens*	Ex vivo, bronchial mucosa, BALF	NLRP3, caspase-1, IL-1 beta, IL-18	No

and type 1 cytokine (IFN-gamma), type 2 cytokine (IL-13), and type 17 cytokine (IL-17A) (Kang et al. 2012).

Inflammasome Activation An increased level of ATP has been found in the lungs in a mouse model of smoke-induced acute lung inflammation and emphysema, and the increased ATP level correlated with pulmonary neutrophilia (Cicko et al. 2010).

Serum uric acid levels were higher in patients with more severe airflow limitation and in those having frequent exacerbations. Besides, high uric acid levels correlated with 30-day mortality, prolonged hospitalization, and more aggressive medical care in COPD patients with exacerbations (Bartziokas et al. 2014).

Recently, Di Stefano et al. reported lack of NLRP3 inflammasome activation, with no differences in caspase-1 activation, IL-1 beta, or IL-18 levels in bronchial biopsies or in BALF in patients with stable COPD compared with control subjects (Di Stefano et al. 2014).

6.3.3 Asthma

Asthma is another important lung disease, characterized by allergic reaction. Allergic inflammatory response in asthma is conventionally characterized by the activation of Th2 pathway. The importance of Th17 response has now been recognized (Table 6.6).

IL-1 Signaling Serum IL-1beta levels and expression of IL-1 beta in the bronchial epithelium and submucosal macrophages were higher in patients with asthma compared with control subjects (Thomas and Chhabra 2003; Sousa et al. 1996). In asthmatic patients, IL-1 beta concentrations in the sputum (Konno et al. 1996) and BALF (Broide et al. 1992) of symptomatic patients were significantly higher than that in asymptomatic subjects. BALF from patients with status asthmaticus had an elevated inflammatory activity due to the presence of excessive bioactive IL-1 beta (Tillie-Leblond et al. 1999). Hastie et al. stratified subjects by sputum granulocytes. Those patients with both increased eosinophils and neutrophils had the lowest lung function and increased symptoms. In this subset of patients, IL-1 beta level in the sputum was positively associated with neutrophil counts (Hastie et al. 2010).

In a mouse model, IL-1 beta combined with TNF alpha can contribute to airway hyperresponsiveness and methacholine-induced bronchoconstriction (Horiba et al. 2011). It was also reported that the ovalbumin-induced airway hypersensitivity response was significantly reduced in IL-1 alpha/beta-deficient mice whereas profoundly exacerbated in mice deficient in IL-1Ra, suggesting that IL-1 signaling was required for Th2 response (Nakae et al. 2003). In a model of mild asthma, IL-1R signaling was reported to be required, as eosinophilic inflammation and goblet cell hyperplasia were strongly reduced in $Il1r1^{-/-}$ mice. In contrast, the IL-1R was not required in an allergic model with adjuvant (Schmitz et al. 2003). Wang et al. applied a recombinant adenovirus expressing human IL-1ra in an ovalbumin-sensitized murine model of asthma. Single intranasal delivery before airway antigen challenge

Table 6.6 Articles containing discussion of inflammasomes in asthma

ID	Species	Design	Element	Contribution
Broide 1992	*Homo sapiens*	Ex vivo, BALF	IL-1 beta	Yes
Konno 1996	*Homo sapiens*	Ex vivo, sputum	IL-1 beta	Yes
Sousa 1996	*Homo sapiens*	Ex vivo, bronchial biopsies	IL-1 beta, IL-1Ra	Yes
Tillie-Leblond 1999	*Homo sapiens*	Ex vivo, BALF	IL-1 beta, IL-1Ra	Yes
Schmitz 2003	*Mus musculus*	In vivo, lung	IL-1R1	Conflicting
Thomas 2003	*Homo sapiens*	Ex vivo, blood	IL-1 beta	Yes
Wang 2006	*Mus musculus*	In vivo, lung; ex vivo, BALF	IL-1Ra	Yes
Idzko 2007	*Homo sapiens, Mus musculus*	Ex vivo, BALF	ATP	Yes
Hastie 2010	*Homo sapiens*	Ex vivo, sputum	IL-1 beta	Yes
Ather 2011	*Mus musculus*	In vivo, lung; in vitro, dendritic cell, macrophage	NLRP3, ASC, caspase-1, IL-1 beta	Yes
Besnard 2011	*Mus musculus*	In vivo, lung	NLRP3, ASC, caspase-1, IL-1 alpha, IL-1 beta, IL-1R	Yes
Horiba 2011	*Mus musculus*	In vivo, lung	IL-1 beta	Yes
Kool 2011	*Homo sapiens, Mus musculus*	In vivo, lung	NLRP3, IL-1 beta	No
Allen 2012	*Mus musculus*	In vivo, lung	NLRP3, IL-1 beta, IL-18	No
Martin 2013	*Mus musculus*	In vivo, lung	NLRP3, IL-1R	Conflicting
Kim 2014	*Homo sapiens, Mus musculus*	In vivo, lung, ex vivo, BALF; in vitro, epithelial cell	NLRP3, caspase-1, IL-1 beta, ROS	Yes

