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Innate Immunity of the Lung: From Basic Mechanisms to Translational Medicine

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Abstract
The respiratory tract is faced daily with 10,000 L of inhaled air. While the majority of air contains harmless environmental components, the pulmonary immune system also has to cope with harmful microbial or sterile threats and react rapidly to protect the host at this intimate barrier zone. The airways are endowed with a broad armamentarium of cellular and humoral host defense mechanisms, most of which belong to the innate arm of the immune system. The complex interplay between resident and infiltrating immune cells and secreted innate immune proteins shapes the outcome of host-pathogen, host-allergen, and host-particle interactions within the mucosal airway compartment. Here, we summarize and discuss recent findings on pulmonary innate immunity and highlight key pathways relevant for biomarker and therapeutic targeting strategies for acute and chronic diseases of the respiratory tract.

The Lung as a Critical Immune Interface

The human respiratory tract is faced daily with 10,000 L of inhaled air containing harmless environmental components but also potentially airborne pathogens. This constant exposure requires a fine-tuned and rapidly acting pulmonary immune system in order to immediately sense

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harmful microbial or sterile threats, and to protect the host at this intimate contact zone [1–3]. For that purpose, the airways are endowed with a broad armamentarium of cellular and humoral host defense mechanisms, most of which belong to the innate arm of the immune system [1, 3]. The complex interplay between resident (airway epithelial cells) and infiltrating immune cells acting in concert with secreted innate immune proteins, such as defensins, mucins, or collectins, shapes the outcome of host-pathogen, host-allergen, and host-particle interactions within the airway microenvironment. Airway epithelial cells, dendritic cells, and (in the lower airways) alveolar macrophages (AM) are the initial checkpoints that encounter inhaled antigens and trigger proinflammatory or tolerogenic/anti-inflammatory downstream immune responses. Major mediators communicating between airway sentinel cells and bone marrow-derived immune cells are chemoattractants, such as lipid mediators (prototypically eicosanoids/leukotrienes), complement factors, and chemokines [4–7]. Of particular importance for the recruitment of leukocytes into the airway microenvironment are the CXC chemokines CXCL1-8 and CXCL12, and the CC chemokines CCL2, CCL17 (TARC), CCL18 (PARC), and CCL20. The biological effect of chemokines is relayed by distinct cytokines that are released by local airway cells and induce microenvironmentally tailored immune contexts, particularly IL-1- α and IL-1-β, IL-10, IL-17, IL-23, IL-25, IL-33, and thymic stromal lymphopoietin. Through the integrated action of proinflammatory lipid, chemokine, complement, and cytokine mediators, different immune cell populations are sequentially recruited into the bronchoalveolar and lung parenchymal compartments. In an acute inflammatory reaction, neutrophils are attracted first and localize mainly in the bronchoalveolar space, where they engage in short-term host-pathogen interactions [8], followed by monocytes and lymphocytes for more sustained/chronic host defense functions, with the latter having a clear tissue predominance for infiltrating the lung parenchyma rather than the bronchoalveolar space [9, 10]. Within the pulmonary tissue, lymphocytes can form organized ectopic tertiary lymphoid organs, termed bronchus-associated lymphoid tissue, which can be permanent or inducible (the latter for humans) [11]. Besides these well-characterized components of the pulmonary immune system, recent studies highlight novel immune cells and mediators, such as innate lymphoid cells (ILC), mucosal-associated invariant T cells (MAIT), chitinase-like proteins (CLP), and others. Here we aim to summarize the different components of the innate pulmonary immune response, with an emphasis on novel directions for drug development. Because it is impossible to cover this vast domain of research within a single review, we chose instead to highlight certain areas based on recent, exciting advances, and translational potential.

Airway Epithelial Cells as the First Line of Innate Immune Sensing

The defense functions of the airway epithelium and submucosa are well recognized and include regulation of barrier tightness, secretion of mucus and antimicrobials, and cooperation with various immune subsets via cytokine, chemokine, and growth factor production. At the root of innate defense in the lung, however, is the ability of the airway epithelium to sense pathogens via a variety of receptors. These include various families of pattern recognition receptors (PRR) such as Toll-like receptors (TLR), RIG-I-like receptors (RLR), protease-activated receptors (PAR), Nod-like receptors (NLR), C-type lectin receptors, and the bitter- and sweet-taste receptors.

TLR and RLR

TLR expression and function in airway epithelium have been widely studied. These PRR are expressed by epithelial cells throughout the respiratory tract and respond rapidly to local microbial and host-derived factors present as a result of infection or tissue damage. Following ligand recognition, TLR activate intracellular downstream signaling cascades leading to changes in gene expression associated with typical innate immune responses and activation of adaptive immunity. Tengroth et al. [12] recently described the importance of the nucleic acid-sensing TLR (TLR3, TLR7, and TLR9) and the RLR RIG-I and MDA-5, which recognize replicating RNA viruses in infected cells, in nasal epithelium. These studies using nasal biopsies and primary human nasal epithelial cells stimulated with artificial TLR and RLR agonists demonstrated how these receptors generate robust IL-6, IL-8, and interferon (IFN)-β responses and act as a first line of defense against viruses invading the respiratory tract. In another study, reactive oxygen species produced via Duox2 in influenza A virus-infected nasal epithelial cells were shown to increase RIG-I and MDA-5 mRNA in a process believed to resist IAV infection [13]. Kim et al. [14] also evaluated inflammatory and antiviral responses to human virus infection in human nasal epithelial cells from chronic rhinosinusitis patients, wherein decreased MDA-5 and IFN-β expressions were evident and human rhinovirus clearance was slightly impaired.

