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**Innate immunity of the lung: basic mechanisms and disease implications**

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**ABSTRACT**

The respiratory tract is daily faced with 10,000 litres of inhaled air. While the majority of air contains harmless environmental components, the pulmonary immune system has also 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 them belonging 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.

**MANUSCRIPT**

*The lung as innate immune sentinel*

The human respiratory tract is daily faced with 10,000 litres 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 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 them belonging 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 are the initial checkpoints that encounter inhaled antigens and trigger pro-inflammatory 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) and chemokines [4-7]. Of particular importance for 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 supported by distinct cytokines that are released by local airway cells and induce microenvironmentally-tailored immune contexts, particularly IL-1-alpha and IL-1-beta, IL-10, IL-17, IL-23, IL-25, IL-33 and TSLP. Through the integrated action of pro-inflammatory lipid mediator, chemokine and cytokine mediators, different immune cell populations are sequentially recruited into the bronchoalveolar and lung parenchymal compartments. Initially, neutrophils are attracted and localize mainly in the bronchoalveolar space where they engage in short-term host-pathogen interactions [8], followed by monocyes 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 form organized ectopic tertiary lymphoid organs, termed bronchus-associated lymphoid tissue (BALT) or inducible BALT (for humans) [11]. Besides these more established components of the pulmonary immune response, recent studies highlight novel immune cells and mediators, such as innate lymphoid cells (ILCs), mucosal-associated invariant T cells (MAITS), chitinase-like proteins and others. Here we aim to summarize the different components of the innate pulmonary immune response with an emphasis on novel directions for translational research and drug development.

*Airway epithelial cells as first line of innate immune sensing*

Pathogens are sensed by a variety of receptors expressed by airway epithelial cells. These include various families of pattern recognition receptors (PRRs) represented, for example, by Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), Protease-activated receptors (PARs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs), and the Bitter and Sweet taste receptors. TLR expression and function in airway epithelium has been widely studied. These PRRs 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 TLRs then activate intracellular downstream signalling 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 TLRs (TLR3, TLR7, TLR9) and the RLRs, RIG-I and MDA-5, which recognise replicating RNA viruses in infected cells, in nasal epithelium. These studies using nasal biopsies and primary human nasal epithelial cells (HNECs) stimulated with artificial TLR and RLR agonists demonstrated how these receptors generate robust IL-6, IL-8 and IFN-β responses and act as a first line of defence against viruses invading the respiratory tract. In another study reactive oxygen species (ROS) 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.* also evaluated inflammatory and antiviral responses to human virus infection in HNECs from chronic rhinosinusitis patients, wherein decreased MDA-5 and IFN-β expression were evident, and human rhinovirus clearance was slightly impaired [14].

Another type of PRR essential for innate immunity in the pulmonary environment are CLRs 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 house dust mite (HDM) [15] leading to secretion of the dendritic cell chemokine CCL20. Other non-fungal 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]. Interestingly according to Post *et al.* [17] who studied allergic sensitisation and HDM-induced allergic airway inflammation, whilst PAR-2 contributes to HDM-induced IgE responses it is dispensable for the induction of pro-inflammatory cytokine by HDM. In another study others demonstrated that in addition to producing cytokines, allergen-activated airway epithelial cells can also release uric acid [18], thereby promoting TH2 sensitisation and amplifying allergic inflammation (reviewed in [19]).

Among NLRs, NOD1, NOD2 and NLRP3 are expressed by airway epithelial cells. Expression of NOD1 has been shown to be down-regulated during pollen season among patients with allergic rhinitis [20] and its normal activation can reduce airway hyper-responsiveness 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 polarised airway epithelial cell barrier function [23].

One particularly exciting new finding on PRR expression and function in airway epithelial cells in recent years has been the discovery 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 specialised solitary ‘sinonasal chemosensory cells’ (SCCs) in the upper respiratory tract [25,26]. Bitter taste receptors are activated by quorum-sensing molecules whereas sweet receptors respond to sugars. For example the bitter taste receptor T2R38 is activated by homoserine lactones from *Pseudomomas aeruginosa*, causing an increase in nitric oxide and enhanced mucociliary clearance [27]. Lee *et al.* [28] have 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 sweet taste receptor T1R2/3. Thus activation of T12/3 and repression of T2R due to increased intranasal glucose may be responsible for chronic rhinosinusitis.

