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Inflammasome Activity in Non-Microbial Lung Inflammation

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Abstract

The understanding of interleukin-1 (IL-1) family cytokines in inflammatory disease has rapidly developed, due in part to the discovery and characterization of inflammasomes, which are multi-subunit intracellular protein scaffolds principally enabling recognition of a myriad of cellular stimuli, leading to the activation of caspase-1 and the processing of IL-1β and IL-18. Studies continue to elucidate the role of inflammasomes in immune responses induced by both microbes and environmental factors. This review focuses on the current understanding of inflammasome activity in the lung, with particular focus on the non-microbial instigators of inflammasome activation, including inhaled antigens, oxidants, cigarette smoke, diesel exhaust particles, mineral fibers, and engineered nanomaterials, as well as exposure to trauma and pre-existing inflammatory conditions such as metabolic syndrome. Inflammasome activity in these sterile inflammatory states contribute to diseases including asthma, chronic obstructive disease, acute lung injury, ventilator-induced lung injury, pulmonary fibrosis, and lung cancer.

Keywords

IL-1; IL-18; inflammasome; lung; inflammation

Inflammasome nomenclature and activation

The intracellular class of receptors named Nucleotide Oligomerization Domain (NOD)-Like Receptors (NLRs) was first identified a decade ago.[1] They possess a common structure, including a C terminal leucine-rich repeat domain, an internal NACHT (or “NAIP”, neuronal apoptosis inhibitory protein), and an N terminal effector domain that can be either a Caspase Activation and Recruitment Domain (CARD), a Pyrin domain (PYD), or a Baculovirus Inhibitor of apoptosis protein Repeat domain (BIR).[2] Based on their homology to the disease resistance plant R proteins, it was initially hypothesized that NLRs participated in the process of apoptosis (which they do), but studies soon revealed that they were in fact pattern recognition receptors (PRRs) that modulated inflammatory responses to a variety of stimuli. Homophilic intramolecular interaction between the CARD or PYD components of the NLRs, in some cases through the adaptor molecule ASC that contains

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both a PYD and a CARD, facilitates the assembly of macromolecular complexes of these proteins.[3,4]

Many of the NLRs were determined to act as scaffolds for the assembly of a complex of caspase-1 activating proteins termed 'the inflammasome', which ultimately functioned to activate members of the pro-inflammatory IL-1 family of cytokines, IL-1β and IL-18.[3] Whereas IL-1β is required for the host response to infection,[5] a pathogenic role for IL-1β has also been implicated in a variety of inflammatory diseases,[6,7] including Muckle-Wells syndrome,[8,9] multiple sclerosis,[10,11] atherosclerosis,[12] rheumatoid arthritis,[13] gout,[14] diabetes,[15] Alzheimer's disease,[16,17] and others. More recently, the emerging role for IL-1β as a T_H17-polarizing cytokine[18] has become of great interest in the field of allergy and asthma. We[19,20] and others[21] have demonstrated IL-1 signaling to be critical in a number of T_H17-asthma models in mice. Although less is understood about IL-18 besides its involvement in NK cell activation and the promotion of T_H1 responses,[22,23] IL-18 has also been recognized as a potent pro-inflammatory cytokine participating in host defense and, in the absence of IL-12, can also enhance T_H2 responses in allergic airway disease models.[24] Unlike many other inflammatory cytokines, IL-1β and IL-18 require enzymatic cleavage from a pro-form to a truncated form in order to be secreted from the cell and function extracellularly.[22]

As of the time of this writing, 23 NLRs have been identified in humans, whereas 34 have been identified in mice.[25] At least two classes of inflammasomes have been described: those that contain an NLR (nucleotide-binding-and-oligomerization domain (NOD) and leucine-rich-repeat-containing) family member domain, and those that contain a PYHIN (pyrin domain (PYD) and HIN-domain containing) family member domain.[25] Leucine-rich repeat (LRR) domains in the NLR molecules have been proposed to facilitate interaction with ligands, as these domains may do in Toll-Like Receptors (TLRs), although the experimental evidence for direct interactions remains to be presented (see ref [26]).

In the lung, NLRP1, NLRP3, NLRP12, NLRC4, and AIM2 have been studied (Fig. 1). NLRP1 was the first to be identified and was found to be the crucial recognition molecule for anthrax lethal toxin.[27] Close on the heels of this discovery came reports implicating NLRP3 activation as the mechanism for which the adjuvant Aluminum hydroxide (Alum) functions to induce inflammation and initiate adaptive immune responses,[28–30] although NLRP3 activation was described as dispensable for immunoglobulin production.[31] More recent studies, however, have questioned this mechanism and ultimately NLRP3 was found to be dispensable[32] for allergic asthma pathogenesis using Alum as an adjuvant along with the soluble protein antigen ovalbumin (OVA).

