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Immunity to fungi in the lung

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Abstract

The respiratory tree maintains sterilizing immunity against human fungal pathogens. Humans inhale ubiquitous filamentous molds and geographically restricted dimorphic fungal pathogens that form small airborne conidia. In addition, pathogenic yeasts, exemplified by encapsulated *Cryptococcus* species, and *Pneumocystis* pose significant fungal threats to the lung. Classically, fungal pneumonia occurs in immune compromised individuals, specifically in patients with HIV/AIDS, in patients with hematologic malignancies, in organ transplant recipients, and in patients treated with corticosteroids and targeted biologics that impair fungal immune surveillance in the lung. The emergence of fungal co-infections during severe influenza and COVID-19 underscores the impairment of fungus-specific host defense pathways in the lung by respiratory viruses and by medical therapies to treat viral infections. Beyond life-threatening invasive syndromes, fungal antigen exposure can exacerbate allergenic disease in the lung. In this review, we discuss emerging principles of lung-specific antifungal immunity, integrate the contributions and cooperation of lung epithelial, innate immune, and adaptive immune cells to mucosal barrier immunity, and highlight the pathogenesis of fungal-associated allergenic disease. Improved understanding of fungus-specific immunity in the respiratory tree has paved the way to develop improved diagnostic, pre-emptive, therapeutic, and vaccine approaches for fungal diseases of the lung.

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Keywords

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1. Common human fungal pathogens and fungus-associated diseases in the lung

Many fungi form small airborne propagules, termed conidia (i.e., vegetative spores) for dispersal in habitats on Earth. Humans and terrestrial animals inhale fungal cells daily, with silent and asymptomatic clearance being the norm. Only a small subset of the > 1 million fungal species can cause invasive disease in the lung [1,2]. Chief among these are the filamentous molds (*Aspergillus* species, *Fusarium* species, agents of mucormycosis) dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis* and *C. posadasii*, *Paracoccidioides brasiliensis*, and *Talaromyces marnefeii*), the encapsulated yeasts *Cryptococcus neoformans* and *C. gattii*, and *Pneumocystis jirovecii*. Notably, *Candida* species are not associated with invasive disease in the lower respiratory tract, though can cause mucosal candidiasis in the oropharynx. Table 1 summarizes major human respiratory fungal pathogens, physical attributes of inhaled conidia and associated clinical syndromes. Thermotolerance to human body temperature and the small size of the infectious propagules (typically range from 1 to 10 μm) represent core properties of the respiratory fungal pathogens listed above [3].

The most common clinical syndrome associated with respiratory fungal pathogens is pneumonia, characterized by the triad of fever, cough, and radiographic findings of lower respiratory tract disease. Hypoxemic respiratory failure is a hallmark of *Pneumocystis* pneumonia and is uncommon in fungal pneumonia caused by filamentous molds. Fungal pneumonia occurs primarily in immune compromised individuals, in which injury to neutrophils and other myeloid cells is pivotal for the development of invasive mold infections (*Aspergillus*, agents of mucormycosis). In contrast, injury to T cell function and to the process of granulomatous inflammation is critical for susceptibility to the genera *Cryptococcus*, *Pneumocystis*, and dimorphic fungi, all of which represent causative agents of AIDS-defining pulmonary opportunistic infections. Rarely, immune competent individuals can become susceptible to primary lung infections by dimorphic fungal pathogens.

Classic risk factors for pulmonary mold infections include prolonged neutropenia and/or monocytopenia (e.g., GATA2 deficiency), functional myeloid cell defects (e.g., chronic granulomatous disease), receipt of systemic corticosteroids, and diabetic ketoacidosis (agents of mucormycosis). Novel risk groups have emerged due to advances in medical technologies, specifically small molecule targeted biologics that interfere with fungal surveillance pathways beyond their intended role to treat autoimmunity and cancer [4,5]. Patients with severe viral infections, in particular influenza [6] and COVID-19 [7], as well as ICU and COPD patients all exhibit heightened risk for lung fungal infections.