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

*Innate immune effector cells: neutrophils and macrophages*

Neutrophils are the most abundant subset of leukocytes patrolling in blood in search of potential injuries and stimuli (e.g. PAMPs, DAMPs, 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 limited capacity for *de novo* mRNA transcription and protein production. However, recent evidence show that they are endowed with extensive adaptive abilities, which underlie an equally extensive functional complexity [8].

Human blood neutrophil lifespan was previously estimated to be shorter than a day, however recent studies suggested an upper limit of 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 referred to as the “marginated” pool [33]. Within the lung alone, this pool constitutes the most prominent reservoir of neutrophils in the systemic circulation (approximately 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 re-released in the blood stream [35]. However, this mechanism of neutrophil retention is impaired in acute respiratory distress syndrome (ARDS) patients, resulting in the exposure of peripheral organs to primed systemic neutrophils, leading to severe complications [36].

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 (CD16high CD62Ldim CD11bhigh) under both healthy and inflamed conditions [38,39]. When crossing into the airway lumen, neutrophils further modulate surface expression of chemokine and Toll-like receptors, which together mediate core inflammatory signaling. These changes in neutrophil phenotypes include 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 (BALF) of patients suffering from chronic airway inflammation upregulate CCR1, CCR2, CCR3, CCR5, CXCR3 and CXCR4 (as observed in CF, 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 are concomitant to *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 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 (or mammalian) Target Of Rapamycin (mTOR) pathways, linked to surface upregulation of functional receptors (e.g., the Receptor for Advanced Glycation End-products -RAGE-) and metabolite transporters (e.g., glucose and amino acid transporters, Glut1 and ASCT2) [43-45]. Since CF airways are enriched in inflammatory mediators and nutrient 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]. A hallmark of neutrophil activity within inflamed airways is the extracellular release of proteases and oxidases (e.g., neutrophil elastase -NE- and myeloperoxidase -MPO-) 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 the regulation of the adaptive immune system, further emphasizing the multidimensional importance of neutrophil plasticity [37]. For example, 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 the 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 through the body [52,53].

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 in the release of extracellular complexes or “traps” formed by decondensed nuclear DNA (e.g., after histone citrullination), histones, and cationic effectors such as NE and MPO. The deployment of neutrophil extracellular traps (NETs), termed “NETosis”, is believed to enable immobilization and possibly killing of pathogens, while precipitating neutrophil death [54,55]. While NETs have been associated with numerous pathologies including autoimmune disorders, and infectious diseases related to bacteria, fungi, as well as 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 NETs have shown both beneficial and harmful effects of these structures (reviewed in [56]). The ability of NETs to spread out and trap microbes could trigger increased killing efficiency and reduction of pathogen burden. Mitigating these positive effects of NETs 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, NE, and MPO 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].