Studies of lung infection have also revealed the important role of NLRs. Geddes *et al*. first described NLRC4 (IPAF, CARD12), which unlike NLRP3 contains its own CARD domain and therefore does not require ASC to bind to Caspase-1.[33] NLRC4 acts as the intracellular sensor for flagellin and is a key modulator of Gram-negative bacterial infection in the lung.[34] The PYHIN domain-containing inflammasomes, AIM2 and IFI16, are unique in that they bind directly to double stranded DNA from cytosolic viruses and bacteria via the HIN200 (hematopoietic expression, interferon-inducibility, nuclear localization, and a

characteristic 200 amino acid sequence) domain. Most recently, the role of NLRP12 was characterized in the Alum/OVA and house dust mite (HDM) mouse models of allergic sensitization, in which it was determined not to play a critical role in the development of T_H2 lung disease.[35]

Ultimately, studies of inflammasome activation in response to adjuvants and microbial products led to a better understanding of the intracellular conditions and endogenous damage-associated molecular patterns (DAMPs) that were directly responsible for inflammasome assembly and activation. Currently, these known mechanisms include induction of reactive oxygen species (ROS), changes in ion influx/efflux from the cell (K^+, Ca^{++}), and leakage of lysosomal contents, especially the cathepsin family of proteases (reviewed in ref[36]). These particular events are not unique to microbial or viral infections, but can also be triggered by inhaled nanomaterials and environmental pollutants, as well as endogenous insults, thereby contributing to lung disease.[37] As the microbial and viral components that stimulate inflammasome activation have been reviewed elsewhere,[38] this review will focus on the participation of inflammasomes in the pulmonary response to non-microbial molecules of both environmental and endogenous origin.

The lung is part of the interface between our bodies and the world around us, and as such comprises the first line of defense against inhaled material. Studies have identified expression of NLRP3 and caspase-1 in human airway epithelial bronchus and primary cells,[39] and IL-1β secretion from these cells has been reported in asthma,[37] acute lung injury,[40] chronic obstructive pulmonary disease (COPD),[37] and certain lung cancers.[41] In addition, recent work has identified both IL-1β and its constitutively expressed homolog IL-1α as being involved in collagen deposition and fibrosis.[42]

Asthma and models of allergic airway disease

Whereas studies investigating NLRP3 and caspase-1 in human asthma are limited,[37] gain of function single nucleotide polymorphisms in human NLRP3 have been linked to aspirin-induced asthma.[43,44] Furthermore, gene analysis studies have identified NOD1 as an asthma susceptibility gene in humans and mice.[43] Clinical data also support a role for IL-1R signaling in asthma. For example, IL-1β is elevated in lavage fluid from patients with status asthmaticus and in sputum from patients with neutrophilic asthma.[45–47] Likewise, production of IL-1β by submucosal macrophages is increased in the bronchial biopsies of asthmatics in comparison to healthy control subjects.[48,49]

IL-1β can directly and indirectly impact the pathogenesis of asthma. In mouse models, IL-1β can contribute to airway methacholine hyperresponsiveness[50] and airway neutrophilia,[51] and can thus contribute directly to the pathogenesis of asthma. In addition, evidence from *in vitro* and *in vivo* studies implicates a requirement for IL-1R signaling in the development and function of T_H17 responses.[52–55] In a model of pulmonary fibrosis, the instillation of IL-1β into the airway is sufficient to induce IL-17 production upon restimulation of cells from lymph nodes draining the lungs, and IL-17 is required for airway inflammation and the development of lung pathology.[56,57] Furthermore, NLRP3 knock-in mice carrying a point mutation commonly found in patients with Muckle Wells Syndrome exhibit a gain of

function phenotype with increased IL-1β production and a predominantly T_H17 inflammation.[58]

The T_H17 adaptive immune response has been linked with neutrophilic, glucocorticoid-resistant asthma in humans and is correlated with disease severity.[59–61] *In vitro* and *in vivo* data have supported a causal role for the T_H17 response in glucocorticoid resistance.[62–64] Additional studies suggest that IL-1R signaling can synergize with IL-17 in the modulation of chemokine release from human bronchial epithelial cells and can impact glucocorticoid responsiveness.[65,66] Given IL-1R's critical role in T_H17 development[52] and IL-1β's wide-ranging involvement in acute inflammatory processes, it seems that inflammasome activity is likely to be involved in at least some subset(s) of asthma. While the contribution of an inflammasome to T_H17 development has not been extensively studied in the lung, the NLRP3-IL-1R-T_H17 axis has been explicitly hypothesized to contribute to allergic airway disease pathogenesis.[67]

