Innate Receptors and Cellular Defense against Pulmonary Infections

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In the United States, lung infections consistently rank in the top 10 leading causes of death, accounting for >50,000 deaths annually. Moreover, >140,000 deaths occur 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 is 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 (e.g., SARS-CoV), and lung infections caused by antibiotic-resistant “ESKAPE pathogens” (three of which target the lung). This review highlights innate immune receptors and cell types that function to protect against infectious challenges to the respiratory system yet also may be associated with exacerbations in chronic lung diseases. The Journal of Immunology, 2014, 193: 3842–3850.

The major function of the respiratory system is to procure O₂ and to eliminate CO₂ 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 detected 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 for infection. Indeed, although community-acquired pneumonia and influenza result in >50,000 deaths in the United States, chronic lower respiratory diseases are the third leading cause of death (>140,000) in the United States (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 “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 focuses 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

Nucleotide-binding oligomerization domain-like receptors. Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are a family of >20 intracellularly localized receptors that recognize numerous pathogen associated molecular patterns (microbial-associated factors recognized by the innate immune system) and damage associated molecular patterns (nonmicrobial products generated during inflammation and tissue injury), including bacterial flagellin, lipoproteins, toxins, and muramyl dipeptide (reviewed in Ref. 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 (reviewed extensively in Ref. 7), these findings launched an explosion of research into non-TLRs that were equally important in innate immune responses to pathogens. NLRs may be subdivided into signaling (NOD1, NOD2), inflammasome-generating (NLRP3, NLRC4), and immunoregulatory (NLRX1, NLRP6, NLRP12) categories (5, 8). NLRs have been studied in lung immune responses to bacterial infections, including Klebsiella pneumoniae (9), Pseudomonas aeruginosa (10), Streptococcus pneumoniae (11), Staphylococcus aureus (12), and Mycobacterium tuberculosis (13), and viral infections, such as influenza (14) and respiratory syncytial virus (RSV) (15).

Abbreviations used in this article: AHR, airway hyperresponsiveness; cDC, conventional DC; CLR, C-type lectin receptor; COPD, chronic obstructive pulmonary disease; CRD, carbohydrate recognition domain; CTLA4, C-type lectin–like domain; DC, dendritic cell; ILC: innate lymphoid cell; LGF-2, laboratory of genetics and physiology 2; MDA5, melanoma differentiation factor 5; MR, mannose receptor; NLR, NOD-like receptor; NOD, nucleotide-binding oligomerization domain; pDC, plasmacytoid DC; PRR, pattern recognition receptor; RIG-I, retinoic acid-inducible gene-1; RLR, RIG-I–like receptor; RSV, respiratory syncytial virus; SR, scavenger receptor.

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Retinoic acid–inducible gene-I–like receptors. 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). Although RIG-I and MDA5 recognize RNA in the cytosol (reviewed in Ref. 16), LGP-2 does not; rather, it is thought to be a negative regulator of RIG-I and MDA5 (17). Intriguingly, however, LGP-2 overexpression results in improved survival, despite similar viral titers as in wild-type mice, yet in the presence of reduced antiviral and inflammatory responses (lower IFN-α, IFN-β, IFN-λ, 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 (19, 20). 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 required for lung innate immune responses to parainfluenza (26) and is also required for regulating chronic inflammation postinfection (27). Recently, it was demonstrated that mice deficient in the guanine nucleotide exchange factor GEF-H1 lack RIG-I– and MDA5-dependent phosphorylation of IRF3 and were more susceptible to lung infection with influenza A (28). Studies also showed that some viruses have become adept at evading RIG-I– 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 inhibits PACT, a cellular dsRNA-binding protein that binds to RIG-I and MDA5 to activate IFN production (31). Although more prominently studied in antiviral responses, studies showed that RLRs (primarily RIG-I) also may participate in innate responses to lung bacterial pathogens, such as Legionella pneumophila (32).