Recent years have seen a rapid advance in our understanding of molecular and cellular response pathways to pulmonary fungal pathogens, driven in part by the study of immune deficiency disorders that confer susceptibility to these infections, the development of appropriate mouse models of disease, and the creation of fungal antigen-specific T cells to examine cell-mediated immunity and experimental vaccine immunity to these pathogens. This review focuses on broad themes that have arisen in studies of pulmonary antifungal immunity. We emphasize the role of different anatomic sites and cellular crosstalk in maintaining sterilizing anti-fungal immunity in the lung and in the pathogenesis of fungus-associated allergenic disease. The reader is referred to outstanding reviews that summarize host genetic risk and pharmacologic susceptibility to pulmonary mycoses [8,9].

2. Architecture of the lung

Humans breathe 10–15 m^3 of air daily. Inhaled air passes through the upper respiratory tract (URT) that includes the nasal cavity, pharynx, and larynx, past the vocal cords, and into the lower respiratory tract (LRT). The airways in the URT consist primarily of ciliated columnar epithelial cells, secretory Goblet cells, chemosensory Tuft cells (aka brush cells), pulmonary neuroendocrine cells, and undifferentiated basal cells (Fig. 1). The mucociliary elevator harnesses the rhythmic, beating action of ciliated epithelial cells and mechanical entrapment of inhaled particles in the mucus layer to clear and expel inhaled particles (e.g., fungal cells, dust, and allergens) via cough.

The conducting airways of the LRT consist of the trachea, bronchi, and bronchioles. Non-ciliated club cells join epithelial and secretory cells to form the lining of bronchi and bronchioles. Basal cells in the tracheobronchial zone can regenerate columnar epithelial cells following tissue injury. In humans and other large mammals, proximal conducting airways transition into the distal respiratory zone, which consists of respiratory bronchioles and alveolar ducts. Finally, air reaches the terminal alveolar sacs. Gas exchange and blood oxygenation occurs in this distal airway and alveolar respiratory zone, with a 1 μm cellular barrier separating the alveolar lumen from lung capillaries. The human lungs contain approximately 300 million alveoli that measure 400–450 μm in diameter [10]. Type I alveolar epithelial cells that derive from surfactant-producing type II alveolar epithelial cells collectively form the cellular lining in alveoli that are surrounded by capillaries, thin interstitial tissue, and nerve cells.

Single-cell sequencing approaches have identified rare cell types in human and murine airways. In the trachea, $Foxj1^+$ pulmonary ionocytes express the cystic fibrosis transmembrane regulator including multi-potent respiratory airway secretory cells that give rise to type II alveolar epithelial cells via Notch and Wnt signaling; these cells can be distinguished from other secretory cells by a distinct secretoglobulin (SCGB) expression profile [11]. $Ascl1^+$ pulmonary neuroendocrine cells (<0.5 % of airway epithelium) receive innervation from efferent and afferent neurons, stimulate type 2 innate lymphoid cells via calcitonin gene-related peptide release, and amplify allergic asthma responses [12]. In general, the functional role of these rare lung cell types in antifungal immunity and fungus-associated allergenic disease remains to be elucidated.

The respiratory tree harbors collections of steady-state and inducible immune cell populations. Frontline, steady-state immunity includes the positioning of alveolar (AMs) and interstitial macrophages (IMs), conventional dendritic cell (cDC) 1 and 2 subsets either in or adjacent to the airways. Single-cell technologies and the use of fluorescent reporters have revealed heterogeneity among previously uniform cell populations. For example, during *Aspergillus* and *Cryptococcus* infection AMs segregate into $CXCL2^+$ and into $CXCL2^-$ subsets [13]. $CXCL2^+$ AMs appear to be pro-inflammatory in phenotype while their $CXCL2^-$ counterparts are characterized by production of C1q and the regulatory cytokine IL-10. $CXCL2^-$ AMs exhibit a transcriptional profile that is more consistent with a regulatory phenotype [13]. Thus, AMs assume context-specific roles as sentinels in the induction of pro-inflammatory responses as well as in the maintenance of tolerance and tissue homeostasis.