C-Type Lectin Receptors

Another type of PRR essential for innate immunity in the pulmonary environment are C-type lectin receptors that sense fungal patterns. On bronchial epithelial cells this is mainly orchestrated by dectin-1, which mediates recognition of β-glucan motifs in *Aspergillus fumigatus* and the house dust mite (HDM) [15], leading to secretion of the dendritic cell chemokine CCL20. Other nonfungal allergens, and specifically those with proteolytic properties such as Derp1 and cockroach allergen, can elicit allergic airway inflammation via PAR-2 when administered through the mucosa [16]. In a study of allergic sensitization and HDM-induced allergic airway inflammation [17], PAR-2 was found to contribute to IgE responses but was dispensable for proinflammatory cytokine secretion induced by HDM. In another study, it was demonstrated that, in addition to producing cytokines, allergen-activated airway epithelial cells can also release uric acid [18], thereby promoting TH2 sensitization and amplifying allergic inflammation [reviewed in 19].

Nod-Like Receptors

Among NLR, NOD1, NOD2, and NLRP3 are expressed by airway epithelial cells. The expression of NOD1 has been shown to be downregulated during pollen season among patients with allergic rhinitis [20], and its normal activation can reduce airway hyperresponsiveness accompanied by a reduction of allergen-specific T-cell proliferation in allergen-induced lung inflammation [21]. NLRP3 mediates cellular responses to inhaled particular matter (e.g., PM10) and has recently been elegantly shown to have an important role in innate but not adaptive immune responses in airway epithelial cells [22]. A novel NLR termed NLRX-1 has been identified in nasal epithelium that is activated by double-stranded RNA and participates in rhinoviral-mediated disruption of polarized airway epithelial cell barrier function [23].

Bitter- and Sweet-Taste Receptors

One particularly exciting new finding relevant to sensing capabilities in the airways is the identification of the G-protein coupled bitter- and sweet-taste receptors (T2R and T1R, respectively) in respiratory epithelia [reviewed in 24]. Extraoral taste receptors have been detected in human bronchial epithelial cells and specialized solitary sinonasal chemosensory cells in the upper respiratory tract [25, 26]. Bitter taste receptors are activated by bacterial quorum-sensing molecules, whereas sweet receptors respond to sugars. For example, the bitter taste receptor T2R38 is activated by homoserine lactones from the gram-negative opportunistic bacterium *Pseudomonas aeruginosa*, causing an increase in nitric oxide production and enhanced mucociliary clearance [27]. Lee et al. [28] studied the regulation of bitter- and sweet-taste receptors in the upper airways and found that antimicrobial peptide induction by T2R is repressed by activation of the sweet-taste receptor T1R2/3. Thus, activation of T1R2/3 and repression of T2R due to increased intranasal glucose may be responsible for chronic rhinosinusitis.

Other Recently Identified Receptors

Beyond these major families of PRR, new roles in innate immunity have emerged recently for other receptors expressed by airway epithelium. Selected examples include: (1) the short-chain fatty acid receptor GPR41, which is present at higher-than-normal levels in bronchial epithelium of cystic fibrosis (CF) patients and is responsible for exaggerated IL-8 induction in these cells in response to short-chain fatty acids from anaerobic bacteria present in CF lungs [29], (2) the fractalkine receptor CX3CR1, which was recently reported to mediate respiratory syncytial virus-induced cytokine production in primary human airway epithelial cells [30], and (3) an isoform of the coxsackievirus and adenovirus receptor CAREx8a, expressed on the apical surface of airway epithelial cells in culture, that enhances adenovirus entry into cells by coopting neutrophils [31].

Neutrophils

Neutrophils are the most abundant subset of leukocytes patrolling in blood in search of potential injuries and stimuli, e.g., pathogen- and damage-associated molecular pattern molecules (PAMP and DAMP), chemokines, cytokines, and lipid mediators, which induce their rapid recruitment to peripheral sites of inflammation. The primary role fulfilled by neutrophils is pathogen killing and removal. Neutrophils are conventionally thought of as short-living cells with a limited capacity for de novo mRNA transcription and protein production. However, recent evidence shows that they are endowed with extensive adaptive abilities, which underlie an equally extensive functional complexity [8].

Neutrophil Lifespan and Margination in the Lung Vasculature

The human blood neutrophil lifespan was previously estimated to be shorter than a day; however, recent studies suggested an upper limit closer to 5 days, even in the

absence of inflammation [32]. This topic remains controversial and requires further investigation. In addition to circulating freely in blood, a large fraction of neutrophils is tethered to the lining of the liver, spleen, bone marrow, and lung vasculature and is referred to as the "marginated" pool [33]. Within the lung alone, this pool constitutes the most prominent reservoir of neutrophils in the systemic circulation (~40% of total body neutrophils) [34]. Key protective mechanisms have been attributed to the lung marginated pool because it enables rapid neutrophil recruitment inside of the tissue following injury and/or infection. Additionally, the lung vasculature has been involved in neutrophil "de-priming" via its ability to filter and inactivate primed cells before they are rereleased in the blood stream [35]. However, this mechanism of neutrophil retention is impaired in acute respiratory distress syndrome patients, resulting in the exposure of peripheral organs to primed systemic neutrophils, leading to severe complications [36].