C-type lectin receptors. C-type lectin receptors (CLR) are a large, conserved family of pattern recognition receptors (PRRs) that primarily bind carbohydrate ligands via a carbohydrate recognition domain (CRD) or C-type lectin–like domain (CTLD) (33). There are 17 known CLR subgroups (34). The most well-described CLRAs 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 they 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. pneumoniae (38), Histoplasma capsulatum (39), Cryptococcus neoformans (40), influenza (41) and severe acute respiratory syndrome (42).

The most prominent member of group V CLRs is the β-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 β-glucans in their cell wall, Dectin-1 may promote innate cellular responses to this pathogen via recognition of an unknown ligand (46). However, data argue both for (47) and against (48) a role for Dectin-1 in host defense against Mycobacterium spp. Recent studies 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 dendritic cells (DCs) and macrophages in the lung, which were dependent on Dectin-1, compared with BL/6 mice (49). In our work, we extended this study by showing that Dectin-1–dependent IL-22 signaling contributed to the development of airway hyperresponsiveness (AHR), proallergic and proinflammatory cytokine and chemokine production, neutrophil recruitment, and IL-17A and IL-22 production (50). In another study using a different fungal asthma model, less severe asthma in mice deficient in MDA5 correlated with significantly lower Dectin-1 mRNA expression (51); however, in a subsequent study, this group reported that TLR6-deficient mice had more severe fungal asthma despite lower Dectin-1 expression and Th17 development (52). Another study investigating Aspergillus 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, β-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, it also was shown to bind an unidentified ligand on T cells, and it can regulate T cell activation and responses (55).

The most prominent members of group VI CLRs are the macrophage mannose receptor (MR) and DEC-205. Similar to group II CLRs, the ligand specificity of group VI is also mannann/mannose moieties, although MR also may bind sialyl LewisX Ag and N-acetyl glucosamine (35). In turn, the pathogens recognized by the MR are similar to those in group II CLRs and include Mycobacterium spp. (56), K. pneumoniae (57), S. pneumoniae (57), and C. neoformans (58). DEC-205 binds ligands on lung-associated pathogens, such as Yersinia pestis plasmogen activator and Escherichia coli K12 strains (59), and it was targeted in vaccine studies for inducing lung immunity to Y. pestis (60) and M. tuberculosis (61).

Scavenger receptors. Scavenger receptors (SRs) are a diverse range of receptors consisting of eight classes with a myriad of ligand specificities, ranging from host proteins to microbial components (62). The best-studied SRs 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 it in immunity against S. pneumoniae (64). However, in a surprising recent finding, SR-A1–deficient mice were observed to be more resistant to polymicrobial sepsis, because 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 showed that SR-A1–deficient mice are more resistant to infection as a...
result of lower Th2 responses, suggesting that *C. neoformans* may use SR-A1 to interfere with the development of anticyptococcal Th1 responses (66). In contrast, mice double deficient in SR-A1 and CD36 (see below) demonstrate resistance to peritoneal *S. aureus* infection but have increased susceptibility to *S. aureus* lung infection (67), suggesting tissue-specific roles for some SRs in host defense. Like SR-A1, MARCO plays a critical role in immunity against *S. pneumoniae* (68), and, based on binding studies, it also may play a role in innate lung responses to *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 also may contribute to detrimental inflammatory responses during influenza infection (71). CD36 is the prototype class B SR and is best known for binding to *Plasmodium* spp., in addition to the induction of antimalarial 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 lipoprotein 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 SRs and shares homology with CLRIs, because it is one of only two SRs to possess a CTLD (62). Although well studied in atherosclerosis, binding studies support a putative role for LOX-1 in innate responsiveness to *E. coli* and *S. aureus* (76). Another study showed that blocking LOX-1 improves morbidty during acute lung injury (77), suggesting that LOX-1 signaling contributes to lung pathophysiology, similar to that proposed for SR-A1. Airway epithelial cell–expressed LOX-1 was recently implicated in the recognition of dsRNA viruses in the lung (78). The lone member of class G SRs is SR-PSOX (79), which is identical to the chemokine CXCL16; thus, it is structurally unique among SRs (80). Another study has shown that expression of CXCR6, the receptor for CXCL16, on lung T cells is a correlate of local protective immunity against *M. tuberculosis* (81). CXCL16 also may play a role in lung NKT cell homeostasis, because these cells are significantly reduced in mice deficient in 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 O₂ and CO₂ occurs. The respiratory tract is lined with several types of pseudo-stratified epithelial cells connected 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 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 enzyme on the apical surface of epithelial cells, which converts H₂O₂ to lactoperoxidase and, subsequently, antimicrobial hypohiociuate 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 PRRs and produce numerous cytokines and chemokines involved in the recruitment of both innate and adaptive cell types (90–93).