The lung environment rapidly and profoundly alters its composition after fungal pathogens trigger an inflammatory response. One example is the presence of inducible tissue-resident immune cells, e.g., mucosa-associated (MALT) and bronchus-associated lymphoid tissue (BALT), that collectively play an important role in immune surveillance and in the rapid orchestration of innate and adaptive immunity to fungal pathogens. In upper airways, microfold cells (M cells) associate with MALT and can facilitate the entry and dissemination of bacterial pathogens [14]. Fungal recognition and growth in the lung trigger the rapid deployment of circulating immune cells, primarily neutrophils and monocytes, to the site of infection, leading to the induction of fungal antigen-specific immune responses. In the ensuing sections, the review will focus on lung-specific mechanisms of host defense and allergy and on the role of crosstalk between lung parenchymal cells and immune cells in these processes.

3. Fungal recognition and innate immune activation in the lung

Although pulmonary fungal pathogens vary widely in cellular morphology, the cell wall consists primarily of conserved polysaccharides that include immune-reactive β-1,3- and β-1,6-linked glucans, chitin, and mannans. Typically, chitin is found in the innermost proximal layer of the cell wall that extends over the plasma membrane, with β-glucans found in intermediate layers, and mannans and mannoproteins in more external layers. The reader is referred to excellent reviews that summarize current knowledge of fungal cell wall biogenesis and assembly [15].

The cell wall of *Aspergillus* species illustrates dynamic changes that occur during fungal cell growth in the lung. Inhaled *A. fumigatus* conidia contain a proteinaceous rodlet layer and a dihydroxynaphthalene (DHN)-melanin pigment, both of which are shed to expose β-glucans during the process of germination. Following germination, *A. fumigatus* hyphae secrete an exopolysaccharide, galactosaminogalactan (GAG), which confers adhesive properties and promotes resistance to neutrophil extracellular traps, as discussed below [16]. GAG can activate inflammasomes in macrophages through its binding to ribosomal proteins, likely inducing pyropoptic host cell death [17], though its mechanism of entry into host cells remains undefined. Most lung fungal pathogens also synthesize polysaccharide moieties that do not trigger robust innate immune responses, exemplified by α-glucans.

In the case of *Histoplasma,* an external α-glucan layer can shield β-glucans and undergo active remodeling by glucanases [18]. The encapsulated yeast *Cryptococcus* forms a large glucuronoxylomannan and galactoxylomannan capsule which conceals underlying immune-reactive glycoprotein components and blunts host innate immune activation [19].

Within the respiratory tree, inhaled fungal cells are opsonized with soluble pattern recognition receptors, surfactant, complement, and antibodies. These interactions facilitate the induction of antifungal effector systems and signaling responses by membrane-bound receptors. For example, the soluble receptor pentraxin-3 (PTX3) binds to galactomannan found on *Aspergillus* conidia and promotes FcγRIIA (*Cd32*)-dependent conidial uptake and subsequent inactivation by neutrophils [20]. *Ptx3* polymorphisms are associated with susceptibility to invasive pulmonary aspergillosis in bone marrow transplant patients, underscoring the importance of this molecule in pulmonary antifungal immunity [21,22]. The soluble mannose receptor binds to mannose moieties on fungal cells, though genetic deficiency does not increase mortality in a murine model of *Pneumocystis* pneumonia [23], consistent with functional redundancy in vivo.