In models of allergic asthma using OVA as a soluble protein antigen, the role of IL-1R signaling and NLRP3 activation has been debated. In an Alum/OVA model of allergic airway disease, the IL-1R was not required for eosinophilic airway inflammation, antibody responses to OVA antigen, or the proliferation of $CD4^+$ T-cells in the mediastinal lymph node (MLN) following antigen challenge.[68] In contrast, IL-1R signaling was required in an Alum-independent sensitizing scheme that involved multiple intraperitoneal (i.p.) injections of OVA at sensitization.[68] Similarly, genetic deficiency in both IL-1α and IL-1β resulted in diminished antibody responses to antigen, decreased proliferation of cells in the draining lymph node, and decreased production of the T_H2 cytokines IL-4 and IL-5 upon restimulation in the presence of antigen.[69] Similar to other Alum-independent sensitizing schemes, sensitization via subcutaneous (s.q.) injection of OVA required IL-1α, IL-1β, and the IL-1R for airway inflammation and MLN production of T_H2 cytokines upon *in vitro* restimulation with OVA.[70] In general, IL-1R signaling is required in the absence of Alum.

The requirement for IL-1R signaling and IL-1β in these models suggests a potential role for an inflammasome. A recent study tested the requirement for NLRP3 for sensitization in Alum/OVA and i.p. injection of OVA in the absence of Alum and determined that the NLRP3 inflammasome was not required.[32] These results further substantiate that IL-1R is unnecessary in the Alum/OVA model of allergic airway disease. However, whereas IL-1R signaling was required in the i.p. OVA method of allergic sensitization, pulmonary inflammation was independent of NLRP3 in this model.[32] This result contrasts with the s.q. model of OVA injection (see Table I), wherein NLRP3 was required for T_H2 cytokine, chemokine, and IL-1β production at antigen challenge.[70] Additional studies will determine whether the role for NLRP3 depends simply upon route of sensitization or, as is more likely, other factors. Furthermore, the absence of a role for NLRP3 in pulmonary inflammation does not rule out a potential contribution of caspase-1 and other non-NLRP3 inflammasomes in activating IL-1β. Another potential mediator of IL-1R-independent sensitization in the lung is uric acid (UA). Allergic sensitization with Alum requires UA as a downstream mediator of inflammation, and *in vivo* sensitizing effects of UA in the generation of allergic airway disease do not require IL-1R, NLRP3, or caspase-1.[71,72]

House dust mite-induced allergic airway disease

There is an emerging body of literature exploring the mechanisms through which the common allergens present in HDM extracts participate in allergic sensitization and the pathogenesis of asthma.[73–76] The extracts (containing whole mite and their own commensal microbiota) from two predominant species of house dust mite, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, have been extensively studied *in vitro* and *in vivo*.[77] Extracts from both *D. pteronyssinus* and *D. farina*e can induce caspase-1 activation and IL-1β release from primary human keratinocytes, activities which require NLRP3.[78] Further, this report also suggests that NLRP3 activation by HDM requires the proteolytic activities of the mite proteins, rather than ROS generation.[78]

In additional studies with HDM, the IL-1R was required for cytokine production by MLN cells restimulated in the presence of antigen following antigen challenge, including IL-17A and the T_H2 cytokines IL-5, IL-10, and IL-13.[72] Whereas NLRP3, caspase-1, and IL-1β are not required, HDM-promoted allergic airway disease requires IL-1α and IL-33 signaling at the time of allergic sensitization, and not at challenge, for eosinophil recruitment into the airway.[71,72] IL-1α release from HDM-stimulated airway epithelium initiates an autocrine pathway to induce T_H2 polarization and allergic airway disease.[72] These findings validate earlier reports that neither the NLRP3 nor the NLRP12 inflammasome contribute to HDM-promoted allergic airway inflammation.[32,35,71] These data also suggest a role for IL-1α in inflammasome-independent IL-1R signaling in other models of allergic airway disease, such as those utilizing OVA injection in the absence of Alum (refer to Table 1).[32] In addition, HDM requires UA as a downstream mediator of allergic sensitization in the airway, and UA's sensitizing effects are independent of an inflammasome.[71]

Reactive oxygen and nitrogen species

Numerous studies of inflammasome regulation indicate that changes in the redox environment, including increases in the production of reactive oxygen and nitrogen species (ROS and RNS) of a cell, can modulate assembly and activation of the NLRP3 inflammasome.[79–82] Much of these studies have been performed in macrophages, in which basal expression of NLRP3 is very low under homeostatic conditions, but upregulated strongly in response to stimulation with, for example, TLR agonists.[83] Many stimuli that activate the NLRP3 inflammasome also induce the cellular production of ROS. For instance, treatment of macrophages with ATP, an agonist of the P2X7 receptor, results in production of ROS and activation of cell signaling pathways that promote both adaptation to subsequent exposure to oxidants or inflammation, and processing and secretion of proinflammatory cytokines.[84] More recently, it was demonstrated[85] that NLRP3 can be directly regulated by thioredoxin inhibitory protein (TXNIP), which itself modulates activity of the intracellular antioxidant protein thioredoxin (TRX). In resting cells, TXNIP interacts with TRX and is therefore unable to activate NLRP3. Upon oxidative stress, TXNIP is released from oxidized TRX and in turn directly binds the leucine-rich region of NLRP3 leading to inflammasome assembly and activation.

