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Innate receptors and cellular defense against pulmonary infections

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Abstract

In the United States, mortality as a result of lung infections consistently ranks in the top ten leading causes of death, accounting for over 50,000 deaths annually. Moreover, there are more than 140,000 deaths annually as a result of chronic lung diseases, some of which may be complicated by an infectious process. The lung is constantly exposed to the environment and consequently, susceptible to infectious complications caused by bacterial, viral, fungal and parasitic pathogens. Indeed, we are continually faced with the threat of morbidity and mortality associated with annual influenza virus infections, new respiratory viruses (such as SARS-CoV) as well as lung infections caused by antibiotic-resistant “ESKAPE pathogens” (three of which target the lung). This review will highlight innate immune receptors and cell types that function to protect against infectious challenges to the respiratory system yet may also be associated with exacerbations in chronic lung diseases.

Introduction

The major function of the respiratory system is to procure O_2 and to eliminate CO_2 from the body, thus breathing is a physiologic function required to sustain life. However, in an aberrant view, breathing may paradoxically be considered as contributing to mortality. This is because with every breath, toxins, noxious gases, pollutants, particulates and allergens may be introduced into the lungs. Moreover, indoor and outdoor air quality and environmental sampling studies detect enumerable microorganism concentrations per cubic meter in public buildings, homes and even healthcare facilities (1) (2). Altogether, these environmental exposures may ultimately lead to inflammatory and pathological changes that increase the risk of infection. Indeed, although community-acquired pneumonia and influenza results in more than 50,000 deaths in the U.S., chronic lower respiratory diseases are the third leading cause of death (> 140,000) in the U.S (http://www.cdc.gov/nchs/fastats/deaths.htm). These chronic lower respiratory diseases largely include such diseases as asthma and chronic obstructive pulmonary disease (COPD), both of which have known associations with microorganisms (3) (4). This association can be viewed in the proverbial

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"chicken or the egg" sense: exposure to microorganisms may cause inflammatory and pathological changes that result in the development of asthma or COPD, or conversely, asthma or COPD may result in a lung microenvironment that is conducive to the acquisition of microorganisms and subsequent infectious exacerbations. This article will focus primarily on innate recognition and cellular host defense mechanisms that drive the elimination of pathogens from the lung that may also contribute to lung diseases such as asthma and COPD.

Non-TLR innate immune receptors functioning in the lung

NOD-like receptors (NLRs)

Nucleotide-binding oligomerization domain (NOD)-containing receptors (NLRs) are a family of more than 20 intracellularly-localized receptors that recognize numerous pathogen associated molecular patterns (PAMPs; microbial associated factors recognized by the innate immune system) and damage associated molecular patterns (DAMPs; non-microbial products generated during inflammation and tissue injury) including bacterial flagellin, lipoproteins, toxins and muramyl-dipeptide (reviewed in (5)). NLRs came to prominence over 12 years ago when mutations in the NOD2 receptor were found to be associated with susceptibility to Crohn's disease (6). Coming on the heels of the initial discovery and subsequent intensive study of TLRs in innate immune responses (extensively reviewed in (7)]), these findings launched an explosion of research into non-TLRs that were equally important in innate immune responses to pathogens. The NLRs may be subdivided into signaling (NOD1, NOD2), inflammasome generating (NLRP3, NLRC4) and immunoregulatory (NLRX1, NLRP6, NLRP12) (8) (5). NLRs have been studied in lung immune responses to bacterial infections including *K. pneumoniae* (9), *Pseudomonas aeruginosa* (10) *Streptococcus pneumoniae* (11), *S. aureus* (12) and *Mycobacterium tuberculosis* (13) and viral infections such as influenza (14) and RSV (15).