Taken together, numerous studies in the past decade have highlighted the adaptability of neutrophils in acute and chronic immune responses, contradicting the conventional view as “simple” cells, incapable of protein synthesis, with limited lifespan, and primarily relying on oxidative and proteolytic killing to carry out their function. The identification of novel neutrophil functions and regulatory mechanisms highlighted their role in balancing pro- and anti-inflammatory signaling, in order to promote a swift return to homeostasis and limit tissue damage and disease progression. The concept of “neutrophil heterogeneity” originated by Gallin et al in 1984 [63] 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, first discovered by Ilya Metchnikoff, belong to the  [mononuclear phagocyte system](https://en.wikipedia.org/wiki/Mononuclear_phagocyte_system" \o "Mononuclear phagocyte system) and represent potent anti-microbial innate immune cells that are found in all tissues across 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 alveolar macrophages. The alveolar macrophage, 15 to 50 μm in diameter, is mainly located in the alveolar space and represents the predominant phagocytic and antigen-presenting cell in the human respiratory tract [65]. Under homeostatic/healthy conditions, alveolar macrophages are the most abundant cellular fraction within BAL fluids, while under acute or chronic inflammatory conditions other leukocyte populations, prototypically neutrophils (acute infections, CF or ARDS) and lymphocytes (sarcoidosis, allergic alveolitis/EAA), accumulate and shift this balance. Distinct to other tissue macrophage subsets, alveolar macrophages feature a remarkably high phenotypic, metabolic and functional plasticity [65-67]. Metabolically, alveolar macrophages exhibit a high basal glucose consumption and respiratory rate, yet a low respiratory burst activity. Phenotypically, alveolar macrophages directly reflect the alveolar host-environment interterface zone and contain granules of exogenous material, as exemplified in chronic smokers where alveolar macrophages accumulate in the BAL, are larger in diameter, activated and stain dark on cytospin preparations. By taking up inhaled environmental particles, pollutants, allergens and airborne microbes, alveolar macrophages serve as airway scavengers to keep the respiratory system clean and homeostatic. Another function related to their potent phagocytic capacity is the maintainance of surfactant homeostasis by engulfing and catabolizing local surrounding surfactant proteins, a functionality that is impaired in a severe disorder called pulmonary alveolar proteinosis (PAP), characterized by a dysfunction of the GM-CSF pathway and related to alveolar macrophage functions [68,69]. By sensing bronchoalveolar PAMP/MAMP and DAMP signals, alveolar macrophages integrate various microbial- and host-derived signals and respond with the concerted release of various pro- or anti-inflammatory mediators into the alveolar space, mainly cytokines such as IL-1-beta, IL-6, IL-10 or TNF-alpha. Recent studies further highlight that alveolar macrophages can have immunoregulatory roles. In murine asthma model systems, pulmonary macrophages were found to generate regulatory T cells to induce airway tolerance [70]. Alveolar macrophages were further found to attach to the alveolar wall (become “sessile”) and communicate with the alveolar epithelium to induce a immunosuppressive/-modulatory signal in order to dampen lung inflammation [71].

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

# Macrophages have a remarkable functional and phenotypic diversity and can be dichotomized into M1 (IFN-gamma/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 on macrophage activation, plasticity and M1/M2 polarization we refer to recent reviews in that field [76-78]. Overall, the complex multifunctionality of alveolar macrophages, interacting as APCs with T cells, clearing apoptotic and necrotic cells through efferocytosis, killing pathogens and releasing both pro- and anti-inflammatory factors, renders a good vs 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]. IPF is a prototypic example of a complex chronic lung disease where the role of pulmonary macrophages remains controversial. In brief, alveolar macrophages seem to play a dual role in lung fibrosis given their release of profibrotic factors (such as TGF-beta1 and PDGF) and thereby driving disease progression and, on the other hand, their potency to liberate proteases (MMPs) that can digest extracellular matrix and thereby act anti-fibrotic/fibrinolytic. For a more thorough discussion of macrophage phenotypes and functions in IPF we refer to a recent review in that field [79].