Neutrophil Adaption to the Pulmonary Microenvironment

As the first circulating immune subset recruited into the lung upon infection or sterile inflammation, neutrophils orchestrate both pro- and anti-inflammatory actions therein, as required to efficiently kill pathogens and resolve inflammation. In fulfilling these tasks, neutrophils undergo profound phenotypic and functional changes, delineating distinct fates. Indeed, various neutrophil fates can be observed in blood and tissue under both homeostatic and pathological conditions such as infection, autoimmunity, and cancer [37]. Within the airways, recruited neutrophils display an activated phenotype ($CD16^{high}$ $CD62L^{dim}$ $CD11b^{high}$) under both healthy and inflamed conditions [38, 39]. When crossing into the airway lumen, neutrophils further modulate the surface expression of chemokine and TLR, which together mediate core inflammatory signaling. These changes in neutrophil phenotypes include a lower expression level of receptors for the CXCL8 (IL8) chemokine, CXCR1 and CXCR2, than in blood. By contrast, a large fraction of neutrophils isolated from the bronchoalveolar lavage fluid of patients suffering from chronic airway inflammation upregulate CCR1, CCR2, CCR3, CCR5, CXCR3, and CXCR4, as observed in CF, chronic obstructive pulmonary disease (COPD), and asthma, as well as TLR2, TLR4, TLR5, and TLR9, as observed in CF and non CF-bronchiectasis, when compared to airway neutrophils from healthy subjects. These phenotypic changes are linked to neutrophil respiratory burst activity and/or bacterial killing and they are concomitant with de novo protein synthesis, granule exocytosis, and later induction of apoptosis [40–42]. While typical surface receptors are altered in neutrophils during chronic lung inflammation, further studies suggested a more profound modulation of their metabolism and function. In particular, recent studies showed that upon recruitment into CF airways neutrophils undergo significant activation of both cAMP response element-binding protein (CREB) and mechanistic (formerly mammalian) target of rapamycin (mTOR) pathways, linked to surface upregulation of functional receptors (e.g., the receptor for advanced glycation end products) and metabolite transporters (e.g., glucose and amino acid transporters Glut1 and ASCT2) [43–45]. Since CF airways are enriched in inflammatory mediators and nutrients such as glucose and amino acids, these results suggest the ability of neutrophils to adapt to specific microenvironments through coordinated stress responses and metabolic reprogramming [reviewed in 46, 47].

Regulatory Activities of Lung Neutrophils

A hallmark of neutrophil activity within inflamed airways is the extracellular release of proteases and oxidases (e.g., neutrophil elastase and myeloperoxidase) following granule mobilization to the cell surface. This process, well recognized in airway diseases such as CF and COPD, induces an upregulation of characteristic markers for secondary and primary granules (CD66b and CD63, respectively) on the surface of airway neutrophils and results in high oxidative and proteolytic activities. The latter was shown to be responsible for the cleavage as key receptors involved in neutrophil antibacterial activities such as CXCR1, CD16, and CD14 [43, 46–48]. Further studies revealed a role for airway neutrophils in regulation of the adaptive immune system, further emphasizing the multidimensional importance of neutrophil plasticity [37]. For example, a strong immunosuppressive function was identified in CF airway neutrophils, which can downregulate T-cell activity through the release and activation of arginase I, concomitant with granule exocytosis [49]. Activated neutrophils may also impact T cells positively within CF airways but also within the lymphatic compartment by displaying antigen-presenting cell capabilities (e.g., expression of CD80, CD86, and MHC II). Interestingly, CXCR4 expression, usually characteristic of immature or senescent neutrophils, is strongly upregulated on activated airway neutrophils and could relate to their acquired ability to egress from inflammatory tissues into lymphatic vessels [40, 43, 50]. Neutrophil transit toward lymph nodes has been associated with T-cell proliferation

and therefore participates in positive regulation of the adaptive immune response by neutrophils [50, 51]. In some cases, lymphatic neutrophils could be used a "Trojan horses" by intracellular pathogens, which can use them as a vehicle to spread throughout the body [52, 53].

Neutrophil Extracellular Traps

Until recently, neutrophils have been primarily recognized as professional killers critical to the initial immune response that leads to pathogen clearance, using both intracellular killing by phagocytosis and extracellular killing by exocytosis of granule components. In the past decade, a third effector mechanism used by neutrophils has been described, which consists of the release of extracellular complexes or "traps" formed by decondensed nuclear DNA (e.g., after histone citrullination), histones, and cationic effectors such as neutrophil elastase and myeloperoxidase. The deployment of neutrophil extracellular traps (NET), termed "NETosis," is believed to enable immobilization and possibly killing of pathogens, while precipitating neutrophil death [54, 55]. While NET have been associated with numerous pathologies including autoimmune disorders and infectious diseases related to bacteria, fungi, and viruses, their role in acute and chronic inflammation has not yet been fully elucidated [8, 54]. In the context of airway diseases, studies focusing on NET have shown both beneficial and harmful effects of these structures [reviewed in 56]. The ability of NET to spread out and trap microbes could enable an increased killing efficiency and reduction of the pathogen burden. Mitigating these positive effects of NET are the facts that pathogens such as *Staphylococcus aureus* were shown to developed NET evasion strategies, and that the extracellular presence of host DNA, histones, neutrophil elastase, and myeloperoxidase can cause direct or indirect cell toxicity and subsequent lung injury [57–59], as well as airway obstruction via an increase in mucus viscosity [60–62].