significantly decreased the severity of airway hyperresponsiveness, reduced pulmonary infiltration, and decreased peribronchial inflammation (Wang et al. 2006).

Inflammasome Activation Direct evidence showed that allergic airway inflammation depended on NLRP3 inflammasome activation, as Th2 lymphocyte activation and cytokine production were reduced in mice deficient in NLRP3, ASC, or caspase-1. The critical role of IL-1R1 signaling was also confirmed in mice deficient in IL-1R1, IL-1

beta, and IL-1 alpha (Besnard et al. 2011). Kim et al. recently demonstrated that levels of NLRP3 and caspase-1 in BALF from the patients with asthma were significantly higher than that in healthy subjects. Furthermore, suppression of mitochondrial ROS generation by NecroX-5 attenuated allergic airway inflammation associated with inhibition of NLRP3 inflammasome and caspase-1 activation in primary tracheal epithelial cells and mouse lung tissues. In addition, blockade of IL-1 beta substantially reduced airway inflammation and hyperresponsiveness in asthmatic mice (Kim et al. 2014). It has been shown that gain of function SNPs in human NLRP3 are linked to food-induced anaphylaxis and aspirin-induced asthma (Hitomi et al. 2009). In multiple asthmatic models of mixed Th2/Th17 responses, serum amyloid A activated NLRP3 inflammasome to induce IL-1 beta secretion in dendritic cells and macrophages and promote $CD4^+$ T cells to secrete IL-17A in an IL-1-dependent manner (Ather et al. 2011). Similarly but differently, Martin et al. reported the importance of caspase-1 and IL-1R, but not NLRP3, for Th17 development in NO_2-promoted allergic airway disease (Martin et al. 2013). Also, Allen et al. determined that the NLRP3 inflammasome was not required in multiple allergic asthma models in mice. Besides, in all the models, the cytokines IL-1 beta and IL-18 in the lung were below the level of detection (Allen et al. 2012). And Kool et al. suggested that NLRP3 and IL-1 beta did not contribute to the Th2 adjuvant effect of uric acid in mice (Kool et al. 2011).

Elevated ATP was found in the BALF of patients with asthma and ovalbumin-challenged asthmatic mice (Idzko et al. 2007). Consistently, P2X7R was found to be upregulated in acute and chronic asthmatic airway inflammation in mice and humans. Mice deficient in P2X7R or treated with specific P2X7R-antagonist had reduced airway inflammation in asthma models (Muller et al. 2011).

6.3.4 Fibrotic Lung Diseases

6.3.4.1 Idiopathic Pulmonary Fibrosis (IPF)

IPF is a progressive while irreversible disease, with a general poor prognosis. IPF is characterized by a histologic or radiologic pattern of usual interstitial pneumonia and progressive fibrosis of lung parenchyma. Bleomycin is a chemotherapeutic drug used clinically for a variety of human malignancies. However, a high dose of bleomycin can lead to lethal lung injury and pulmonary fibrosis in human patients, as well as in rodent models. Therefore rodent models of bleomycin-induced lung fibrosis have been widely used for the investigation of human IPF. Bleomycin-induced fibrosis is also discussed in this section. Table 6.7 listed the articles containing discussion of inflammasomes in IPF.