*Innate lymphoid cells*

ILCs are a recently identified group of heterogeneous innate immune cells belonging to the lymphoid lineage but lacking antigen-specific receptors [81]. Mechanistically, ILCs are involved in protective anti-microbial responses, particularly at mucosal barrier organs, but have also pathogenic roles in inflammation, autoimmunity, allergy and fibrosis within tissues [81,82]. ILCs 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, ILCs do not express RAG (recombination-activating gene) genes, implying that ILCs can be, in contrast to T and B cells, activated directly [83]. ILCs regularly 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, ILCs are divided into three distinct subsets. ILC1s, which include NK cells, are defined, in analogy to Th1 cells, by their ability to release interferon-γ (IFN-γ) and tumor necrosis factor (TNF) and the expression of the T-box transcription factor T-bet or eomesodermin (Eomes) [85]. Functionally, NK cells require only Eomes and IL-5, but not IL-7 or T-bet. Across tissues, ILC1 cells are found mostly in liver, thymus, uterus, skin, lung, secondary lymphoid tissue, spleen and gut. ILC1s have been demonstrated to accumulate in response to viral and bacterial infections in mice [86]. This has probable relevance for chronic human disease conditions, as circulating ILCs were increased in COPD patients upon exacerbations [87]. Type 2 ILC (ILC2s), the counterpart of Th2 cells, produce IL-4, IL-5, IL-9 and IL-13 in response to IL-25, IL-33 and TSLP (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]. ILC2s are localized mostly in the healthy skin, lung, and adipose tissue of mice and humans and have been mainly involved in tissue inflammation, remodeling and fibrosis. Interestingly, ILC2s are the main cell type among ILCs found in the murine lung, however, representing overall only 0.4-1% of total live lung cells. A recent study demonstrated, using single-cell RNA sequencing of lung-resident ILCs, that in the context of allergic lung inflammation the alarmin cytokines IL-25 and IL-33 were linked to the activation and expansion of lung-resident ILC2s [88]. *In vivo* activation by IL-25 induced high expression of the Neuromedin U (NMU) receptor (NMUR1) in ILC2s. Interestingly, the combined treatment with IL-25 and NMU synergistically promoted allergic inflammation. In line with previous studies showing increased numbers of ILC2s in the blood of asthma patients [90], this study suggests that ILC2s could represent a future and potentially predictive biomarker for patients with asthma. Type 3 ILCs contain natural cytotoxicity receptor positive (NCR+) ILC3 and NCR- LTi cells, which depend on the transcription factor RORγt and produce either IL-22 (NCR+ ILC3 or ILC22 cells) or both IL-17 and IL-22 (NCR- LTi or ILC17 cells) in response to IL-23 [82,91]. LTi cells were reported to contribute to the development of secondary lymphoid tissue, where they activate stromal cells through the lymphotoxin-α1β2-mediated LTβR signaling pathway. This triggers the expression of adhesion molecules (e.g. ICAM, VCAM) and chemokines (CXCL13, CCL19 and CCL21) required for the formation of lymphoid follicles [92]. We have shown previously that B-cell-dependent inducible bronchus associated lymphoid tissue (iBALT) formation is essential for emphysema development in the cigarette smoke-induced COPD mouse model [93]. Therefore, when viewed in combination, it is tempting to speculate that LTi cells may play a key role in the development of COPD immune pathogenesis. Although the mechanistic and functional contribution of ILCs in animal models of asthma and COPD has been interrogated, there is limited evidence for a potential role in human disease conditions, requiring further studies in that field. With regards to lung fibrosis, the potential role of ILCs is discussed in a comprehensive review [94]. In brief, ILC2s and ILC3s have been involved in the pathogenesis of lung fibrosis. IL-17A plays a key role in pulmonary inflammation and fibrosis and has been implicated in the pathomechanisms underlying and driving asthma, COPD, IPF and CF [95-97]. Given ILC3s as essential source of IL-17 at mucosal sites, these innate tissue cells are suggested as early orchestrators of lung tissue remodeling and fibrogenesis. The potential role of ILCs in CF lung disease is elusive, yet Moretti and coworkers showed recently that a mast cell - ILC2 - Th9 pathway promotes pulmonary inflammation in murine infection models of CF-like lung disease [98].

*Mucosal-Associated Invariant T cells*

Mucosal Associated Invariant T cells (MAITs) are a group of innate-like T lymphocytes, that are highly aboundant in human blood (~1-10%; [99]) and in mucosal tissues including intestines, lungs and livers [100-103]. These cells are characterized by their expression of the invariant T cell recpeor (TCR) α chain, TRAV1-2 joined with TRAJ33 and a limited range of TCRß chains and abundant expression of CD161 and CD218 (IL18Rα) [101,104,105]. Recently, studies have shown that MAIT cells can recognize Vitamin B metabolic byproducts produced by a range of micro organisms presented by the ubiquitously expressed, MHC1 related protein, MR1 [106-109]. Activated MAIT cells have been observed to generate high levels of IFN-γ, TNF-α, IL-17 and cytotoxic/cytolytic perforin and Granzymes A, B and K[110-115].

MAIT cells frequencies in normal human lungs are variable, ranging from 2-20% of all T cells in the lungs [103,116]. Given their abundance in the blood, many studies have studied peripheral blood MAIT cells in various respiratory infections and maladies. There were no changes in MAIT cell frequency in the blood of inhaled corticosteroid (ICS) naïve COPD relative to healthy donors, however, their frequency was significantly reduced in ICS treated COPD patient’s blood and bronchial biopsies [103]. Reduced MAIT cell frequency in the blood of was more pronounced in moderate to severe COPD patients and was associated with elevated serum C-reactive protein levels and reduced lung function (as assessed via FEV1/FVC ratio) [117]. Consistent with a role of ICS in modulating MAIT cell numbers, these cells were also observed to be significantly reduced in ICS treated asmatic patient’s blood and lung tissue relative to normal individuals [118,119]. This was especially evident in severe asthmatic patients [119]. These studies suggest that MAIT cells are sucipitable to ICS treatment and that their deficiency is associated with severe respiratory pathology.