**Alveolar macrophages.** Along with epithelial cells, alveolar macrophages in the lung are a 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; thus, they 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 Ref. 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 showed 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, Ags, 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, MIP-1β, 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 and mediate microbial killing through production of ROS and secretion of azurophilic granule contents (myeloperoxidase, elastase, defensins, specific granule contents (lactoferrin, cathelicidins) and gelatinase granule contents (lysozymes) (108) and via the formation of neutrophil extracellular traps (109). **Dendritic cells.** 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 DCs. In mice, there are three types of DCs in the naive lung: CD11b + CD103 - conventional DCs (cDCs) that reside in the lamina propria, CD11b + CD103 + cDCs that express tight junctions and intercalate between airway epithelia cells to sample airway environment, and plasmacytoid DCs (pDCs) found in the conducting airways (110). During inflammatory responses, a fourth type of DC, monocyte-derived FcεRI + inflammatory DCs, may be found in the lung (111). DCs robustly express TLRs, NLRs, CLRs, and RLRs, which allows for inflammatory DCs, and pDCs contribute to innate antiviral responses (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 that is involved in both innate and adaptive immune responses. They are evolutionarily conserved because homologs can be found in jawless vertebrates; although γδ T cells originate from the same thymic precursor as αβ T cells, they appear to be involved in several nonredundant functions (115). Unlike traditional αβ T cells, γδ T cells express a contrasting TCR that is not MHC restricted (116). γδ T cells were first described in the lung more than 25 years ago and were identified to make up 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. pneumoniae* (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 (ILCs) are thought to be the innate counterparts to Th subsets based on their respective cytokine production: IFN-γ (Th1) and IFN-α/β (Th1-like) responses, a fourth type of DC, monocyte-derived FcεRI + inflammatory DCs, may be found in the lung (110). cDCs, monocyte-derived FcεRI + inflammatory DCs, and pDCs contribute to innate antiviral responses (influenza, RSV) (112, 113) and *M. tuberculosis* (114) lung infection through the production of type 1 IFNs.