Surfactant consists primarily of phosphatidylcholine (approx. 80%), phosphatidylglycerol (5–10%), cholesterol (5–10%), and surfactant proteins A-D (2–5%). Genetic deletion of individual surfactant proteins causes mild or no defects in antifungal immunity in mouse models of aspergillosis [24]. In fact, surfactant protein D can be harnessed by *C. neoformans* for protection against oxidative damage [25]. However, pulmonary alveolar proteinosis (PAP) can lead to substantial susceptibility to lung fungal infections by dimorphic fungi and, more rarely, by filamentous molds [26]. PAP patients accumulate enormous quantities of surfactant due to defective granulocyte-macrophage colony-stimulating factor (GM-CSF)-dependent surfactant catabolism by alveolar macrophages. These studies link surfactant homeostasis to antifungal immunity in the lung.

Although terminal complement deficiency has not been linked to susceptibility to fungal disease, the complement inhibitor eculizumab, a treatment for hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinemia, is associated with invasive pulmonary fungal infections [27–30]. Thus, pharmacologic C5a blockade likely impairs myeloid phagocyte recruitment and activation in response to fungal exposure. The inbred DBA/2 and A/Sn mouse strains lack C5 complement and represent susceptible strains compared to resistant C57BL/6 and Balb/c mice in a corticosteroid model of aspergillosis, with delayed lung neutrophil influx as a key difference in the host response [31]. *Aspergillus* secreted proteases have the capacity to cleave human complement proteins [32,33] which reduces conidial complement opsonization and may represent an immune evasion mechanism.

The membrane-spanning C-type lectin receptors (CLRs) Dectin-1 (*Clec7a*), Dectin-2 (*Clec6a* in humans, *Clec4n* in mice), and Dectin-3 (*Clec4d*) recognize fungal β-glucans (Dectin-1) and mannans/mannoproteins (Dectin-2/−3), respectively, that are widely exposed by fungal pathogens during growth and morphologic transitions that occur in the respiratory tree (see [34] for detailed review on CLR signaling). For example, *Coccidioides* arthroconidia expose β-glucans prior to their dimorphic transition into mature spherules that contain endospores. Recent work has expanded the repertoire of CLR ligands expressed

by lung fungal pathogens. For example, an O-linked C-terminal mannan moiety on *Blastomyces* endoglucanase acts as a novel Dectin-2 ligand and potential vaccine adjuvant [35,36]. Dectin-1, −2, and −3 signaling converge on spleen tyrosine kinase, protein kinase C-δ, and CARD9, resulting in canonical NF-κB activation to promote the release of pro-inflammatory cytokines that include TNF, pro-IL-1β, IL-6, and neutrophil-and monocyte-recruiting chemokines such as CXCL2 and CCL2. CARD9 signaling further controls the induction of T helper 17 cells during respiratory and systemic fungal infections [37]. Beyond Dectin-1, CD23 (*Fcer2*) [38], a low affinity IgE receptor, EphA2 [39–41], and lactosyl ceramide [42] may bind to fungal β-glucans and initiate inflammatory responses, though the in vivo role of these receptors and contributions to collective β-glucan-sensing in pulmonary host defense remain largely undefined.

Brown and colleagues functionally characterized Mel-Lec (*Clec1a*), a CLR that binds fungal DHN-melanin [43]. In contrast to Dectin-1, -2, and -3 which are primarily expressed by murine lung-resident macrophages and dendritic cells as well as lung-infiltrating monocytes and neutrophils, Mel-Lec is expressed by murine lung endothelial cells and protects against disseminated aspergillosis, but not against pulmonary aspergillosis in otherwise immune competent mice. In humans, myeloid cells exhibit Mel-Lec expression, though the downstream signaling events remain unknown. The identification of a *Clec1a* polymorphism as a risk factor for aspergillosis in hematopoietic cell transplant patients argues for a functional role in host defense [43].