Experimental evidence suggested that MAIT cells can be activated with epithelial cells-infected with multiple bacterial strains [110]. Indeed, an important role of these cells in anti-bacterial immunity is supported by studies showing a significant inverse correlation between peripheral blood MAIT cell numbers and CF disease severity and inverse association with *Pseudomonas aeruginosa* infection and disease exacerbation [120]. Consistently, circulating MAIT cells were also observed to be decreased in the peripheral blood of patients with tuberculosis (TB) and nontuberculous mycobacterial infection [121,122] and their deficiency was correlated with disease severity [121]. *In vitro* stimulation of freshly isolated MAIT cells using PMA, ionomycin, IL-15, anti-CD28 antibodies and/or mycobacterial lysates suggested a severe functional deficiency in TB patient relative to healthy donor derived MAIT cells, as assessed by the induction of IFN-γ and IL-17 [121,123]. Various studies have shown an important, non redudntant, role for IL-12, IL-18, and IL-2 signaling in MAIT cell activation [113,115,124-126], and a significant reduction of, IL-12 and/or IL-2 receptors in *in vitro* stimulated peripheral blood MAIT cells from TB patients [123,126]. Finally, two reports have suggested that functionally deficient MAIT cells from the peripheral blood of TB patients and HIV+TB patients have elevated levels of cell surface PD-1 expression relative to those from healthy donors [127,128], 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 defeciencies in these cells is observed in patients with active bacterial infecitons.

Identification of mechanisms propagated by MAIT cells in pulmonary immunity were hindered hindered due to the low abundance of these cells in germ free laboratory mice; however, with the recent development of iVα19 TCRα [129] transgenic and B6-MAITCAST [130] and the commercial availability of murine MR1 tetramers, many studies have been performed characterizing the role of these cells in models of pulmonary inflammation and infection. Utilizing iVα19-transgenic MR1 sufficient or iVα19-trangenic MR1 deficient mice to study the role of MAIT cells in anti-bacterial immunity, Le Bourhis et al. [122] observed that MR1 sufficient mice, with more activated MAIT cells, had a lower bacterial burden relative to MR1 deficient mice. In a model of pulmonary bacterial infection, one study have shown evidence for the importance of MAIT cells in protecting against *Francisella tularenis* (LVS)pulmonary infection [131]. Utilizing C57BL6 *MR1+* or *MR1-* mice, this group observed an MR1 dependent recrutement and/or expansion of MAIT cells in LVS infected mice, and a lower bacterial burden in the lungs of the MR1-sufficient relative to MR1-deficient murine lungs. *In vitro* coculture studies utilizing MAIT cells and LVS infected macrophages indicated that MAIT cell derived IL-12p40, TNF and IFN-γ were indespensible in controlling intracellular bacterial growth in macrophages. Finally, this study have observed delayed recruitment of effector CD4+ helper and CD8+ cytotixic T cells in MR1-deficient mice relative to their MR1 sufficent counterparts. In a subsequent report, this group have identified MAIT cell derived GM-CSF to be required for the differentiation of CCR2+ monocytes into dendritic cells and the subsequent recruitment of effector helper and cytotixic T cells for efficient bacterial clearance [132]. 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 subsequent briding of the innate and adaptive immune mechanisms.

Given the identification of bacterial and fungal Vitamin B metabolites as MR1 presented antigens [106-109], MAIT cells were thought not to play a role in viral infection. However, a recent study have observed higher MAIT cell numbers in H7N9 influenza patients who recover from infection, relative to those who succumbed to the infection [125]. Utilizing an *in vitro* co-culture system of influenza infected airway epithelial cells line (A549) with human peripheral blood mononuclear cells, this group have observed an MR1 independent, CD14+ cell and IL18 dependent activation of MAIT cells as assessed by intracellular elevation of IFN-γ and granzyme B proteins [125]. Indeed, this was confirmed in another study, where MAIT cells were observed to be activated in an MR1 independent and IL-18, IL-12 and IL-15 dependent manner in response to various viral infections, including dengue, HCV and influenza viruses [133]. These studies suggest that MAIT cells may play an important role in viral infections.