**Table I. Non-TLR PRRs in innate lung defense**

<table>
<thead>
<tr>
<th>PRR Family</th>
<th>Ligand</th>
<th>Lung-Associated Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLRs</td>
<td>DAP, MDP</td>
<td>Lung response to <em>K. pneumoniae</em>, <em>P. aeruginosa</em>, <em>S. pneumoniae</em>, <em>S. aureus</em>, <em>M. tuberculosis</em>, influenza, and RSV</td>
</tr>
<tr>
<td>RLRs</td>
<td>Cytoplasmic RNA</td>
<td>Induction of type 1 antiviral response</td>
</tr>
<tr>
<td>Group II (calcium dependent, single CRDs)</td>
<td>Mannose-containing ligands</td>
<td>Recognition of <em>Mycobacterium</em> spp., <em>K. pneumoniae</em>, <em>S. pneumoniae</em>, <em>H. capsulatum</em>, <em>C. neoformans</em>, influenza, and SARS</td>
</tr>
<tr>
<td>Group V (calcium independent, single CTDs)</td>
<td>β-glucan</td>
<td>Mediates innate immune responses against several fungal pathogens: <em>A. fumigatus</em>, <em>C. immitis</em>, and <em>P. carinii</em> as well as host defense against <em>Mycobacterium</em> spp.</td>
</tr>
<tr>
<td>Group VI (calcium dependent, multiple CRDs)</td>
<td>Mannose/mannose moieties</td>
<td>Bacterial recognition: <em>Mycobacterium</em> spp., <em>K. pneumoniae</em>, <em>S. pneumoniae</em>, and <em>C. neoformans</em>, potential role in induction of allergic response</td>
</tr>
<tr>
<td>SRs</td>
<td>Mannose/mannose moieties</td>
<td>Bacterial recognition: <em>Y. pestis</em>, <em>M. tuberculosis</em>, <em>E. coli</em> strain K12</td>
</tr>
<tr>
<td>Class A</td>
<td><em>P. aeruginosa</em>, <em>C. neoformans</em>, β-glucans, Gram-negative bacteria</td>
<td>Recognition of <em>S. pneumoniae</em>, pathophysiology of sepsis/shock, DC migration</td>
</tr>
<tr>
<td>Class B</td>
<td>LPS, LTA, CpG</td>
<td>Defense against <em>S. pneumoniae</em>, <em>E. coli</em>, and <em>S. aureus</em>; DC migration</td>
</tr>
<tr>
<td>Class E</td>
<td>Gram-positive or -negative bacteria</td>
<td>Immune response against <em>E. coli</em> and <em>S. aureus</em>, recognition of double-stranded viruses in the lung</td>
</tr>
<tr>
<td>Class G</td>
<td>CXCR6, Gram positive or -negative bacteria</td>
<td>Identical to CXCL16, protective immunity to <em>M. tuberculosis</em>, potential role in NKT homeostasis</td>
</tr>
</tbody>
</table>

GlcNAc, N-acetyl glucosamine; SARS, severe acute respiratory syndrome.
from the ILC1 subset, IL-5 and IL-13 (Th2) from the ILC2 subset, and IL-17/IL-22 (Th17/Th22) from the ILC3 subset (124). Innate helper type-2 cells (ILC2), also called nuocytes (125) or natural helper cells (126), are part of the ILC family that are developmentally related to NK cells (ILC1) and lymphoid tissue inducer cells (ILC3). Early studies putatively suggested that 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 antiparasitic 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 also can play a role in the exacerbation of AHR seen in asthma, because 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 promote allergic Th2 cell responses (130). ILC3s are found predominantly in mucosal tissues like the gut, yet ILC3s were 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 ∼2.5 million people die in the United States each year, with nearly 200,000 of these deaths 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 indicate that these lung diseases may be associated with infectious complications. It is easy to speculate that, in asthma or COPD, immune responses during microbial exposure may exacerbate disease (3, 4). For example, studies showed that lung infection with *Haemophilus influenzae* induces NLRP3 expression (134). This is hypothesized to be a potentially immunopathogenic mechanism in COPD, because *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 showed that single-nucleotide polymorphisms in *Nod1* and *Nod2* are associated with an increased risk for asthma (137, 138), whereas recent studies implicated genetic mutations in SR-A1 in the 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 subclinical 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 also may contribute to immunopathogenesis in lung diseases. For example, although the function of the SR/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 spum 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 lead 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, cystic fibrosis, and COPD (143–145).

Conclusions

Because the lung is continually exposed to the environment, innate immune mechanisms must be equipped to handle the recognition of a diverse array of foreign ligands (Table I) and respond in a rapid and robust manner 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 come at the price of developing or exacerbating a lung-specific condition, such as asthma or COPD. This complex system is illustrated in Fig. 1; the homeostatic lung is poised to react to microbial exposure via epithelial cells, alveolar macrophages, DCs, ILCs, and γδ T cells (Fig 1A). Exposure to a bacterial, viral, parasitic, or fungal pathogen results in the activation of these cell types, initiating an inflammatory cascade that leads to the recruitment of neutrophils (Fig 1B). However, in some instances, exposure to or prolonged colonization with an organism results in the persistent recruitment or presence of Th cells (Th2, Th17) or inflammatory ILCs (ILC2, ILC3), which may result in a hypersensitivity reaction and the development of asthma or COPD (Fig 1C).

Disclosures

The authors have no financial conflicts of interest.

References

3848 BRIEF REVIEWS: HOST DEFENSE MECHANISMS OF THE LUNG