RIG-I-like receptors (RLRs)

Retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) include three DExD/H box RNA helicases, RIG-I, melanoma differentiation factor 5 (MDA5) and laboratory of genetics and physiology 2 (LGP-2). While RIG-I and MDA5 recognize RNA in the cytosol (reviewed in (16)), LGP-2 does not and is rather thought to be a negative regulator of RIG-1 and MDA5 (17). Intriguingly however, LGP-2 overexpression results in improved survival despite similar viral titers as wild-type mice, yet in the presence of reduced antiviral and inflammatory responses (lower IFN-α, β and λ as well as RANTES and TNF-α levels), after influenza exposure (18). Ligation of RIG-I and MDA5 leads to activation of the adaptor protein MAVS (19) and subsequent induction of type I antiviral and associated inflammatory responses via IRF3 and IRF7 (20) (19). RIG-I initiates immune responses to influenza (21), RSV (22) and human metapneumovirus (23). Although there is some overlap (22) (24), MDA5 may show specificity over RIG-I for some viruses, such as parainfluenza (25). In fact, recent evidence suggests that MDA5 is not only required for lung innate immune responses to parainfluenza (26), but is also required for regulating chronic inflammation after infection (27). Recently, it was demonstrated that mice deficient in the guanine nucleotide exchange factor GEF-H1 were shown to lack RIG-I and MDA5-

dependent phosphorylation of IRF3 and were more susceptible to lung infection with influenza A (28). Studies have also shown that some viruses have become adept at evading RIG-1 and MDA5-mediated events. For example, the NS1 protein of influenza A virus may bind to the RIG-I–IPS1 complex and blocks downstream signaling (29). Similarly, the V proteins of many paramyxoviruses interact with MDA5 and may inhibit its function (30). More recently, the 4a protein of the Middle East respiratory syndrome coronavirus (MERS-CoV) inhibits PACT, a cellular dsRNA-binding protein which binds to RIG-I and MDA5 to activate IFN production (31). Although more prominently studied in antiviral responses, studies have shown that RLRs (primarily RIG-I) may also participate in innate responses to lung bacterial pathogens, such as *Legionella pneumophila* (32).

C-type lectin receptors (CLRs)

CLRs are a large, conserved family of pattern recognition receptors that primarily bind carbohydrate ligands via a carbohydrate recognition domain (CRD) or C-type lectin-like domain (CTLD) (33). Currently, there are 17 known CLR subgroups (34). The most well-described CLRs include group II (calcium-dependent with single CRDs), group V (calcium-independent with single CTLDs) and group VI (calcium-dependent with multiple CRDs). Prominent members of group II CLRs are DC-SIGN, Mincle, SIGNR and Dectin-2 and primarily recognize mannose containing ligands (35). With respect to lung infections, group II CLRs are associated with the recognition of and subsequent binding/entry of or innate responsiveness to *Mycobacterium* spp. (36), *K. pneumoniae* (37), *S. pneumonia* (38), *Histoplasma capsulatum* (39), *Cryptococcus neoformans* (40), influenza (41) and SARS (42).

The most prominent member of group V CLRs is the beta-glucan receptor Dectin-1. Dectin-1 is reported to mediate multiple innate immune responses upon myeloid cell recognition of various lung fungal pathogens, including *Aspergillus fumigatus* (43), *Coccidioides immitis* (44) and *Pneumocystis carinii* (45). Although *Mycobacterium* spp. do not have beta-glucans in their cell wall, Dectin-1 may promote innate cellular responses to this pathogen via recognition of an unknown ligand (46). However, data argues both for (47) and against (48) a role for Dectin-1 in host defense against *Mycobacterium* spp. Recent studies have focused on a role for Dectin-1 in *A. fumigatus*-associated asthma. In a chronic live *A. fumigatus* conidia exposure model, BALB/c mice displayed significantly more TNF-α-producing DCs and macrophages in the lung compared to BL/6 mice, which was dependent on Dectin-1 (49). In our own work, we proceeded this study by showing that Dectin-1 dependent IL-22 signaling contributed to the development of AHR, pro-allergic and pro-inflammatory cytokine and chemokine production, neutrophil recruitment and IL-17A and IL-22 production (50). In another study employing a different fungal asthma model, lower asthma severity in mice deficient in TLR9 correlated with significantly lower Dectin-1 mRNA expression (51), yet this group reported in a subsequent study that TLR6 deficient mice had more severe fungal asthma despite lower Dectin-1 expression and Th17 development (52). Another study investigating *A. versicolor*-associated asthma demonstrated no effect on AHR in the absence of Dectin-1, although Dectin-1 drove Th17 responses (53). In contrast, *Cladosporium cladosporioides*-associated asthma resulted in elevated Th2 responses and AHR, which was not dependent on Dectin-1 (53). However,

beta-glucans in the *C. cladosporioides* cell wall may be exposed after heat-killing the organism, which then results in Dectin-1 dependent responses (54). Finally, although Dectin-1 is most recognized as an essential initiator of the innate immune response against various fungal pathogens, Dectin-1 has also been shown to bind an unidentified ligand on T cells and can regulate T cell activation and responses (55).