IL-1 Signaling Pan et al. observed that in IPF patients, cytokine IL-1 beta was positive in alveolar macrophages and type 2 pneumocytes in acute pulmonary fibrotic changes, but not in areas of old fibrosis, suggesting that IL-1 beta may play a role in the initial pulmonary fibrotic responses (Pan et al. 1996). In vitro study

found that alveolar macrophages from healthy human subjects released IL-1 beta after bleomycin challenge (Scheule et al. 1992).

With a single base variation at position +2018 of the IL-1Ra gene, there is an increased risk of developing cryptogenic fibrosing alveolitis (Whyte et al. 2000). Two other studies examining another polymorphism at intron 2 of the IL-1Ra gene found no association with increased susceptibility to IPF (Hutyrova et al. 2002; Riha et al. 2004).

Gasse et al. reported that in bleomycin-induced lung inflammation fibrosis depended on IL-1R1 signaling, as neutralization of IL-1 beta or specific blockage of IL-1R1 by antibody reduced bleomycin-induced pathology (Gasse et al. 2007). Overexpression of IL-1 beta for 7–10 days in rats was reported to induce an increase of TGF-beta in BALF and progressive interstitial fibrogenesis for the next 60 days, resembling human pulmonary fibrosis (Kolb et al. 2001). IL-1 beta was further reported sufficient to induce IL-17 production, required for inflammatory response to bleomycin (Wilson et al. 2010; Gasse et al. 2011).

Table 6.7 Articles containing discussion of inflammasomes in IPF

ID	Species	Design	Element	Contribution
Scheule 1992	*Homo sapiens*	In vitro, macrophage	IL-1 beta	Yes
Pan 1996	*Homo sapiens*	Ex vivo, lung tissue specimens	IL-1 beta	Conflicting
Whyte 2000	*Homo sapiens*	Ex vivo, lung biopsy	IL-1Ra	Yes
Kolb 2001	*Rattus norvegicus*	In vivo, lung; ex vivo, BALF	IL-1 beta	Yes
Kuwano 2001	*Mus musculus*	In vivo, lung	Caspase-1	Yes
Hutyrova 2002	*Homo sapiens*	Ex vivo, blood	IL-1Ra	No
Kitasato 2004	*Homo sapiens*	Ex vivo, lung tissue, serum, BALF	IL-18, IL-18R alpha	Yes
Riha 2004	*Homo sapiens*	Ex vivo, blood	IL-1Ra	No
Nakatani-Okuda 2005	*Mus musculus*	In vivo, lung	IL-18	Yes
Gasse 2007	*Mus musculus*	In vivo, lung	IL-1R1, IL-1 beta, ASC, IL-18	Conflicting
Gasse 2009	*Mus musculus*	In vivo, lung	NLRP3, caspase-1, IL-1 beta, IL-18, uric acid	Conflicting
Hoshino 2009	*Homo sapiens, Mus musculus*	Ex vivo, lung tissue; in vivo, lung, serum	IL-18, IL-18R alpha, IL-1 beta, caspase-1	Yes
Riteau et al. 2010	*Homo sapiens, Mus musculus*	In vivo, lung; ex vivo, BALF	ATP, P2X7R, IL-1 beta	Yes
Liu 2011	*Homo sapiens*	Ex vivo, serum, BALF	IL-18	No
Xu 2012	*Homo sapiens, Mus musculus*	In vivo, lung, in vitro, macrophage	NLRP3, caspase-1,	Yes

IL-18 Signaling Kitasato et al. reported elevated levels of IL-18 in the serum and BALF of patients with IPF and strongly expressed IL-18 and IL-18R alpha in the fibroblastic foci (Kitasato et al. 2004). Hoshino et al. reported excessive IL-18 and IL-18R alpha expression in the lungs of patients with bleomycin-induced lung injury. They also found that intravenous administration of bleomycin induced the expression of IL-1 beta and IL-18 in the serum and lungs of mice. Moreover, lung injury, assessed by fibrosis score, hydroxyproline levels, and wet lung weight, was significantly attenuated in mice deficient in caspase-1, IL-18, or IL-18R alpha (Hoshino et al. 2009).

However, Liu et al. failed to find an increase in serum and BALF levels of IL-18 in IPF patients (Liu et al. 2011). Il18−/− mice showed much worse lung injuries after treatment with bleomycin, as assessed by survival rate, histological images, and leukocyte infiltration. Besides, pretreatment with IL-18 before bleomycin instillation appeared to be protective in lung injuries (Nakatani-Okuda et al. 2005).