CARD9 deficiency is the only known primary immune deficiency disorder that exclusively manifests with life-threatening invasive fungal disease, particularly at extrapulmonary sites including the brain, dermis, and visceral organs [44–47]. These clinical observations imply that alternate innate defense pathways can compensate for CARD9 defects more effectively in the respiratory tree than at extrapulmonary sites. The rapid release of IL-1α following pulmonary *Aspergillus* infection represents an alternate mechanism of rapid innate immune activation, in parallel to the NLRP3 and AIM2 inflammasome-dependent activation of caspase-1 and the induction of caspase-8 activity which results in IL-1β release [41,48]. IL-1α and IL-1β activate IL-1 receptor/MyD88 signaling in radioresistant lung epithelial cells to regulate the quantity and anti-fungal activities of myeloid phagocytes, as discussed in the ensuing section.

4. The epithelium and orchestration of antifungal Immunity

The respiratory epithelium plays a key role in the initiation and amplification of the innate immune response to lung fungal pathogens. During *Aspergillus* infection, chemokine-dependent neutrophil recruitment occurs in two distinct phases. First, IL-1R/MyD88 signaling in club cells leads to the rapid production of CXCL1 and CXCL5 and the initial neutrophil influx into infected airways [49] (Fig. 2A). Second, Card9 signaling in leukocytes sustains chemokine-dependent neutrophil recruitment, highlighting compartment-specific and collaborative control of neutrophil influx in the fungus-infected lung [49]. Beyond IL-1R/MyD88- and CARD9-dependent neutrophil recruitment, 5-lipoxygenase (5-LO) activity in hematopoietic cells generates leukotriene B_4 (LTB_4) which can mediate neutrophil swarming via LTB_4 receptor signaling and promote neutrophil influx in the

Aspergillus-infected lung [50,51]. Lung stroma-derived soluble galectin-3 further promotes neutrophil homing into infected airways [52].

In addition to its role in neutrophil trafficking, the pulmonary epithelium orchestrates myeloid phagocyte effector activity and adaptive immune responses. During *Blastomyces* infection, IL-1R and NF-κB signaling in lung epithelial cells releases CCL20 that regulates the influx of $CCR6^+$ innate lymphoid cells (ILCs) (Fig. 2B). ILCs and natural T helper 17 cells produce IL-17A and GM-CSF that enhances fungal killing by phagocytic cells [53]. Binding of *Pneumocystis* to type II alveolar epithelial cells induces IL-1R and NF-κB signaling that regulates T helper 17 and B cell adaptive immune responses required for fungal clearance [42,54–56]. Pulmonary infection with *Cryptococcus neoformans* induces epithelial cell production of IL-25, and disruption of IL-25R signaling in *Il17rb*$^{-/-}$ mice improves survival by suppressing T helper 2 responses, promoting T helper 1 responses, and reducing dissemination of the fungus to the central nervous system [57]. Thus, cytokine-driven epithelial activation is a key feature of immune activation and fungal clearance in the respiratory tree.

The role of the respiratory epithelium and its cellular constituents in direct fungal sensing and recognition remains poorly defined, despite the discovery that human epithelial cells in bronchioles and alveoli can express Dectin-1 [58]. To study these interactions, researchers have turned to cell lines (e.g., BEAS-2B cells as a model for human bronchial epithelial cells or A549 adenocarcinoma cells as a model for type II alveolar epithelial cells) and to air-liquid interface (ALI) cultures of primary airway epithelial cells [59]. *Aspergillus* can induce Dectin-1 expression in a human bronchial epithelium cell line in a TLR2-dependent manner, resulting in the production of pro-inflammatory cytokines such as TNF, antimicrobial peptides, and reactive oxygen species (ROS) [60]. Dectin-1 facilitates the uptake of *Aspergillus* conidia into A549 cells through phospholipase D signaling [61,62]. While the majority of *Aspergillus* conidia ingested by A549 cells are killed, surviving conidia can germinate and form invasive hyphae [63]. Blocking Dectin-1 protects A549 cells from monolayer detachment upon challenge with *Aspergillus*, but infected *Clec7a*$^{-/-}$ mice demonstrate worse pulmonary epithelial damage than control mice [62]. Studies with epithelial cells maintained in ALI cultures indicate that an *Aspergillus* cell wall component initiates neutrophil recruitment and trans-migration to the apical airway surface [59], implying that direct epithelial fungal sensing may facilitate leukocyte chemotaxis across epithelial layers. While these results suggest that pulmonary epithelial cells may participate in beneficial or deleterious immune responses during fungal infections, it remains largely unproven whether fungal sensing or uptake by epithelial cells represents a core feature of the pulmonary immune response, since in vitro observations may not recapitulate in vivo properties of primary lung epithelial cells. Definitive experimental evidence for candidate fungal receptors and signal transducers rests on conditional gene deletion strategies in defined lung epithelial subsets and rigorous analysis of infectious outcomes in relevant animal models.