The most prominent members of group VI CLRs is the macrophage mannose receptor (MR) and DEC-205. Similar to group II CLRs, the ligand specificity of group VI is also mannan/mannose moieties, although MR may also bind sialyl LewisX antigen as well as n-acetylglucosamine (GlcNAc) (35). In turn, the pathogens recognized by the MR are similar to that in group II CLRs and include *Mycobacterium* spp. (56), *K. pneumoniae* (57), *S. pneumonia* (57) and *C. neoformans* (58). DEC-205 binds ligands on lung associated pathogens such as *Yersinia pestis* plasminogen activator and *Escherichia coli* K12 strains (59) and has been targeted in vaccine studies for inducing lung immunity to *Y. pestis* (60) and *M. tuberculosis* (61).

Scavenger receptors

Scavenger receptors are a diverse range of receptors consisting of eight different classes with a myriad of ligand specificity ranging from host proteins to microbial components (62). The best-studied scavenger receptors are those found in class A, which include SR-A1 and MARCO. Early studies with SR-A1 identified it as a potential PRR for the bacterial components (63) with subsequent studies identifying a prominent role for SR-A1 in immunity against *S. pneumonia* (64). However, in a surprising recent finding, SR-A1 deficient mice were observed to be more resistant to polymicrobial sepsis, as lung NF-κB activity was attenuated in the absence of SR-A1, indicating that SR-A1 plays a role in pathophysiology of sepsis/shock (65). Similarly, studies with the lung fungus *C. neoformans* has shown that SR-A1 deficient mice are more resistant to infection as a result of lower Th2 responses, suggesting that *C. neoformans* may employ SR-A1 to interfere with the development of anti-cryptococcal Th1 responses (66). In contrast, mice double deficient in SR-A1 and CD36 (see below) demonstrate resistance to peritoneal *S. aureus* infection, but increase susceptibility to *S. aureus* lung infection (67), suggesting tissue-specific roles for some scavenger receptors in host defense. Like SR-A1, MARCO also plays a critical role in immune against *S. pneumonia* (68) and, based on binding studies, may also play a role in innate lung responses *E. coli* and *S. aureus* (69). Both MARCO and SR-A1 also appear to play a role in regulating allergic responses in the lung at the level of DC migration (70). MARCO may also contribute to detrimental inflammatory responses during influenza infection (71). CD36 is the prototype class B scavenger receptor and is best known for binding to *Plasmodium* spp. in addition to the induction of anti-malarial proinflammatory responses (72). However, malaria infection is often accompanied by acute lung injury with recent data suggesting that CD36 functions to sequester *Plasmodium* spp. which results in the complicating inflammatory response (73). CD36 binds the LprA liporprotein of *M. tuberculosis* to drive macrophage and DC responsiveness (74), although CD36 deficient mice do not appear to be susceptible to acute or chronic *M. tuberculosis* infection, unless this is combined with SR-AI/II deficiency (75).

LOX-1 is a member of class E scavenger receptors and shares homology with CLRs as it is one of only two scavenger receptors to possess a CTLD (62). Although well studied in atherosclerosis, binding studies support a putative role for LOX-1 in immune responsiveness to *E. coli* and *S. aureus* (76). Another study has shown that blocking LOX-1 improves morbidity during acute lung injury (77), suggesting that LOX-1 signaling contributes to lung pathophysiology, similar to that proposed for SR-A1. Airway epithelial-expressed LOX-1 has recently been implicated in the recognition of double-stranded RNA viruses in the lung (78). The lone member of class G scavenger receptors is SR-PSOX (79), which is identical to the chemokine CXCL16, and thus structurally unique among scavenger receptors (80). Other studies show that expression of CXCR6 (CXCL16 receptor) on lung T cells is a correlate of local protective immunity against *M. tuberculosis* (81). CXCL16 may also play a role in lung NKT cell homeostasis, as these cells are significantly reduced in mice deficient in the CXCR6 (82). Moreover, NKT cells are elevated in the lungs of germ-free mice leading to increased morbidity in an asthma model, which correlated with increased lung expression of CXCL16 (83).