Neutrophil Plasticity and Heterogeneity

Taken together, numerous studies in the past decade have highlighted the adaptability of neutrophils in acute and chronic immune responses, contradicting the conventional view that they are preprogrammed, poorly adaptable cells, incapable of de novo protein synthesis, with a limited lifespan and primarily relying on oxidative and proteolytic killing to carry out their function. The identification of novel neutrophil functions and regulatory mechanisms highlights their role in balancing pro- and anti-inflammatory signaling in order to promote a swift return to homeostasis and limit tissue damage. The concept of "neutrophil heterogeneity" originated by Gallin et al. [63] in 1984 has now emerged in full bloom, encompassing the formation of distinct subsets in both blood and peripheral tissues and raising particular interest in the functional characterization of these subsets for novel neutrophil-targeted therapies for CF, COPD, neutrophilic asthma, and other chronic airway diseases.

Macrophages

Macrophages, first discovered by Ilya Metchnikoff, belong to the mononuclear phagocyte system and represent potent antimicrobial innate immune cells that are found in all tissues in the human body. Macrophages in the pulmonary compartment are classified and termed according to their anatomical location in the lung as alveolar or interstitial macrophages [64]. Since interstitial macrophages are less defined and more heterogeneous depending on the pulmonary subcompartment, the species studied, and the disease model investigated, we will focus here on AM.

AM Functions

AM are 15–50 μm in diameter, they are mainly located in the alveolar space, and they represent the predominant phagocytic and antigen-presenting cell in the human respiratory tract [65]. Under homeostatic/healthy conditions, AM are the most abundant cellular fraction within bronchoalveolar lavage fluids, while under acute or chronic inflammatory conditions other leukocyte populations, prototypically neutrophils (e.g., in acute infections, CF or acute respiratory distress syndrome) and lymphocytes (e.g., in sarcoidosis and allergic alveolitis) accumulate and shift this balance. Distinct from other tissue macrophage subsets, AM are endowed with a remarkable phenotypic, metabolic, and functional plasticity [65–67]. Metabolically, AM exhibit a high basal glucose consumption and respiratory rate but a low respiratory burst activity. Phenotypically, they directly reflect the alveolar host-environment interface zone and contain granules of exogenous material, as exemplified in chronic smokers in whom AM accumulate in the bronchoalveolar lavage fluid, are larger in diameter and activated, and stain dark on cytospin preparations. By taking up inhaled environmental particles, pollutants, allergens, and airborne microbes, AM serve as airway scavengers to keep the respiratory system clean and homeostatic. Another function related to their potent phagocytic capacity is the maintenance of surfactant homeostasis by engulfing and catabolizing lo-

cal surrounding surfactant proteins, a functionality that is impaired in a severe disorder called pulmonary alveolar proteinosis, characterized by a dysfunction of the granulocyte/monocyte cell stimulating factor pathway and related AM functions [68, 69]. By sensing bronchoalveolar PAMP and DAMP, AM integrate various microbial- and host-derived signals and respond via the concerted release of various pro- or anti-inflammatory mediators (mainly cytokines such as IL-1-β, IL-6, IL-10, or tumor necrosis factor [TNF]-α) into the alveolar space. Recent studies further highlight that AM can have immunoregulatory roles. In murine asthma model systems, pulmonary macrophages were found to generate regulatory T cells to induce airway tolerance [70]. AM were further found to attach to the alveolar wall (becoming "sessile") and communicate with the alveolar epithelium to induce an immunosuppressive/-modulatory signal in order to dampen lung inflammation [71].

AM Ontogeny

Ontologically, tissue macrophages either derive from circulating/recruited monocytes or are established during embryogenesis (yolk sac and fetal liver), independently of monocytes, as supported by recent murine studies, and they populate different organs as long-lived tissue-resident macrophages [64, 72]. However, the precise origin of AM across species remains a matter of intense ongoing investigations. Previous studies have shown that AM develop from fetal monocytes that differentiate into long-lived mononuclear cells in the first week of life, mediated through the granulocyte/monocyte cell-stimulating factor [73]. In murine fate-mapping studies, yolk sac-derived erythro-myeloid progenitors have been identified as the origin of several tissue-resident macrophage populations, including AM [74]. The airway environment/niche seems to be essential as well to shaping the unique phenotype and functional characteristics of AM in vivo [75]. For a more detailed and comprehensive review of the ontogeny of AM, we refer readers to a recent dedicated review [64].