Collectively, these studies suggest that MAIT cells are indespensible in the immune protection of the respiratory system against viral and bacterial infections. There is mounting evidence for changes in bacterial composition in exacerbated COPD, where there was more abundant microbial spiecies commonly observed in exacerbated COPD [134,135]. Further, severe asthmatic patients and asthmatic exacerbations are known to occur after respiratory viral infections (reviewed in [136,137]). Given the potential role of MAIT cells in controlling bacterial and viral infections, their deficiency in severe ICS resistant COPD and asthma may reflect enhanced sucipitability of these patients to pulmonary infections and may contribute to the severity of the disease.

*Novel mediators/Chitinase-like proteins*

There are many novel mediators that participate in lung innate immunity. These mediators include chitinase and chitinase like proteins (CLPs) that are conserved group of proteins that belong to the 18-glycosyl hydrolase family [138]. Although mammals do not synthesize chitins, the presence of chitinases and CLPs suggest their role in digestions of chitin-containing food or protection against chitin containing pathogens. This hypothesis was based on the initial epidemiologic evidences showing increased expression of these proteins in populations that are exposed to more chitin-containing pathogens and food products [139,140]. However, later studies casted doubts on this hypothesis indicating limited correlation between Chit1 deficiency and exposure to chitin containing parasites as well food [141-143].

CLPs have high binding capacity to chitin but lacks enzymatic activity to cleave chitin suggesting a limited direct role against chitin-containing pathogens or in digestion of chitin-containing food. Due to the conserved presence without any obvious roles, recent advances have shown that CLPs as well as chitinases play important roles in immune-related pathophysiology. Elevated levels of chitinase activity has been observed in lysosomal storage disease such as Gaucher’s disease or lung diseases where inflammatory response plays a major role in the pathogenesis such as chronic obstructive pulmonary disease (COPD), asthma, sarcoidosis, cystic fibrosis, etc [144-147]. Acidic mammalian chitinase (Chit2), one of two true chitinase present in mammals, have been shown to mediate type 2 inflammation and pathology in mouse model of asthama [147]. Similar role for chitotriosidase (Chit1) was observed during fungal lung infection, where cleavage of fungal chitin by chitotriosidase meadiates pathological responses [148]. In both the asthma models and fungal infection models, better outcomes and survival were observed in mice lacking AMCase and Chit1 [147,148]. To put in perspective, a substantial human population (3-20%) lacks true chitinase activity due to a 24-bp mutation in Chit1 gene (the major contributor of chitinase activity in humans), suggesting their non-essential but potential harmful effects during pathological challenges [149-151].

On the other hand, CLPs are well conserved but have high divergence in mammals (YKL-39 & YKL-40 in humans and BRP-39, Ym1 & Ym2 in mice), suggesting their important protective roles to the host [138]. The divergence in CLPs among mammals have been attributed to the difference in microbial threat faced by each individual species [138]. Chil1 (BRP-39 in mice and YKL 40 in humans) is one of the most prevalent CLP present in humans. Chil1 is highly expressed in immune cells including macrophages and neutrophils suggesting a immune-specific roles. Indeed; studies using bacterial lung infections indicated their important roles in inflammasome regulation *in-vivo* and *in-vitro* [152,153]. 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 advantage to the host by limiting bacterial growth and exuberant inflammation leading to lung injury that improes survival [152,153]. BRP-39 has been shown to bind IL-13 receptor α involving the protein TMEM to exert its effect [154,155].

The other members of CLPs in mice include Ym1 and Ym2 [138]. These two proteins are hightly expressed in the lung and their expression is increased during the induction of type 2 inflammation such as nematode infection and house dust mite (HDM) allergen model of asthma [156,157]. Ym1 overexpression leads to increase in lung neutrophilia and blocking Ym1 using monoclonal antibody resulted in decreased neutrophil accumulation in lung during HDM model in mice. γδ T cells are the major target of CLPs where overexpression of CLPs result in increase production of IL-17A [156]. These experiments suggest important roles played by Ym1 in mediating inflammation in the lung. Overall, chitinase and CLPs are associated with many inflammatory diseases and their causal role in various diseases has been established using mouse models. These proteins might provide novel diagnostic and therapeutic targets to understand, treat and moniter therapeutic efficacies in many inflammatory and infectious diseases.