Furthermore, stimulation of P2X7, a potent activator of NLRP3, is accompanied by ROS generation from NADPH oxidases.[84,86] Studies using antioxidants support a model in which ROS production induced by NLRP3 agonists induce the assembly of the inflammasome complex.[87] Nonetheless, studies performed with mononuclear phagocytes from patients with chronic granulomatous disease, in which a mutation of the $p47^{phox}$ subunit of NADPH oxidase renders the enzyme complex inactive, reported robust IL-1β secretion despite an inability of these cells to generate NADPH oxidase-dependent ROS.[88,89] Since NADPH oxidase is not the sole source of cellular ROS, the importance of mitochondrial-derived ROS has been recently explored. Mitochondria are the primary source of ROS under physiological conditions, and cellular stress, such as increases in metabolic rate, hypoxia, or cellular disruption, induce the mitochondria to generate increased amounts of ROS.[90] Inhibition of critical respiratory chain enzymes promotes mitochondrial ROS generation and induces NLRP3 inflammasome activation.[91] We have recently reported that uncoupling mitochondrial oxidative phosphorylation enhances NLRP3 activation by preventing disassembly of the NLRP3 complex.[82]

Mice exposed to ozone require NLRP3, ASC, and caspase-1 to develop airways hyperresponsiveness (AHR), and also partially require these components for inflammation.[92] In addition, NLRP3 can be suppressed or activated, depending on the redox environment. The role of ROS in inflammasome modulation depends on the stimuli, the cell type, dose of ROS inhibitor utilized, basal redox status, and timing of the changes in redox status.[80,93,94] Several studies have implicated interferon-induced nitric oxide[83] as a key player that, via S-nitrosylation, can inhibit assembly of the NLRP3 inflammasome.[83,95]

Additionally, ROS have the ability to directly affect gene regulation, for instance in the case of the transcription factor nuclear erythroid 2 p45-related factor 2 (Nrf2), which regulates expression of important antioxidant enzymes.[96] Recent studies have demonstrated that Nrf2 exacerbates mouse models of atherosclerosis, and is required for the NLRP3-dependent induction of IL-1 in response to cholesterol crystals.[97] Much has also been written regarding the redox control of the transcription factor NF-κB,[79,98] which can control the gene induction of pro-IL-1β [99] and can be regulated by interactions with ASC.[100] The multitude of targets of ROS/RNS ensure that there will be overlap of inflammation control by the inflammasome and transcription factors involved in the inflammatory/antioxidant response. Overall, the mechanisms of ROS involvement in NLRP3 inflammasome activation remain the subject of intense scrutiny.

Nitrogen dioxide-promoted allergic airway disease

Another model that permits study of the impact that changes in the redox environment exert in the lung is the direct exposure of mice to nitrogen dioxide (NO_2) for a short period of time, which results in substantial generation of ROS and other RNS, along with epithelial injury.[79,101,102] Exposure to NO_2 has been positively correlated with asthma severity, disease exacerbation, and risk of death.[103,104] NO_2 has also been implicated in asthma development in previously healthy children.[105] In addition to being an environmental pollutant and a toxic byproduct of combustion,[106] NO_2 can also be generated endogenously,

such as during respiratory viral infections, severe cases of which are also positively correlated with the development of asthma in children.[107]

Exposure to high concentrations of NO_2 can cause acute lung injury, whereas a brief 1-hour exposure at a low concentration (in the presence of OVA antigen) is capable of sensitizing mice to the innocuous inhaled antigen OVA.[108,109] Following antigen challenge, this sensitizing scheme induces methacholine hyperresponsiveness, elevates antigen-specific IgG1 and IgE levels, recruits inflammatory cells to the airway, and promotes T_H2 and T_H17 cytokine production upon *in vitro* restimulation of $CD4^+$ splenic T-cells in the presence of OVA-presenting APCs from antigen-naïve mice.[108,110] Importantly, acute exposure to NO_2 promotes the production of IL-1β, as well as other pro-inflammatory cytokines, from $CD11c^+$ cells *ex vivo*, implicating a role for inflammasome activation at the time of sensitization.[110] Our group has recently reported the importance of caspase-1 and IL-1R, but not NLRP3, for T_H17 development in NO_2-promoted allergic airway disease.[20]