Inflammasome Activation Bleomycin-induced lung injury depended on NLRP3 inflammasome, as mice deficient in NLRP3 or caspase-1 displayed reduced neutrophil influx and IL-1 beta production in the lung. It was found that bleomycin-induced inflammasome activation is mediated by uric acid. Reduction of uric acid levels with inhibitor or uricase led to a decrease in IL-1 beta production, lung inflammation, and fibrosis. In addition, bleomycin-induced inflammation was IL-18-independent (Gasse et al. 2009). It has also been reported that mice lacking ASC had reduced neutrophil recruitment and a reduction in IL-1 beta production following bleomycin challenge (Gasse et al. 2007). Another example is from the research of statin. Numerous case reports suggested that statins could cause various types of interstitial lung diseases. Statin pretreatment enhances caspase-1-mediated responses in vivo and in vitro, which could be abolished in macrophages from mice deficient in NLRP3 (Xu et al. 2012).

The role of caspase-1 in bleomycin-induced lung injury has also been investigated. Kuwano et al. reported that bleomycin enhanced caspase-1 activity in addition to elevated expression in inflammatory cells. They also demonstrated that a pan-caspase inhibitor zVAD-FMK was able to attenuate bleomycin-induced lung injuries (Kuwano et al. 2001)

ATP levels were elevated in BALF from patients with IPF and from mice treated with bleomycin. Mice deficient in P2X7R or neutralized against ATP in the airways potently inhibit bleomycin-induced lung inflammation and remodeling (Riteau et al. 2010).

6.3.4.2 Cystic Fibrosis

Cystic fibrosis is caused by mutations of the cystic fibrosis transmembrane conductance regulator and is the most common autosomal recessive disorder in western countries. Patients with cystic fibrosis often experience recurrent and chronic infections with *Pseudomonas aeruginosa*, as well as *Staphylococcus aureus* and *Haemophilus influenzae* (discussed in Sect. 1.1.3).

Grassme et al. demonstrated the activation of caspase-1 and upregulation and membrane recruitment of ASC in the lungs of CF mice. These activations were associated with elevated levels of the signaling lipid-derived mediator, ceramide. Consistently, they also observed a normalization of IL-1 beta in the lungs after treatment with caspase-1 inhibitors (Grassme et al. 2014).

6.3.4.3 Silicosis

Crystalline silica is very common in occupational and environmental settings. Prolonged exposure in the workplace may lead to the development of silicosis, which is irreversible, progressive pulmonary fibrosis. Silica exposure is a high-priority public health concern. Alveolar macrophages, and their production of IL-1 beta, have been suggested to play a crucial role during the early inflammatory response after exposure to silica. Table 6.8 lists the articles containing discussion of inflammasomes in silicosis.

IL-1 Signaling Silica induced a release of IL-1 beta in human alveolar macrophages in a caspase-1-dependent manner (Iyer et al. 1996) and in the lungs of silica-exposed mice (Davis et al. 1998).

A polymorphism in IL-1Ra (+2018), but not IL-1 beta (+3953), was increased in a population of Caucasian coal miners with silicosis, indicating that this variant may confer susceptibility to developing silicosis (Yucesoy et al. 2001).

In addition, neutralizing IL-1 beta with monoclonal antibody reduced silica-induced inflammation and fibrosis by inhibiting mRNA expression of inflammatory and fibrogenic mediators (TGF beta, collagen I, and fibronectin) and modulating the Th1/Th2 balance toward a Th2-dominant response (Guo et al. 2013). The anti-fibrotic effect of inhibiting IL-1 beta was also reported by Piguet et al. where the administration of recombinant IL-1Ra reduced collagen deposition and the formation of fibrotic nodules in mice (Piguet et al. 1993). More directly, exposure of mice deficient in IL-1 beta to silica resulted in reduced lung inflammation, apoptosis, and significantly smaller silicotic lesions than in wild-type mice over a 12 weeks course (Srivastava et al. 2002).