*Summary and disease implications*

The multidimensional nature of pulmonary innate immunity can be subdivided into three categories: (i) cellular vs non-cellular components, (ii) protective vs harmful mechanisms and (iii) translational disease relevance for biomarker and therapeutic targeting approaches.

To summarize on (i): innate immune responses at mucosal sites in general comprise two arms: cellular [158] and non-cellular/humoral components. Particular 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 anti-microbial proteins, such as defensins and collectins, that act anti-microbial. Among innate immune cells, alveolar macrophages 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 non-microbial (dust, cigarette smoke) airborne exposures and serving as a rheostat to maintain alveolar heomeostasis. While alveolar macrophages dominate in the lower/alveolar space, neutrophils accumulate in the more proximal/bronchial airway compartments. Lymphocytes, in turn, are mainly found in lung tissue/parenchyma [10], while they are scarce in the bronchoalveolar space, which might be due to suppressive neutrophil-T cell interactions [49]. Novel innate immune cell types, such as MDSCs, MAIT cells and ILCs add to the emerging complexity of several layers of innate host defense shields in the pulmonary mucosal environment. While our understainding on their regulatory and pathophysiological role in murine model systems is increasing, their relevance for human pathologies remains poorly defined.

To summarize on (ii): protective vs harmful activities of innate immune cells and proteins mainly depend on the spatiotemporal context: intracellular enzymes, such as elastase or MMPs, act protective by degrading phagocytosed microbial proteins, while the same enzymes liberated into the extracellular microenvironment can cause severe tissue injury by degrading extracellular matrices, such as elastin, and thereby remodeling the fragile pulmonary architecure. Temporally, innate immune effector responses are mostly protective in the titial phases of infection and inflammation, but become harmful and auto-inflammatory if they fail to resolve and perpetuate, exemplified in chronic lung diseases [42], such as CF, IPF and COPD. From a cellular perspective, pulmonary innate immune cells can be further subdivided into two simplified categories: granulocytic cells (neutrophils, eosinophils and basophils) that are short-lived and bear a higher acute pathogenic potential by rapidly releasing their toxic and tissue-damaging ingrendients (proteases, oxidants) upon local airway activation [8,46], and mononuclear cells (monocytes, alveolar/interstitial macrophages and dendritic cells) that live longer, are more robust and controlled in terms of enzyme release and mainly serve as APCs and protective 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 ARDS, whereas long-lived innate immune cells, such as macrophages and ILCs, probably orchestrate the chronic outcome of tissue inflammation and remodeling in chronic pulmonary conditions like lung fibrosis/IPF and COPD. Notably, different macrophage subtypes, M1 vs M2, have been proposed to differentially affect pulmonary disease outcome in asthma, COPD, asthma and CF.

To summarize on (iii): therapeutic approaches targeting innate immune cells and particularly innate immune cell-derived proteases are reasonable given the surplus of these enzymes in the pulmonary microenvironment (particularly in CF and COPD), yet clinical studies were so far either limited by safety (for small molecule approaches targeting MMPs) or by efficacy (for supplementation of anti-proteases, prototypically alpha-1 antitrypsin) [159,160]. Therapeutic strategies targeting rarer innate immune cell subpopulations, such as ILCs or MAIT cells, are hampered by (i) the early/poor understanding of their protective vs harmful potential in human disease conditions and (ii) the lack of knowledge how to target these cell types specifically. Recently, novel innate immune mediators have been emerged as potential biomarkers and/or drug targets for respiratory diseases. Of note, alarmins/DAMPs (such as S100 proteins, ATP or HMGB1) seem to play a role in lung immunity and bind to pattern recognition receptors like TLR4 and RAGE. Targeting these innate inflammation-amplifying loops while leaving bacterial sensing intact will pose a challenge to future drug development approaches in that space. Collectively, innate immunity of the lung is multi-faceted and multi-layered given the anatomical complexity (upper versus lower airways, bronchoalveolar space versus lung parenchyma), the mucosal barrier interactions with microbial colonizers and the spatiotemporal dynamics of infiltrating (e.g. neutrophils) and resident (e.g. alveolar macrophages or ILC subtypes) immune cells. The key challenge for biomarker and therapeutic success will be to define beneficial vs harmful innate immune cell subsets across species and to identify ways to selectively target respective cell types or their released mediators.

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