As in other models of RNS- and ROS-induced epithelial injury, exposure to NO_2 results in rapid activation of NF-κB in airway epithelium,[108] which along with OVA inhalation is sufficient to allergically sensitize mice to antigen [111]. These findings identify NF-κB activation as a downstream component of NO_2-promoted sensitization. Furthermore, constitutively active NF-κB induces a mixed T_H2/T_H17 adaptive immune response at the time of antigen challenge, similar to that observed in NO_2-promoted allergic airway disease.[111,112] Constitutively active NF-κB, NO_2 exposure, and LPS inhalation (which also promotes a mixed T_H2/T_H17 immune response), upregulate the acute phase response protein Serum Amyloid A3 (SAA3) in the lung.[19,107] Importantly, like IL-17, SAA is also an asthma biomarker in humans.[59–61,113] Inhalational administration of recombinant apoSAA to mice also induces the upregulation of *Saa3* in the lung, sensitizes mice to OVA antigen, and generates a mixed T_H2/T_H17 immune response following antigen challenge.[19] Thus, SAA3 is a candidate downstream mediator of allergic sensitization in multiple T_H17-inducing sensitization schemes, including NO_2-promoted allergic airway disease.[19]

Using recombinant apoSAA, we have reported that IL-1R signaling is required for the T_H17 response elicited during apoSAA-promoted allergen sensitization.[19] NLRP3 and caspase-1 were required for *in vitro* IL-1β production upon exposure to apoSAA, as well as *in vivo* pulmonary inflammation and IL-1β production resulting from acute apoSAA exposure.[19] Similar to other endogenous DAMPs,[114,115] we believe that endogenous SAA may provide a danger signal that culminates in the formation of the NLRP3/caspase-1 inflammasome and activation of IL-1β. Additional studies using *Saa3*-genetically modified mice will elucidate the contribution of endogenous SAA3 to the pathogenesis of allergic airway disease.

Cigarette smoke

Cigarette smoking greatly increases the risk for lung diseases, including asthma, emphysema, COPD,[116] and cancer,[117] and also increases the lung's susceptibility to bacterial and viral infections.[118] Models of cigarette smoke (CS) exposure have implicated IL-1 as a critical inflammatory cytokine in the pathological response. The airway neutrophilia that accompanies cigarette smoke inhalation is temporarily accompanied by

increases in cleaved caspase-1, as well as IL-1β and IL-18 secretion.[119] Further studies have suggested that, though the immune response to CS is dependent upon IL-1 receptor (IL-1R) signaling,[120] as well as the P2X7 receptor and caspase-1[119], it may not require NLRP3/caspase-1 cleavage of IL-1β.[121] It is also of note that mouse models of COPD due to chronic cigarette smoke exposure have recently demonstrated increases in T_H17 cells and IL-17A/F levels,[122,123] indicating another causal role for the IL-1-T_H17 axis in lung disease.

Another component of cigarette smoke exposure, the α,β-unsaturated aldehyde acrolein, is elevated in the lungs of COPD patients.[116] The effects of acrolein in the lung are mediated through its ability to recruit neutrophils and promote their survival,[124] inhibit macrophage phagocytosis, and suppress NF-κB activation, leading to downstream decreases in IL-1β and impaired bacterial and viral clearance.[125] In addition, a microarray study of mouse lungs treated with acrolein demonstrated strong upregulation of the IL-18 receptor gene, *Il18r1*.[126] IL-18 signaling has previously been demonstrated to be critical in the response of pulmonary macrophages to cigarette smoke.[127] A recent study suggests some functional overlap between IL-1β and IL-18, including the induction of IL-17 production by $CD4^+$ and γδ T-cells *in vitro*.[128] IL-18 may also provide a critical signal in IL-1R-dependent signaling by promoting the expression of IL-1β.[128] Taken together, these data suggest a possible role for individual chemical components of cigarette smoking to act as triggers for the inflammasome, though as of yet no studies have implicated any of the inflammasomes specifically.

Long-term exposure to tobacco smoke accounts for 80–90% of lung cancers, so it is not surprising that inflammasomes, which may be activated in response to cigarette smoke, may also be implicated in the pathogenesis of lung cancer. However, inflammasomes are also likely to participate in lung carcinogenesis from other causes. Chow *et al*. examined the role of NLRP3 in natural killer (NK) cell-mediated control of tumor initiation, growth, and metastasis, using a model of methylcholanthrene (MCA)-induced sarcoma and B16F10 experimental metastases.[129] They found that NLRP3 is required for NK-mediated control of MCA-induced cancer and experimental primary tumor growth. Specifically, loss of NLRP3 caused intratumoral accumulation of $CD11b^+Gr\text{-}1^{int}$ myeloid cells that promoted NK-cell anti-metastatic function by secreting the NK cell chemokines CCL5 and CXCL9. Tumor incidence was reduced in NLRP3−/− mice; however, NLRP3 may not be the only inflammasome complex involved, as caspase-1−/− and IL-1R1−/− mice were also resistant to tumors. NK cells do not express NLRP3 themselves, indicating that loss of NLRP3 in a secondary cell type would be the primary influence upon NK cells. Additionally, NK cells are defective in IL-18−/− mice, as IL-18 is required for NK priming and proper NK production of IFN-γ.[130] Interestingly, it was recently reported that chemotherapy used to treat tumors can induce NLRP3-dependent IL-1β production in myeloid-derived suppressor cells, promoting IL-17 production from $CD4^+$ T cells, and diminishing the anti-cancer efficiency of the chemotherapeutics.[131]