AM Polarization

Macrophages have a remarkable functional and phenotypic diversity and can be dichotomized into M1 (IFN-γ/classically activated) and M2 (IL-4/alternatively activated) polarization phenotypes with different roles in cancer, infection, allergy, and fibrosis. Despite compelling evidence in vitro, the in vivo relevance of this classification has been challenged and is continuously refined given the high plasticity and heterogeneity of macrophages depending on the respective tissue compartment and disease model analyzed. For a more detailed review of macrophage activation, plasticity, and M1/M2 polarization, we refer readers to recent reviews in that field [76–78]. Overall, the complex multifunctionality of AM, interacting as antigen-presenting cells with T cells, clearing apoptotic and necrotic cells through efferocytosis, and killing pathogens and releasing both pro- and anti-inflammatory factors, makes a "good-versus-bad-cop" assignment for these cells for the majority of lung diseases challenging. In vivo macrophage depletion studies revealed different outcomes depending on the lung disease model and the time point of intervention used [64, 65, 79, 80]. Idiopathic pulmonary fibrosis (IPF) is a prototypic example of a complex chronic lung disease in which the role of pulmonary macrophages remains controversial. In this context, AM seem to play a dual role in lung fibrosis given their release of profibrotic factors (such as TGF-β_1 and PDGF), thereby driving disease progression and, on the other hand, their ability to release proteases (MMP) that can digest the extracellular matrix and thus exert antifibrotic/fibrinolytic activities. For a more thorough discussion of macrophage phenotypes and functions in IPF, we refer readers to a recent review in that field [79].

Innate Lymphoid Cells

ILC are a recently identified group of heterogeneous innate immune cells belonging to the lymphoid lineage but lacking antigen-specific receptors [81]. Mechanistically, ILC are involved in protective antimicrobial responses, particularly at mucosal-barrier organs, but they also play pathogenic roles in inflammation, autoimmunity, allergy, and fibrosis within tissues [81, 82]. ILC are distinguished from canonical T and B cells by their ontogeny/development and the expression of a distinct set of cellular markers [81]. Of note, ILC do not express RAG (recombination-activating gene) genes, implying that ILC, in contrast to T and B cells, can be activated directly [83]. ILC typically express IL-2Rα (CD25), IL-7Rα (CD127), and IL-7Rγ (CD132) [84]. Depending on their ability to synthesize and release cytokines and their transcription factor profile, ILC are divided into 3 distinct subsets.

Type I ILC

ILC1, which include NK cells, are defined by analogy to Th1 cells according to their ability to release IFN-γ and TNF, and expression of the T-box transcription factor T-bet or eomesodermin (Eomes) [85]. Across tissues, ILC1

cells are found mostly in the liver, the thymus, the uterus, skin, secondary lymphoid tissue, the spleen, the gut, and the lung. ILC1 have been demonstrated to accumulate in response to viral and bacterial infections in mice [86]. ILC1 were increased in lung specimen from patients with severe COPD, while type 2 ILC (ILC2) were decreased [87].

Type 2 ILC

ILC2, the counterpart of Th2 cells, produce IL-4, IL-5, IL-9, and IL-13 in response to IL-25, IL-33 and thymic stromal lymphopoietin and express high levels of the Th2 signature transcription factor GATA-3, which is necessary for their functional maturation and maintenance [88, 89]. ILC2 are localized mostly in the healthy skin, adipose tissue, and lung of mice and humans and have been mainly involved in tissue inflammation, remodeling, and fibrosis. Interestingly, ILC2 are the main ILC subset found in the murine lung, although they represent only 0.4–1% of total lung cells. Using single-cell RNA sequencing of lung-resident ILC, a recent study demonstrated that in the context of allergic lung inflammation the alarmins/cytokines IL-25 and IL-33 can induce activation and expansion of lung-resident ILC2 [88]. In vivo activation by IL-25 induced a high expression of neuromedin U receptor 1 in ILC2. Interestingly, the combined treatment with IL-25 and neuromedin U synergistically promoted allergic inflammation. In line with previous studies showing increased numbers of ILC2 in the blood of asthma patients [90], this study suggests that ILC2 could represent a potentially predictive biomarker for patients with asthma. Interestingly, the deletion of IL-33 prevented cigarette smoke-primed exacerbations in response to viral infection in mice and cigarette smoke decreased the expression of the IL-33 receptor ST2 on ILC2 [91]. Therefore, the IL-33/ILC2 axis may offer a potential therapeutic target for controlling chronic lung diseases like asthma and COPD.

Type 3 ILC

Type 3 ILC contain natural cytotoxicity receptor-positive (NCR^+) ILC3 and NCR^- lymphoid tissue inducer (LTi) cells, which depend on the transcription factor RORγt and produce either IL-22 (NCR^+ ILC3, a.k.a., ILC22 cells) or both IL-17 and IL-22 (NCR^- LTi, a.k.a., ILC17 cells) in response to IL-23 [82, 92]. LTi cells were reported to contribute to the development of secondary lymphoid tissue, wherein they activate stromal cells through the lymphotoxin-$\alpha_1\beta_2$-mediated LTβR signaling pathway. This triggers the expression of adhesion molecules (e.g., ICAM and VCAM) and chemokines (CXCL13, CCL19, and CCL21) required for the formation of lymphoid follicles [93]. Previous studies established that B-cell-dependent inducible bronchus associated lymphoid tissue formation is essential for emphysema development in the cigarette smoke-induced COPD mouse model [94]. Based on these and the above data, it is tempting to speculate that LTi cells play a key role in the development of COPD immunopathogenesis. However, while mechanistic and functional contributions of ILC in animal models of asthma and COPD have been studied to a certain extent, there is very limited evidence for a potential role in human disease conditions so far. With regards to lung fibrosis, the potential role of ILC is discussed in a comprehensive review [95]. In brief, given that IL-17A plays a key role in pulmonary inflammation and fibrosis in COPD, IPF, and CF [96–98], and given that ILC3 are an essential source of IL-17 at mucosal sites ILC3s are suggested to function as early orchestrators of lung tissue remodeling and fibrogenesis. Very recently, a mast cell/ILC2/Th9 pathway has been shown to drive pulmonary inflammation in murine infection models of CF-like lung disease [99], although the precise role and functional relevance of this pathway and ILC overall in human CF lung disease remains to be defined by further translational studies.