Cellular effectors of lung innate immunity

Epithelial cells

Epithelial cells serve not only as a physical barrier to the outside environment but also represent one of the first lines of innate host defense against respiratory pathogens (84). The respiratory system is divided into the upper airway tract, composed of the nasal sinuses and pharynx, and the lower tract, composed of the trachea, which successively branches in bronchi, bronchioles, and the alveoli where exchange of O_2 and CO_2 occurs. The respiratory tract is lined with several types of pseudo-stratified epithelial cells connect by tight junctions that perform a variety of innate host defense functions in the airways including particulate-sweeping by ciliated columnar cells, mucus production by goblet cells and surfactant production by Clara cells (85). The alveoli are composed of type I alveolar epithelial cells, which are primarily responsible for gas exchange and type II alveolar epithelial cells, which serve primarily as immune responders (86). Mucociliary clearance is a key component of innate lung epithelium host defense. Mucins produced by goblet cells are rapidly hydrated into mucus, which traps pathogens and allows for their continual removal from the distal airways via by movement by ciliated epithelial cells into the pharynx where it is swallowed (87). In addition to barrier protection and mucus production, epithelial cells directly contribute to microbial killing via dual oxidase (Duox) expression on the apical surface of epithelial cells, which converts hydrogen peroxide to lactoperoxidase and subsequently antimicrobial hypothiocyanite ions (88). Airway epithelial cells also secrete antiviral type I IFN, lactoferrin, β-defensins and NO in response to many respiratory infections (89). Studies in both humans and animals show that airway epithelial cells express many pattern recognition receptors (PRRs) and produce numerous cytokines and chemokines involved in the recruitment of both innate and adaptive cell type (90) (91) (92,93).

Alveolar macrophages

Along with epithelial cells, alveolar macrophages in the lung are an additional first-line defense mechanism against invading pathogens (94). Alveolar macrophages are responsible

for clearing all foreign particles or pathogens that enter the alveoli. These cells are highly phagocytic, express numerous PRRs and produce an extensive array of pro- and anti-inflammatory cytokines, chemokines, and leukotrienes and this are crucial for providing the initial innate immune recognition and response signals (95). Alveolar macrophage host defense capabilities are often determined by their plasticity between classically activated M1 macrophages and alternatively activated M2 macrophages (reviewed extensively in (96)). Conventionally, it was thought that alveolar macrophages were the terminal differentiation state of blood monocytes in the lung after they progress through an interstitial macrophage state (97) or a parenchymal lung macrophage state (98) (which could be the same cell population). Other studies in mice suggest that fetal monocytes are responsible for alveolar macrophages from the lung within the first week of life (99). However, other murine studies suggest that alveolar macrophages may be established before birth and differentiation through monocytes is not required (100). Interestingly, in Th2 associated lung inflammation, studies have shown that development of M2 macrophages occurs not through precursors from the blood, but by local proliferation of macrophages in response to IL-4 (101). Collectively, these studies support both an embryonic and fetal origin of lung macrophages. Although the host defense aspects of these observations are not completely clear, we can speculate that the need for immediate surveillance of inhaled particles, antigens and pathogens has evolutionarily necessitated the presence of alveolar macrophages in the lung at or shortly after birth. Indeed, alveolar macrophages from neonatal mice express PRRs such as TLR4 and TLR2 and are responsive to LPS and zymosan (102).

Neutrophils

Responding to the various chemokines produced by macrophages and epithelial cells, including IL-8/KC, MIP-1α and β and MIP-2, neutrophils are recruited into the lung as part of an ongoing inflammatory response where their predominant function is the intracellular and extracellular killing of microbes. Neutrophil killing is an essential aspect of host defense in a variety of bacterial and fungal pulmonary infections including *A. fumigatus* (103), *Bordetella pertussis* (104), *P. aeruginosa* (105), *S. pneumoniae* (106) and *K. pneumoniae* (107). Like alveolar macrophages, neutrophils express numerous PRRs, mediate microbial killing through production of ROS, secretion of azurophilic granule contents (myeloperoxidase, elastase, defensins, specific granule contents (lactoferrin, cathelicidins), gelatinase granule contents (lysozyme) (108) and via the formation of neutrophil extracellular traps (NETs) (109).