Diesel exhaust particles (DEP)

Diesel exhaust is comprised of gaseous and particulate components that vary depending on engine type, duty cycle, and fuel source. Loss of glutathione S-transferase M1 (GSTM1), an

important cellular antioxidant enzyme (reviewed in ref[132]), exacerbates DEP-induced airway inflammation and increases the levels of IL-1β.[133] In addition, the previously mentioned redox-sensitive transcription factor, Nrf2, has been shown to play a key role in modulating the anti-oxidant response to DEP, with Nrf2−/− mice demonstrating an increased susceptibility to low-dose DEP exposure. Subsequently, these mice develop exacerbated allergic airway disease in an Alum/OVA model.[134] These data implicate a role for oxidative stress as a mediator of DEP-induced pulmonary inflammation, but do not address whether an inflammasome participates in IL-1β activation. Following exposure to DEP, mice genetically deficient in either NLRP3 or caspase-1 had similar levels of BAL IL-1β in comparison to wildtype mice, whereas another inflammasome-dependent cytokine, IL-18, was decreased [135]. Attempts to explain this dichotomy have focused on neutrophil proteases. Neutrophils recruited into the airways in response to DEP show increases in neutrophil elastase, proteinase-3, and cathepsin G,[135] molecules that are also able to cleave IL-1 family members into biologically active forms. Similar to a mouse model of IL-1β-dependent arthritis, in which inhibition of elastase resulted in less IL-1β and lower disease scores,[136] neutrophil-derived enzymes, not inflammasome-dependent caspase-1 activity, are thought to be the critical proteases for IL-1β cleavage in DEP-induced inflammation.[135]

Silicosis and asbestosis

Inhalation of silica and asbestos particles induce pulmonary inflammation, fibrosis, and, in their most pathogenic forms, cancer in the form of mesothelioma. The role of NLRP3 in pulmonary fibrosis has been recently reviewed.[42] Both NLRP1 and NLRP3 have been implicated as intracellular sensors of asbestos exposure; NLRP1 as a regulator of survival/apoptosis following exposure, and NLRP3 as the inducer of inflammation and IL-1β secretion.[137] Interestingly, whereas NLRP3 signaling has been reported to regulate inflammation in response to asbestos, several studies have now indicated that it does not control asbestos-induced cancers. NLRP3−/− mice have defects in IL-1β secretion and immune cell recruitment following asbestos exposure, however, they have a similar incidence of malignant mesothelioma (MM) as wild type mice.[138] Furthermore, studies of patients suffering from asbestos-induced MM indicate that there may be a higher incidence of single nucleotide polymorphisms (SNPs) in NLRP1, but not NLRP3.[137]

The inflammatory and fibrotic responses seen in silica challenge both require NLRP3,[139,140] however reports conflict on the mechanism of inflammasome activation. Dostert *et al*. reported that for both inflammation and fibrotic changes, the (redox) environment is critical. In macrophages, frustrated phagocytosis of asbestos fibers leads to NADPH oxidase-dependent ROS generation that is critical for NLRP3 activation, as was determined by treating THP-1 cells with shRNA for p22phox.[86] Conversely, studies performed by Hornung *et al*. using bone marrow-derived macrophages from gp91phox knockout mice, which lack proper NADPH-oxidase activity and superoxide production, demonstrated normal responses to silica crystal exposure.[141] One possible explanation may lie in the differential redox status of transformed cell lines versus primary mouse cells as was discussed in a recent review of the literature.[80] In addition, timing of ROS production may determine the outcome, as ROS overproduction has multiple effects beyond inflammasome activation.[93]

Engineered nanomaterials

Engineered nanomaterials (commonly referred to as nanoparticles) are widely used in the manufacture of numerous commercial products, including cosmetics, paint, paper, food, and in biomedical applications. While originally thought to be too small to cause a cellular response, the inflammation-inducing properties of nanoparticles has made them effective adjuvants that can be used to stimulate adaptive immune responses.[142] Treatment of several lung cell lines with Nano-TiO_2 and Nano-SiO_2 caused cell toxicity and the production of ROS,[143–145] and both of these nanoparticles were shown to activate NLRP3 and induce IL-1β release.[146,147] Inhalation of Nano-TiO_2 is linked to lung inflammation that is strongly suppressed in IL-1R−/− mice.[146] Carbon black nanoparticles have also been reported to cause an inflammasome-dependent form of cell death, termed pyroptosis, which is accompanied by caspase-1 cleavage and IL-1β release.[148]