Inflammasome Activation Stimulation of macrophages with silica resulted in the secretion of IL-1 beta and IL-18 in an inflammasome-dependent manner, as macrophages deficient in NLRP3, ASC, or caspase-1 all displayed a marked defect in their ability to secrete cytokines. They also found that activation of the NLRP3 inflammasome by silica required both a K^+ efflux and the generation of ROS (Cassel et al. 2008). Similarly, NLRP3 inflammasome activation was triggered by ROS generated by NADPH oxidase. In a model of asbestos inhalation, $Nalp3^{-/-}$ mice showed diminished recruitment of inflammatory cells to the lungs, paralleled by lower cytokine production (Dostert et al. 2008). Hornung et al. demonstrated that silica activated caspase-1 and induced the release of mature IL-1 beta in human PBMCs. IL-1 mediated the neutrophil influx after exposure to silica crystals. The phagocytosis of silica by macrophages resulted in lysosomal destabilization and

Table 6.8 Articles containing discussion of inflammasomes in silicosis

ID	Species	Design	Element	Contribution
Piguet 1993	*Mus musculus*	In vivo, lung	IL-1 beta	Yes
Iyer 1996	*Homo sapiens*	In vitro, macrophage	IL-1 beta	Yes
Davis 1998	*Mus musculus*	In vivo, lung	IL-1 beta	Yes
Yucesoy 2001	*Homo sapiens*	Ex vivo, lung tissue	IL-1Ra, IL-1 beta	Conflicting
Srivastava 2002	*Mus musculus*	In vivo, lung	IL-1 beta	Yes
Cassel 2008	*Mus musculus*	In vitro, macrophage	NLRP3, ASC, caspase-1, IL-1 beta, IL-18, K^+ efflux, ROS	Yes
Dostert 2008	*Homo sapiens, Mus musculus*	In vitro, macrophage	NLRP3, ASC, caspase-1, IL-1 beta, ROS, NADPH	Yes
Hornung 2008	*Homo sapiens, Mus musculus*	In vitro, macrophage	NLRP3, caspase-1, IL-1 beta, lysosomal destabilization	Yes
Ji 2012	*Homo sapiens*	Ex vivo, blood	NLRP3	Yes
Riteau 2012	*Homo sapiens, Mus musculus*	In vitro, macrophage	NLRP3, IL-1 beta, ATP, P2X7R	Yes
Guo 2013	*Mus musculus*	In vivo, lung	IL-1 beta	Yes
Peeters 2013	*Homo sapiens*	In vitro, epithelial cell	NLRP3, caspase-1, IL-1 beta	Yes
Moncao-Ribeiro 2014	*Mus musculus*	In vitro, macrophage	IL-1 beta, P2X7R	Yes

subsequent rupture releasing proteolytic enzymes, such as cathepsin B into the cytosol, and the activation of the NLRP3 inflammasome (Hornung et al. 2008). In a case-control study, Ji et al. found that an SNP in the NLRP3 gene (rs1539019) was associated with a significant increase in coal workers pneumoconiosis in a Chinese population. This association was more pronounced in patients with stage I disease suggesting a potential role for the NLRP3 inflammasome in the development of silicosis (Ji et al. 2012). NLPR3 activation has also been reported in nonmyeloid cells. NLRP3 activation, as well as activation of caspase-1, led to maturation and secretion of IL-1 beta in human bronchial epithelial cell lines and primary human bronchial epithelial cells (Peeters et al. 2013).

ATP was released by macrophages after exposure to silica. The activation of the NLRP3 inflammasome relied on purinergic receptors and pannexin/connexin hemichannels. The use of specific P2X7 receptor inhibitors, or abrogation of ATP in primed human monocytic cell lines, was able to prevent silica-induced IL-1 beta production (Riteau et al. 2012). This was further manifested in P2X7R knockout mice. Inflammatory cell infiltration and collagen deposition, cell apoptosis, and

NF-κB activation as well as TGF-beta, nitric oxide, ROS, and IL-1 beta secretion were reduced in knockout mice (Moncao-Ribeiro et al. 2014).

6.3.4.4 Asbestosis

Similar to silicosis, asbestosis often occurs as an occupational disease, particularly in developing countries. The inhalation of asbestos can also lead to lung cancer, mesothelioma, and pleural diseases. The articles containing discussion of inflammasomes in asbestosis are summarized in Table 6.9.