Mucosal-Associated Invariant T Cells

MAIT are a group of innate-like T lymphocytes that which are highly abundant in human blood (~1–10% [100]) and in mucosal tissues such as the intestine and lungs [101–104]. These cells are characterized by their expression of the invariant T-cell receptor (TCR) α chain, TRAV1–2 joined with TRAJ33 and a limited range of TCRβ chains, and abundant expression of CD161 and CD218 (IL18Rα) [102, 105, 106]. Recently, studies have shown that MAIT cells can recognize vitamin B metabolic byproducts produced by a range of microorganisms presented by the ubiquitously expressed class I MHC-related protein MR1 [107–110]. Activated MAIT cells have been shown to secrete high levels of IFN-γ, TNF-α, IL-17, and cytotoxic/cytolytic perforin and granzymes A, B, and K [111–116].

MAIT Cell Frequency and Susceptibility to Corticosteroid Treatment

The frequency of MAIT cells in normal human lungs ranges from 2 to 20% of all T cells [104, 117]. Given their abundance in blood, many studies have examined blood

MAIT cells in various respiratory diseases. There were no change in MAIT cell frequency in the blood of inhaled corticosteroid (ICS)-naive COPD patients relative to healthy donors; however, their frequency was significantly reduced in ICS-treated COPD patients' blood and bronchial biopsies [104]. The reduced MAIT cell frequency in blood was more pronounced in moderate-to-severe-COPD patients, and it was associated with elevated serum C-reactive protein levels and a reduced lung function [118]. Consistent with a role of ICS in modulating MAIT cell numbers, these were also found to be significantly reduced in the blood and lung tissue of ICS-treated asthma patients relative to normal individuals [119, 120], a result that was especially prominent in patients with severe asthma [120]. Together, these studies suggest that MAIT cells are susceptible to ICS treatment and that their deficiency may be associated with a more severe respiratory pathology.

MAIT Cells in Lung Pathologies

Experimental evidence suggested that MAIT cells can be activated upon epithelial cell infection by multiple bacterial strains [111]. Indeed, an important role of these cells in antibacterial immunity is supported by studies showing a significant inverse correlation between peripheral blood MAIT cell numbers and CF disease severity and an inverse association with *P. aeruginosa* infection and the frequency of pulmonary exacerbations [121]. Similarly, blood MAIT cells were also observed to be decreased in patients with tuberculosis (TB) and nontuberculous mycobacterial infection [122, 123], and their deficiency was correlated with disease severity [122]. In vitro stimulation of freshly isolated MAIT cells using phorbol ester, ionomycin, IL-15, anti-CD28 antibodies, and/or mycobacterial lysates suggested a severe functional deficiency in TB patient-derived relative to healthy donor-derived MAIT cells, as assessed by the induction of IFN-γ and IL-17 production [122, 124]. Various studies have shown an important, nonredundant role for IL-12, IL-18, and IL-2 signaling in MAIT cell activation [114, 116, 125–127], and a significant reduction of IL-12 and/or IL-2 receptors in in vitro-stimulated blood MAIT cells from TB patients [124, 127]. Finally, 2 reports suggested that functionally deficient MAIT cells from the blood of TB patients and HIV/TB coinfected patients have elevated levels of cell surface PD-1 expression relative to healthy controls [128, 129], suggesting that immune checkpoint pathways may functionally regulate these cells during infection. Collectively, these studies suggest that MAIT cells are functionally important in controlling bacterial infections, and deficiencies in these cells occur in patients with active bacterial infections.

Lung MAIT Cells in the Context of Bacterial Infection

Identification of mechanisms propagated by MAIT cells in pulmonary immunity has been hindered by the low abundance of these cells in germ-free mice. However, following the development of iVα19 TCRα [130] transgenic and B6-MAITCAST [131] mice, and the commercial availability of murine MR1 tetramers, recent studies have characterized the role of these cells in models of pulmonary inflammation and infection. Utilizing iVα19-transgenic MR1-sufficient or iVα19-transgenic MR1-deficient mice to study the role of MAIT cells in anti-bacterial immunity, Le Bourhis et al. [123] observed that the former had more activated MAIT cells and a lower bacterial burden relative to the latter. In a model of pulmonary bacterial infection, one study provided evidence for a key role of MAIT cells in protecting against *Francisella tularensis* (LVS) pulmonary infection [132], based on the observation of an MR1-dependent recruitment and/or expansion of MAIT cells in LVS-infected mice, and a lower bacterial burden in the lungs of MR1-sufficient relative to MR1-deficient mice. In vitro coculture studies utilizing MAIT cells and LVS-infected macrophages indicated that MAIT cell-derived IL-12p40, TNF, and IFN-γ were indispensable in controlling intracellular bacterial growth in macrophages. Finally, this study showed a delayed recruitment of effector CD4+ helper and CD8+ cytotoxic T cells in MR1-deficient mice relative to their MR1-sufficient counterparts. In a subsequent report, this group identified MAIT cell-derived granulocyte/monocyte cell stimulating factor to be required for differentiation of CCR2+ monocytes into dendritic cells and the subsequent recruitment of effector helper and cytotoxic T cells for efficient bacterial clearance [133]. Collectively, these studies suggest that MAIT cells elaborate a protective effect against bacterial infection via multiple mechanisms, including macrophage activation and monocyte-to-dendritic cell differentiation, and bridging of innate and adaptive immunity.