Recent studies have also revealed the inflammatory potential of multi-walled carbon nanotubules (MWCNT), which are gaining popularity in industrial and biomedical manufacturing. These particles have proven to promote pro-inflammatory mediator production by multiple cell lines[149,150] and promote allergic sensitization and exacerbation of airway hyperresponsiveness in mice.[151] Examination of the mechanisms through which MWCNT induce inflammation and subsequent lung pathologies has revealed a role for the NLRP3 inflammasome. Hamilton *et al*., used mouse primary alveolar macrophages, as well as *in vivo* studies, to demonstrate that MWCNT challenge resulted in NLRP3 activation via lysosomal disruption, and this was largely due to nickel contamination of the MWCNT preparations.[152] Inhaltion of larger nickel compounds has long been known to cause lung pathologies,[153] but it has only recently emerged that nickel nanoparticles also have inflammatory capabilities that include the induction of IL-1β,[154] which have been compared to the effects of inhaled silica crystals.[155]

Metabolic syndrome

In addition to the inhaled materials that can cause lung disease, it is important to consider the chronic conditions that are affecting increasing numbers of people. Metabolic syndrome is the term for a group of risk factors, namely obesity and insulin resistance, that occur together and enhance the risk for coronary artery disease, stroke, and type 2 diabetes, and that also have an impact on lung diseases such as asthma and COPD.[156,157] Obesity can induce a state of chronic, sterile, low-grade inflammation that includes induction of acute phase cytokines such as IL-1β.[158] The role of IL-1 signaling in multiple other instances of sterile inflammation [the induction or perpetuation of an inflammatory state in the absence of a microbial insult, typically the consequence of cell death accompanied by the release of intracellular molecules (DAMPs) that are normally hidden from recognition by innate immune cells[159]], including gout, atherosclerosis, type 2 diabetes and arthritis, has been thoroughly reviewed by Lukens *et al*.[160] IL-1β is associated with insulin resistance in diabetes and inflammation in obesity.[161–163] Obesity is of concern in the asthma field as well.[164] Studies have implicated saturated fatty acids as ligands for TLRs, which results in upregulation of IL-1β mRNA, and primes the NLRP3 inflammasome.[165] The saturated fatty acid, palmitic acid, has been reported to activate the NLRP3 inflammasome to cause IL-1β

and IL-18 secretion through a mechanism involving mitochondrial ROS, AMP-activated protein kinase, and unc-51-like kinase-1, thereby impairing insulin sensitivity.[166] Another lipid intermediate, ceramide, is upregulated in obesity and has been demonstrated to be an NLRP3 activator.[161,162] High levels of glucose can also trigger inflammasome activity, via direct activation of NLRP3 by TXNIIP. These high glucose levels can provide both a priming signal to increase expression of for IL-1β mRNA, as well as a secondary signal for NLRP3 activation by triggering ROS generation. Mice deficient in caspase-1 are resistant to high fat diet (HFD)-induced insulin resistance,[161] and the same was proven to be true for NLRP3−/− and ASC−/− mice.[167]

Markers of autophagy, a catabolic mechanism for the degradation of cellular proteins, are also increased in obesity, and inhibition of autophagy further exacerbates inflammation and increases IL-1β, IL-6, and IL-8, indicating that autophagy may function to limit the inflammatory response in obesity.[168] Recent studies have directly implicated autophagy as a process necessary for the removal of NLRP3 inflammasome complexes[169] and pro-IL-1β[170] in the cell. Furthermore, blockade of autophagy in dendritic cells increases IL-1β and IL-23, and supernatants from these cells primed γδ T cells to secrete IL-17, IFN-γ, and IL-22.[170] More in depth information on the emerging roles of autophagy in pulmonary disease can be found in a recent review by Mizumura et al.[171]

An increasing number of studies have linked obesity to the development of asthma;[164,172–174] likewise, obese asthmatic patients demonstrate improvements in their asthmatic symptoms concurrent with weight loss.[175] A recent study suggests that dietary intake may play a role in asthma exacerbations, as worsened asthma symptoms were found in patients whose diets were high in fat and low in fiber.[176] Animal models uphold this dynamic; obese mice have an increased basal airway hyperresponsiveness and exaggerated pulmonary responses to inhaled agonists such as ozone,[177] as well as increased hyperresponsiveness and serum IgE levels in an Alum/OVA model of allergic sensitization.[178] Whether this is a result of increased basal inflammasome activation in the lung due to obesity remains to be examined.