5. Epithelial invasion and tissue damage during mucormycosis

Epithelial and endothelial cells can be hijacked by invading fungi to facilitate tissue invasion and necrosis, most prominently by angioinvasive *Mucorales* fungi. These agents of mucormycosis cause devastating, disfiguring rhino-orbital infections in patients with uncontrolled diabetic ketoacidosis (DKA) as well as pulmonary infections in patients with hematologic malignancies. Biochemical pull-down assays initially identified glucose-regulated protein 78 (GRP78) as an endothelial cell receptor for *Rhizopus oryzae* [64]. GRP78 binding to spore coat protein homologs 2 and 3 (CotH2, CotH3) facilitated fungal endocytosis by endothelial cells, leading to tissue damage [64,65]. *Mucorales* fungi also produce mucoricin, a 17 kDa ricin-like toxin that injures cultured lung epithelial cells by damaging membrane permeability and impairing protein synthetic function [66]. Treatment of infected DKA mice with antibodies against GRP78, CotH, or mucoricin significantly improved survival rates [64].

Further research has advanced the concept that differential expression of fungal receptors by epithelial cells along the respiratory tract may determine the site of fungal invasion. Under hyperglycemic conditions, cultured nasal epithelial cells highly upregulate GRP78 which binds to *R. delemar* via CotH3 [67]. In contrast, A549 cells express the integrin $\alpha_3\beta_1$ that binds to *R. delemar* via CotH7, and the expression of $\alpha_3\beta_1$ is not regulated by DKA conditions. Infected, neutropenic mice have improved survival when treated with antibodies against the integrin β_1 subunit [67]. Similarly, the *Aspergillus* thaumatin-like protein CalA protein can bind to the $\alpha_5\beta_1$ integrin that is expressed by epithelial and endothelial cells. The ΔCalA deletion mutant exhibits reduced virulence in a corticosteroid model of disease [68]. These findings may explain why patients with hematologic malignancies tend to develop pulmonary, rather than rhino-orbital mold infections, unlike patients with DKA. Thus, *Mucorales* and other molds can hijack cellular receptors within epithelial and endothelial cells in the respiratory tree to cause local tissue damage and necrosis.

6. Innate antifungal effector mechanisms

Sterilizing mucosal barrier immunity in the lungs is critical to preventing invasive fungal infections. For example, patients with chronic granulomatous disease (CGD), a primary immunodeficiency disorder in which NADPH oxidase activity and superoxide anion production is impaired in phagocytic cells, have an exquisite susceptibility to infections by filamentous fungi, particularly *Aspergillus* and *Mucorales,* and to systemic *Candida* infections [69]. During a robust host immune response, myeloid cell-derived ROS induce a form of regulated cell death in *Aspergillus* conidia [70]. Thus, host-derived ROS can exploit gene-dependent cell death pathways in fungi to mediate sterilizing immunity in the respiratory tree. However, the *Aspergillus* anti-cell death protein Bir1 can counteract this process. Bir1 overexpression promotes fungal survival in myeloid cells and facilitates hyphal tissue invasion [70]. The production of mitochondrial ROS in alveolar macrophages can enhance *Aspergillus* conidial killing, but catalase-dependent neutralization of mitochondrial-derived H_2O_2 is insufficient to alter murine susceptibility to aspergillosis, both in the presence and absence of NADPH oxidase activity [71,72].