Lung MAIT Cells in the Context of Viral Infection

Given the identification of bacterial and fungal vitamin B metabolites as MR1-presented antigens [107–110], MAIT cells were thought not to play a major role in viral infection. However, a recent study found higher MAIT cell numbers in H7N9 influenza patients who recovered from infection relative to those who succumbed to the

infection [126]. Utilizing an in vitro coculture system of influenza-infected airway epithelial cells (A549) with human peripheral blood mononuclear cells, an MR1-independent, CD14+ cell- and IL-18-dependent activation of MAIT cells was observed, featuring increased intracellular IFN-γ and granzyme B levels [126]. These results were later confirmed in another study in which MAIT cells were found to be activated in an MR1-independent but IL-18-, IL-12-, and IL-15-dependent manner in response to various viral infections, including dengue, hepatitis C, and influenza viruses [134]. Together these studies suggest that MAIT cells may play an important role in host responses to viral infections.

Novel Mediators: CLP

In recent years, several novel mediators have been identified that participate in innate immunity in the lungs. These include chitinase and CLP, a conserved group of proteins that belong to the 18-glycosyl hydrolase family [135]. CLP are well conserved but with high divergence in mammals (represented by YKL-39 and YKL-40 in humans vs. BRP-39, Ym1, and Ym2 in mice), suggesting important but potentially variable roles in hosts [135]. The divergence in CLP among mammals has been attributed to the difference in microbial threats faced by individual species [135].

Chitin, Chitinases, and CLP

Although mammals do not synthesize chitins, the presence of chitinases and CLP suggests a potential role in the digestion of chitin-containing food and/or protection against chitin-containing pathogens. This hypothesis was based in part on epidemiological evidence showing increased expression of these proteins in populations exposed to higher levels of chitin-containing pathogens and food products [136, 137]. However, later studies cast doubts on this hypothesis, indicating a limited correlation between Chit1 deficiency and exposure to chitin-containing parasites and food [138–140]. CLP have a high binding capacity to chitin but lack enzymatic activity to cleave chitin, which suggests a limited direct role in the protection against chitin-containing pathogens or in the digestion of chitin-containing food. In keeping with their conserved presence, recent advances have shown that CLP as well as chitinases play important roles in immune-related pathophysiology.

Chitinases in Lung Pathologies

Elevated levels of chitinase activity has been observed in lysosomal storage disease such as Gaucher disease, as well as in inflammatory lung diseases such as COPD, asthma, sarcoidosis, and CF [141–144]. Acidic mammalian chitinase (AMCase/Chit2), 1 of 2 true chitinases present in mammals, was shown to mediate type 2 inflammation and pathology in a mouse model of asthma [144]. A similar role was observed for chitotriosidase (Chit1) during fungal lung infection, where cleavage of fungal chitin by chitotriosidase mediates pathological responses [145]. In both asthma and fungal infection models, better outcomes and survival were observed in mice lacking AMCase and Chit1 [144, 145]. To put this into a human perspective, a substantial portion of the population (3–20%) lacks true chitinase activity due to a 24-bp mutation in the Chit1 gene, the major contributor of chitinase activity in humans, suggesting a nonessential but nevertheless potentially harmful role during pathological challenges [146–148].

CLP in Lung Pathologies

Chil1 (BRP-39 in mice and YKL 40 in humans) is one of the most prevalent CLP, with a high expression in leukocytes including macrophages and neutrophils suggesting immune-specific roles. Indeed, studies focusing on bacterial lung infection indicated an important role for Chil1 in inflammasome regulation in vivo and in vitro [149, 150]. The absence of BRP-39 in mice during lung infection with gram-positive *Streptococcus* or gram-negative *Pseudomonas* leads to exaggerated inflammasome activation. BRP-39 limits macrophage pyroptosis during bacterial infection to give an advantage to the host by limiting bacterial growth and exuberant inflammation leading to lung injury, thereby improving survival [149, 150]. BRP-39 has also been shown to bind IL-13 receptor α, relying on the protein TMEM to exert its effect [151, 152]. Other examples of CLP in mice include Ym1 and Ym2 [135]. These 2 proteins are highly expressed in the lung, and their expression is increased during the induction of type 2 inflammation such as in nematode infection and the HDM allergen model of asthma [153, 154]. Ym1 overexpression leads to an increase in lung neutrophilia, and blocking Ym1 using monoclonal antibody results in a decreased neutrophil accumulation upon HDM challenge in mouse lungs. γδ T cells are the major target of CLP, responding to the overexpression of CLP with an increased production of IL-17A [153]. Overall, chitinases and CLP are associated with many inflammatory diseases, and their causal role in various diseases has been es-

tablished using mouse models. These proteins might provide novel diagnostic and therapeutic targets to understand, treat, and monitor therapeutic efficacy in various inflammatory and infectious diseases of the respiratory tract and beyond.