Dendritic cells

In order to preserve the delicate architecture of the lung that facilitates gas exchange, alveolar macrophages are designed to dispose of invading organisms before they have a chance to initiate a more robust inflammatory response. However if the alveolar macrophages are overwhelmed, microbes are more likely to encounter pulmonary dendritic cells. In mice, there are three types of dendritic cells in the naïve lung: $CD11b^{+}CD103^{-}$ conventional dendritic cells (cDC) that reside in the lamina propria, $CD11b^{-}CD103^{+}$ cDC that express tight junctions and intercalates between airway epithelia cells in order to sample airway environment and plasmacytoid dendritic cells (pDCs) found in the conducting airways (110). During inflammatory responses, a fourth type of dendritic cell, monocyte-

derived FcεRI+ inflammatory dendritic cells (mDCs), may be found in the lung (110). DCs robustly express TLRs, NLRs, CLRs and RLRs which allow them to sense a wide variety of innate stimuli. Upon activation, cDCs, and pDCs mature and migrate to lung draining lymph nodes where they present antigen in order to direct a T cell response (111). In addition, cDCs, mDCs and pDCs also contribute to innate antiviral response (influenza, RSV) (112) (113) and *M. tuberculosis* (114) lung infection through the production of type 1 IFNs.

γδ T cells

Since the discovery of γδ T cells, they have remained a fascinating heterogeneous subset of cells, involved in both innate and adaptive immune responses. They are evolutionarily conserved as homologs can be found in jawless vertebrates and although γδ T cells originate from the same thymic precursor as αβ T cells; they appear to be involved in several non-redundant functions (115). Unlike traditional αβ T cells, γδ T cells express a contrasting TCR, which is not MHC restricted (116). γδ T cells were first described in the lung more than 25 years ago and were identified to be as high as 8–20% of CD3+ cells in the lung (117). We now know that γδ T cells play an early protective role in the lung during infection with pathogens such as *K. pneumoniae* (118), *M. tuberculosis* (119), *S. aureus* (120) and *S. pneumonia* (121). γδ T cells are important sources of “innate IL-17A” in the lung during infection with *A. fumigatus* (122) and *C. neoformans* (123).

Innate lymphoid cells

Innate helper cells/innate lymphoid cells (ILC) are thought to be the innate counterparts to T helper subsets based on their respective cytokine production: IFN-γ (Th1) from ILC1 subset, IL-5 and IL-13 (Th2) from the ILC2 subset and IL-17/IL-22 (Th17/Th22) from ILC3 subset (124). Innate helper type-2 cells (ILC2), also called nuocytes (125) or natural helper cells (126), are part of the innate lymphoid cell (ILC) family that are developmentally related along with NK cells (ILC1) and lymphoid tissue inducer (LTi) cells (ILC3). Early studies putatively suggested an ILC2 population existed in the lung after the production of IL-5 and IL-13 was observed in mice lacking conventional T and B cells (127). ILC2s exert a powerful anti-parasitic defense against *Nippostrongylus brasiliensis* and are sufficient for worm expulsion mediated through production of IL-13 (128), ILC2s also promote tissue repair during influenza infection (129). However ILC2 in the lungs can also play a role in the exacerbation of airway hyper-responsiveness seen in asthma, as IL-25 and IL-33 promote the expansion of IL-13-producing ILC2s that then stimulate mature DCs to migrate to the draining lymph node where they then promote allergic Th2 cell responses (130). ILC3s are found predominantly in mucosal tissues like the gut, yet ILC3s have been identified as sources of innate IL-17 and IL-22 early after exposure to bacterial pathogens such as *S. pneumoniae* (131) or in models of experimental asthma (132) (133).