Trauma and stress

Cellular DAMPs can be released in response to stress or physical lung injury. A recent study examined the role of the NLRP3 inflammasome in response to hemorrhagic shock in a model of acute lung injury.[40] Of note was their observation that lung endothelial cells were the primary producers of IL-1β in response to high mobility group box-1 (HMGB1) and the induction of ROS following hemorrhagic shock. A link has also been demonstrated between ventilator induced lung injury (VILI) and inflammasome activation. Dolinay *et al*. reported a critical role for caspase-1 and IL-18 in VILI,[179] while Kuipers *et al*. found NLRP3−/− mice to be protected from VILI.[180] Though an exact mechanism has yet to be determined, it is believed that the cell trauma induced during VILI may expose endogenous intracellular DAMPs, including HMGB1, heat shock proteins, S-100 proteins, and mitochondrial alarmins that are capable of activating the inflammasome.[181]

More recently, Wu *et al*. determined that sterile inflammation in response to patient ventilation was NLRP3-dependent.[182] Using an *in vitro* flexible membrane model, they demonstrated that alveolar macrophages subjected to cyclic stretch released uric acid, activated the NLRP3 inflammasome, and induced the release of IL-1β and IL-18. Utilizing a range of inhibitors, they also determined that mitochondrial ROS generation (but not NAPDH oxidase activity) was required for this inflammasome activation.[182]

Summary

In addition to microbial and viral insult, the lung is under a constant barrage of environmental agonists that can induce inflammation and inflammasome activation and participate in the pathogenesis of pulmonary disease (Fig. 2). New studies are highlighting the important endogenous DAMPs that can act to stimulate NLRP3 signaling, and investigating the mechanisms by which inhaled particulates and gasses, physical trauma, and altered physical states such as obesity can lead to inflammasome-dependent lung pathology. Of key importance to many of these mechanisms is the redox balance of the cell; generation of ROS from multiple sources and multiple cell types can lead to modulation of inflammasome complexes and can determine the outcome of lung inflammation. Therapeutic interventions targeted at inflammasome activation, inflammatory cytokines such as IL-1β and IL-18, as well as their receptors, may provide benefit to a myriad of pulmonary diseases.

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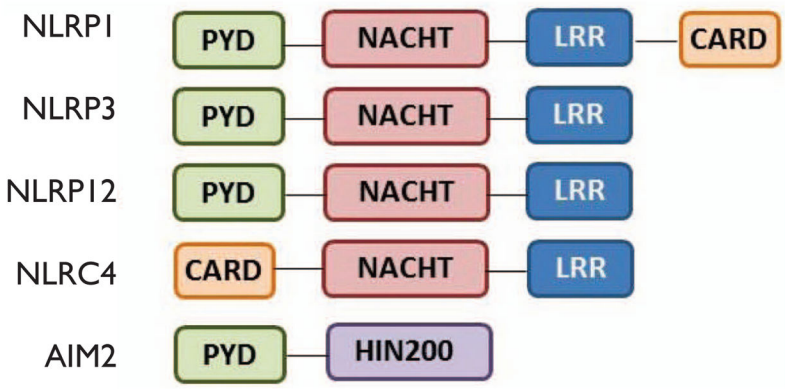

Figure 1.
Differing structures of the inflammasomes implicated in lung disease

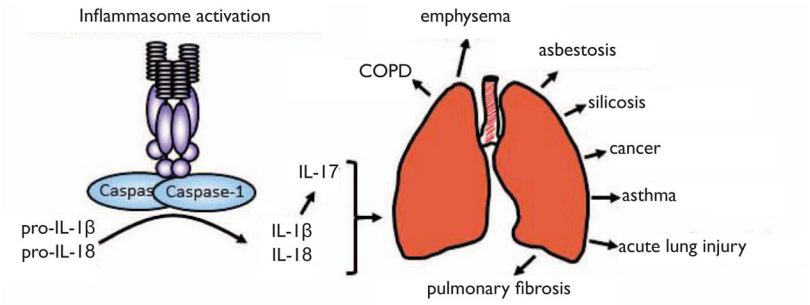

Figure 2.

Pulmonary diseases in which inflammasome activation is involved, either through the production of caspase-1-regulated cytokines (IL-1β or IL-18) and/ or IL-17. COPD, chronic obstructive pulmonary disease.

Table I

Importance of NLRP3 components and IL-1 signaling in non-microbial models of allergic airway disease.

	NLRP3	Caspase-1	IL-1Rα	IL-1β	IL-1α
i.p. Alum/OVA	−	?	−	−	−
i.p. OVA (no Alum)	−	?	+	+	+
s.q. OVA (no Alum)	+	?	+	+	+
UA/OVA	−	−	−	−	−
HDM	−	−	+	−	+
NO_2/OVA	−	+	+	+	−
SAA/OVA	+*	+*	+*	?	?

+=required, −=not required, ?=not specifically published, +*=required only for certain parameters. Alum, aluminum hydroxide; OVA, ovalbumin; i.p., intraperitoneal; s.q., subcutaneous; UA, uric acid; HDM, house dust mite extract; SAA, serum amyloid A.