IL-1 Signaling Cells recovered in BALF or alveolar macrophages from patients with asbestosis were reported to release higher levels of IL-1 beta in comparison with control groups (Zhang et al. 1993; Perkins et al. 1993). In vivo models also demonstrated that asbestos exposure can result in enhanced IL-1 beta secretion in BALF (Haegens et al. 2007).

Inflammasome Activation Hillegass et al. reported that asbestos exposure was associated with an increase in NLRP3 expression and caspase-1 activation in mesothelial cells, leading to secreted IL-1 beta and IL-18, which could be attenuated by downregulation of NLRP3. They also reported that asbestos challenge had no significant effect on the NLRP1 or AIM2 inflammasomes (Hillegass et al. 2013). Girardelli et al. reported that in a cohort of Italian patients with asbestos-induced mesothelioma, SNPs in the NLRP1, but not NLRP3 gene, may be associated with the disease (Girardelli et al. 2012). Furthermore, $Nlrp3^{-/-}$ mice were reported to have defects in IL-1 beta secretion and immune cell recruitment following asbestos exposure. However, NLRP3 was not critical in the chronic development of asbestos-induced mesothelioma, as a similar incidence of malignant mesothelioma in knockout mice (Chow et al. 2012).

Table 6.9 Articles containing discussion of inflammasome in asbestosis

ID	Species	Design	Element	Contribution
Perkins 1993	*Homo sapiens*	In vitro, alveolar macrophage	IL-1 beta	Yes
Zhang 1993	*Homo sapiens*	In vitro, BALF cells	IL-1 beta	Yes
Haegens 2007	*Mus musculus*	In vivo, lung, BALF	IL-1 beta	Yes
Chow 2012	*Mus musculus*	In vivo, lung	NLRP3, IL-1 beta	Conflicting
Girardelli 2012	*Mus musculus*	In vitro, macrophage	IL-1 beta, P2X7R	Yes
Hillegass 2013	*Homo sapiens, Mus musculus*	In vitro, mesothelial cells	NLRP3, caspase-1, IL-1 beta, IL-18, NLRP1, AIM2	Conflicting

Table 6.10 Articles containing discussion of inflammasomes in pulmonary hypertension

ID	Species	Design	Element	Contribution
Villegas 2013	*Mus musculus*	In vivo, lung	NLRP3, caspase-1, IL-1 beta, IL-18	Yes
Cero 2015	*Mus musculus*	In vivo, lung	NLRP3, ASC, IL-1 beta, IL-18	Conflicting

6.3.5 Pulmonary Hypertension

Pulmonary hypertension is characterized by sustained elevation of the pulmonary arterial pressure (>25 mm Hg). Prolonged high pressure in pulmonary artery system may lead to right ventricular failure. Table 6.10 lists the studies on inflammasomes in pulmonary hypertension.

In a mice model, hypoxia exposure caused pulmonary hypertension, including increased right ventricular systolic pressure and pulmonary vascular remodeling, along with activation of the NLRP3 inflammasome and caspase-1, as well as IL-1 beta and IL-18 production. These effects could be reversed with a superoxide dismutase mimetic (Villegas et al. 2013). In another study, $Asc^{-/-}$ mice, but not $Nlrp3^{-/-}$, mice were resistant to hypoxia-induced pulmonary hypertension, as evidenced by no significant changes in levels of caspase-1, IL-18, or IL-1 beta, reduced right ventricular systolic pressure and reduced pulmonary vascular remodeling, indicating the possible involvement of alternate inflammasome complexes involving ASC (Cero et al. 2015).

6.4 Conclusion

Inflammasomes have emerged as an important regulator of the innate immune system and have significantly affected the understanding of the pathogenesis of many diseases. In this chapter, we reviewed the evidence of inflammasome-related components in the progression of pulmonary diseases. We can easily appreciate how the discovery of the inflammasome affects our understanding of the role of IL-1 and IL-18 signaling in lung disease. Still, in some diseases, the importance of inflammasomes has not been fully investigated. Besides, NLRP3 inflammasome in macrophage is currently the most clearly defined type. The potential of other inflammasomes in nonmyeloid cells needs to be further studied in the process of injury and recovery in lung diseases.

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