Antimicrobial immune responses complicating chronic lung diseases in humans

As referred to earlier, recent mortality data (CDC, 2011) indicated that approximately 2.5 million people die in the US each year with nearly 200,000 of these associated with a lung infection (~50,000 deaths from influenza, pneumonia) or a lung disease (~140,000+ from asthma, COPD etc.). With respect to the latter, disease coding data indicates that these lung

diseases may be associated with infectious complications. To this end, it is easy to speculate that in asthma or COPD, immune responses during microbial exposure may serve to exacerbate disease (3) (4). For example, studies have shown that lung infection with *H. influenzae* induces NLRP3 expression (134). This is hypothesized to be a potentially immunopathogenic mechanism in COPD, as *H. influenzae* is strongly associated with COPD and individuals with COPD have elevated levels of uric acid (135), which activate NLRP3 (136). Thus, a consequence of *H. influenzae* exposure in COPD is the upregulation and activation of NLRP3 inflammatory signals that could lead to more severe lung disease. Genetic data has shown that SNPs in *Nod1* and *Nod2* are associated with increased risk of asthma (137) (138) while recent studies have implicated genetic mutations in SR-A1 in development of or exacerbations in COPD (139) (140). It is tempting to speculate that mutations in PRRs such as NOD1, NOD2 and SR-A1 may result in increased colonization/exposure or sub-clinical infection with microorganisms that could lead to enhanced inflammatory responses and subsequent increased asthma or COPD severity. In contrast to lower PRR expression, differential expression of cellular receptors or numbers of cellular effectors may also contribute to immunopathogenesis in lung diseases. For example, although the function of the scavenger receptor/chemokine CXCL16 in lung host defense is not completely clear, its expression on CD8+ T cells in the lung correlates with disease severity in COPD (141). Furthermore, a recent study investigating the distribution of γδ T cells in the lungs of human subjects with COPD made the surprising finding of significantly lower numbers of γδ T cells in sputum and lung lavage fluid from those with COPD, which correlated with lung function decline (142). Collectively, these observations lay the foundation for examining CXCL16/CXCR6 expression and function as well as γδ T cells in lung infection models of organisms that are commonly associated with COPD (4). Finally, defects in lung epithelium barrier and mucus production, which often leads to hyper-neutrophilic inflammation in the lungs, coupled with recurrent infections and exacerbations are the hallmarks of many human chronic pulmonary diseases such as asthma, CF and COPD (143) (144) (145).

Conclusions

As the lung is continually exposed to the environment, innate immune mechanisms must but equipped to handle the recognition of a diverse array of foreign ligands (Table 1) and respond in a rapid and robust manner in order to clear invading pathogens before they functionally compromise the lung. The importance of innate immunity is reinforced by the identification of numerous genetic polymorphisms that result in lung infections (146). However, innate host defense against lung pathogens may consequently come at the price of developing or exacerbating a lung-specific condition such as asthma or COPD. This complex system is illustrated in Figure 1 whereby the homeostatic lung is poised to react to microbial exposure via epithelial cells, alveolar macrophages, DCs, ILCs and γδ T cells (Figure 1A). Exposure to a bacterial, viral or fungal pathogen results in the activation of these cell types, initiating an inflammatory cascade resulting in the recruitment of neutrophils (Figure 1B). However, in some instances, exposure to or prolonged colonization with an organism results in persistent recruitment or presence of T helper (Th2; Th17) or

inflammatory ILCs (ILC2; ILC3) that may result in a hypersensitivity reaction and the development of asthma (Figure 1C).

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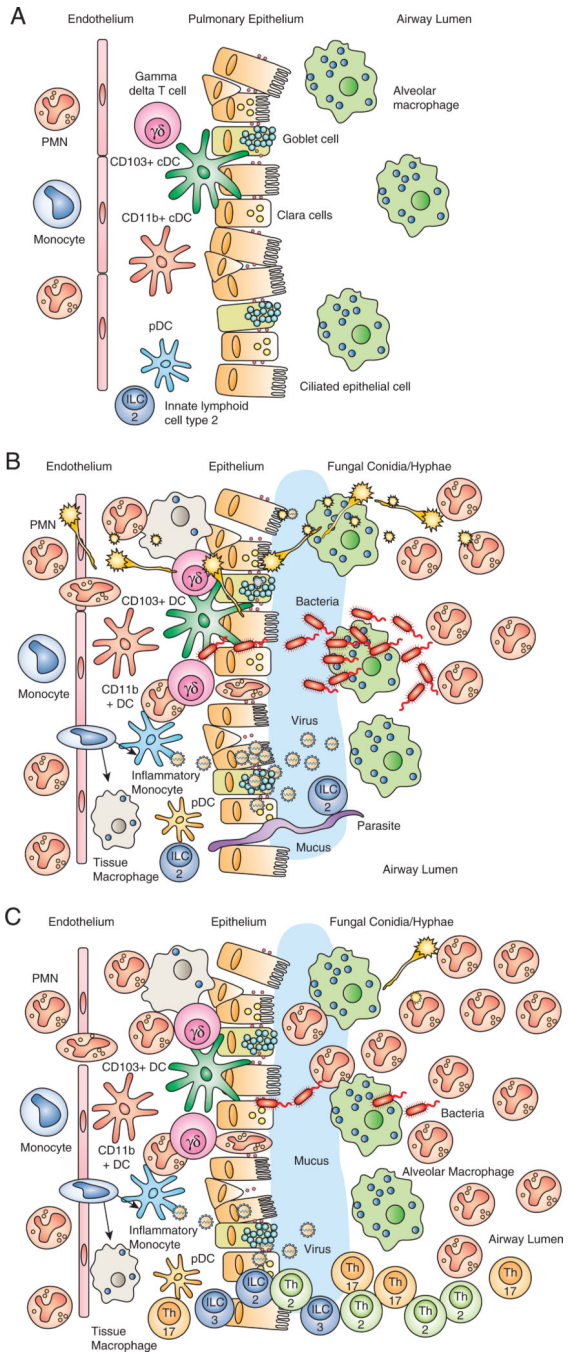