Summary and Translational Implications

The multidimensional nature of pulmonary innate immunity can be viewed from 3 vantage points: (1) cellular [155] versus noncellular components, (2) protective versus harmful mechanisms, and (3) translational disease relevance for biomarker development and therapeutic targeting.

Cellular versus Noncellular Components

Specific to the pulmonary compartment is the mucociliary escalator as a physical innate host defense barrier in conjunction with airway epithelial cell-derived innate effector proteins (prototypically antimicrobial proteins, such as defensins and collectins). Among innate immune cells, AM represent a potent phagocytic immune cell sentinel in the lower airway compartment equipped with a broad cellular armamentarium to protect the airspace from microbial and nonmicrobial (dust and cigarette smoke) airborne exposures and serving as a rheostat maintaining alveolar homeostasis. While AM dominate in the lower/alveolar space, neutrophils are often found to accumulate in the more proximal/bronchial airway compartments. Lymphocytes, in turn, are mainly found in the lung tissue/parenchyma [10], while they are scarce in the bronchoalveolar space, which could be due in part to suppressive neutrophil-T-cell interactions [49]. Newly identified innate immune cell types, such as myeloid-derived suppressor cells, MAIT cells, and ILC add to the emerging complexity and layering of innate host defense shields in the pulmonary mucosal environment. While our understanding of the regulatory and pathophysiological roles of these subsets is increasing in murine model systems, their relevance for human pathologies remains poorly defined.

Protective versus Harmful Activities

The activities of innate immune cells and proteins mainly depend on the spatiotemporal context. For example, intracellular enzymes such as elastase or matrix metalloproteases provide protection by degrading phagocytosed microbial proteins, yet the very same enzymes liberated into the extracellular microenvironment can cause severe tissue injury by degrading extracellular matrix proteins, such as elastin, thereby remodeling the fragile pulmonary architecture. Temporally, innate immune effector responses are mostly protective in the initial phase of infection and inflammation, but they can become harmful and induce autoinflammatory complications if they fail to resolve, as exemplified in chronic lung diseases such as CF, IPF, and COPD [42]. From a cellular perspective, pulmonary innate immune cells can be further subdivided into 2 simplified categories: first, granulocytes (neutrophils, eosinophils, and basophils) that are short-lived and bear a higher acute pathogenic potential by rapidly releasing their toxic and tissue-damaging components (proteases and oxidants) upon local activation in airways [8, 46], and, second, mononuclear cells (monocytes, alveolar/interstitial macrophages, and dendritic cells) that are generally longer lived and more controlled in terms of enzyme and mediator release, mainly serving as antigen-presenting cells and scavengers of apoptotic bodies/debris and invading microbes. Short-lived innate immune cells play a major role in the early phase of acute respiratory conditions, such as neutrophils in lung infections or acute respiratory distress syndrome, whereas long-lived innate immune cells, such as macrophages and ILC, orchestrate chronic outcomes of tissue inflammation and remodeling in chronic pulmonary conditions like lung fibrosis/IPF and COPD. Notably, different macrophage subtypes have been proposed to differentially affect pulmonary disease outcomes in asthma, COPD, IPF, and CF.

Translational Disease Relevance for Biomarker Development and Therapeutic Targeting

Therapeutic approaches targeting innate immune cells and particularly innate immune cell-derived proteases appear reasonable given the excess of these enzymes in the pulmonary microenvironment (particularly in CF and COPD). However, clinical studies have been so far limited either by safety (for small molecule approaches targeting MMP), or by efficacy (for supplementation of antiproteases, such as α-1 antitrypsin) [156, 157]. Therapeutic strategies targeting rarer innate immune cell subpopulations, such as ILC or MAIT cells, are hampered by: (1) the incomplete understanding of their protective versus harmful potential in human disease and (2) the current lack of knowledge of how to target these cell types specifically without affecting other conventional lymphocyte subsets. Recently, novel innate immune mediators have emerged as potential biomarkers and/or drug targets for respiratory diseases. For example, alarmins/

DAMP (such as S100 proteins, ATP, or HMGB1) play an inducing role in lung immunity by binding to PRR like TLR4 and RAGE. Targeting these innate inflammation-amplifying loops while leaving bacterial sensing intact is an exciting challenge to tackle in future drug development approaches. Examples for current pharmacotherapeutic strategies targeting innate immune components in the respiratory space include: (1) monoclonal antibodies against innate immune cytokines (such as thymic stromal lymphopoietin [158, 159] or IL-33/ST2), (2) small molecule inhibitors targeting innate immune pathways or innate immune cell recruitment (such as CXCR2 antagonists [160–162] to dampen neutrophil recruitment), and (3) even newer technologies such as siRNA knockdown, microRNA, mRNA supplementation, or CRISPR/Cas9. A common challenge for these different therapeutic modalities is delivery into the lower airways, crossing the mucus barrier, and efficient uptake by pulmonary target cells.

Collectively, the innate immunity of the lung is multifaceted and multilayered with anatomical complexity (upper vs. lower airways, bronchoalveolar space vs. lung parenchyma), mucosal barrier interactions with microbes, and spatiotemporal dynamics of infiltrating (e.g., neutrophils) and resident (e.g., AM or ILC) immune cells. The key challenge for biomarker development and therapeutic success will be to define beneficial versus harmful innate immune subsets across species and disease conditions and to identify ways to selectively and safely target these subsets or their released mediators in order to prevent, attenuate, or resolve pulmonary pathologies.

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