When neutrophils encounter fungal cells that are too large to phagocytose, NADPH oxidase activity is critical for the formation of neutrophil extracellular traps (NETs) [73]. NETosis is a form of regulated cell death, in which neutrophils extrude chromatin threads decorated with cationic histones and DNA and release proteinaceous chelators of essential ions (e.g., calprotectin which traps Fe^{2+}, Zn^{2+}, and Mn^{2+}) to immobilize fungal filaments and deplete essential nutrients in their immediate environment. [73] The release of extracellular ROS by neutrophils in response to large filaments amplifies IL-1β release which in turn boosts additional neutrophil recruitment to the site of infection [74]. In contrast, fungal cell phagocytosis and the generation of intracellular ROS limit IL-1β release and the ensuing formation of neutrophil clusters [74]. Neutrophils preferentially undergo NETosis in response to *Aspergillus* hyphal forms over conidia, causing a fungistatic effect that helps to prevent dissemination [75,76].

Nutritional immunity, the sequestration of essential ions from scavenging microbial pathogens, or alternatively, the use of concentrated metal ion levels to create a toxic environment for pathogens, operates within fungus-containing phagosomes as well. *Rhizopus* conidia establish intracellular persistence in alveolar macrophages but fail to germinate due to intracellular iron restriction [77]. Similarly, neutrophils from CGD patients can restrict Aspergillus growth by iron chelation using secreted lactoferrin [78]. In the case of *Histoplasma*, GM-CSF-responsive macrophages control the transcription and intracellular localization of metallothioneins and zinc transporters to withdraw zinc from the *Histoplasma*-containing phagosome, to regulate the activity of a phagosomal proton pump, and to enhance the oxidative burst [79,80].

Fungi have developed ways to subvert host effector mechanisms to their advantage. For example, mold conidia that contain DHN-melanin arrest the process of LC3-associated phagocytosis, delaying glycolytic flux, macrophage phagosomal maturation, and exposure to the respiratory burst [81,82]. During primary infection, *B. dermatitidis* is resistant to killing by alveolar macrophages because of its ability to inhibit NO production [83], and in a *B. dermatitidis* vaccination model, inducible NOS (iNOS) deficiency impairs host clearance of the fungus [84]. A *Blastomyces* di-peptidyl peptidase (i.e., Dpp IVA) can cleave host-derived chemokines that mediate the influx of $CCR2^{+}$ monocytes. This immune evasion mechanism bypasses their effector activity [85]. *Cryptococcus* species are facultative intracellular organisms that can harness macrophages to replicate and disseminate in the host [86,87]. Recently, a secreted *Cryptococcus* protein, Cpl1, was discovered to polarize interstitial macrophages to a non-protective type 2 phenotype in a process that requires TLR4 signaling and facilitates tissue invasion [88]. *Talaromyces* yeast cells can parasitize macrophages to avoid exposure to neutrophil oxidative products that are toxic to this fungus [89]. In addition, *Talaromyces* can induce β-glucan-dependent shuttling between neutrophils and macrophages, though the contribution of yeast cell transfer between leukocytes to immune evasion and infectious outcomes remains uncertain [90].