Figure 1.

(A) The lung at baseline is constantly exposed to fungal spores, bacteria and viral particles through alveolar macrophages phagocytosis, IFN production by epithelial cells and the mucocilliary escalator. **(B)** If these defenses become overwhelmed during an active infection, a robust inflammatory process involving alveolar macrophages, DCs, γδ T cells, ILCs, neutophils and epithelial cells commences and involves a variety of antimicrobial mediators. **(C)** However, during persistent exposure, the inflammatory response remains,

contributing to the exacerbation of chronic lung diseases like COPD and asthma through an abundance of neutrophils, Th2/Th17, ILC2 and ILC3 cells.

Table 1

Non-TLR PRRs in innate lung defense

PRR Family		Ligand	Lung-associated pathogen
NLR	NOD-like receptors		
	NOD1, NOD2	DAP, MDP	Lung response to *K. pneumoniae, P. aeruginosa, S. pneumoniae, S. aureus, M. tuberculosis*, influenza, and RSV
RLR	RIG-1-like receptors		
	RIG-1, MDA5	Cytosolic RNA	induction of type 1 antiviral response
	LGP-2	None	potential negative regulator of RIG-1 and MDA5
CLR	C-type lectin receptors:		
	Group II (calcium-dependent, single CRDs)		
	DC-SIGN, Mincle, SIGNR, Dectin-2	Mannose-containing ligands	Recognition of *Mycobacterium spp., K. pneumoniae, S. pneumoniae, H. capsulatum, C. neoformans*, influenza, and SARS
	Group V (calcium-independent, single CTLDs)		
	Dectin-1	Beta-glucan	Mediates innate immune responses against several fungal pathogens: *A. fumigatus, C. immitis, and P. carinii* as well as host defense against *Mycobacterium* spp.
	Group VI (calcium dependent, multiple CRDs)		
	Mannose Receptor (MR)	Mannan/mannose moieties, sialyl LewisX antigen, GlcNAc	Bacterial Recognition: *Mycobacterium spp., K. pneumoniae, S. pneumoniae*, and *C. neoformans*; potential role in induction of allergic response
	DEC-205	Mannan/mannose moieties	Bacterial recognition: *Y. pestis, M. tuberculosis, E. coli* strain K12
SR	Scavenger Receptors		
	Class A		
	SR-A1	Bacterial components, LPS, LTA, CpG	Recognition of *S. pneumoniae*, pathophysiology of sepsis/shock, DC migration
	MARCO	LPS, LTA, CpG	Defense against *S. pneumoniae, E. coli, and S. aureus*, DC migration
	Class B		
	CD36	*Plasmodium* spp., *C. neoformans*, Beta-glucan, Gram (−) bacteria	Pro-inflammatory responses
	Class E		
	LOX-1	Gram (+/−) bacteria	Immune response against *E. coli* and *S. aureus*, recognition of double-stranded viruses in the lung
	Class G		
	SR-PSOX	CXCR6, Gram (+/−) bacteria	Identical to CXCL16, protective immunity to *M. tuberculosis*, potential role in NKT homeostasis