7. Innate immune crosstalk regulates antifungal effector activity in the lung

Emerging studies have advanced the concept that lung-infiltrating myeloid phagocytes engage in multi-directional crosstalk and condition the inflammatory environment in the lung to boost the recruitment and antifungal properties of other innate immune cells. Inflammatory monocytes are important early responders and central players in the control of pulmonary fungal pathogens including *Aspergillus*, *Blastomyces*, *Cryptococcus neoformans*, *Coccidioides*, and *Histoplasma* [91]. The role of monocytes in antifungal immunity is protective, with the notable exception of cryptococcosis, in which monocytes may have harmful or protective roles depending on host and fungal factors [92–95]. In the lung, monocytes differentiate into monocyte-derived DCs (Mo-DCs) and macrophages (Mo-Macs) to directly kill fungal cells [91]. Monocytes also direct the recruitment of other innate cells to the site of infection and establish an inflammatory environment in the lung conducive to fungal cell elimination. Important monocyte-derived cytokines and chemokines include TNF, IL-1α/β, CXCL1, CXCL2, CXCL9 and CXCL10, among others [41,96,97]. These inflammatory mediators are important for the establishment of a protective milieu in the lung and enhance the recruitment of other innate cells, including neutrophils. Fungus-engaged Mo-DCs cooperate with fungus-engaged neutrophils to produce CXCL9 and CXCL10 for the CXCR3-dependent recruitment of plasmacytoid DCs in the *Aspergillus*-infected lung [98] (Fig. 2A).

Beyond their role in innate immune cell recruitment, monocytes and Mo-DCs control a type I and type III interferon cascade in the *Aspergillus*-infected lung that is essential for the optimal antifungal response of neutrophils [99]. The activation of STAT1-dependent signals on neutrophils downstream of the type III IFN receptor is required for optimal ROS activation and *Aspergillus* killing [99] (Fig. 2A). Whether this pathway is also involved in the regulation of antifungal neutrophils in response to other fungal pathogens remains to be established, but it is clearly involved in other inflammatory processes, most notably in response to viral infection [100–103]. The monocyte-dependent recruitment of plasmacytoid DCs, prototypic anti-viral and type I IFN-producing cells, into the fungus-infected lung complements and augments monocyte-dependent regulation of neutrophil NADPH oxidase activity. This provides a feedforward amplification mechanism to boost the antifungal properties of neighboring myeloid phagocytes by infected innate immune cells (Fig. 2A). Innate immune crosstalk is multidirectional, with neutrophils also acting as important regulators of other innate cells [104], specifically for the optimal antifungal activation of monocytes which includes monocyte maturation and Mo-DC ROS formation [105]. The common involvement of IFN activation during fungal and viral infections may be an intriguing basis for secondary susceptibility to fungal infection post influenza and SARS-Cov2 infection [106]. Future studies will be needed to unravel the complex mechanisms involved in the maintenance of antifungal immunity in the context of infection with other pathogens.

8. Cell-mediated immunity to lung fungal pathogens and implications for vaccine strategies

Pneumocystis, *Cryptococcus*, and dimorphic fungal pathogens observed in patients living with AIDS underscores the importance of T cells to anti-fungal immunity. $CD4^+$ T helper cells represent the critical T cell lineage implicated in antifungal immunity or allergy-associated tissue injury (discussed in ensuing section) in three general ways [107]. First, the activation and differentiation of T helper cells into $Tbet^+$ T helper 1 cells depends on fungal antigen transport to draining lymph nodes and interaction with IL-12 producing dendritic cells. In turn, T helper 1 cells migrate to the lung and provide cytokines, primarily IFN-γ, that activate the antifungal activities of macrophages. This circuit of cross-regulation is central to the potential utility of antifungal vaccines [108].

Second, GATA-3^+ T helper 2 cells that produce IL-4, IL-5, and IL-13 drive characteristics of allergenic responses that include eosinophilia, Goblet cell hyperplasia, and IgE class switching. Augmentation of the endogenous T helper 2 response either through administration of IL-2/IL-2 antibody complexes or disruption of regulatory T cell-dependent suppression of T helper 2 cells accelerated lethal disease in a model of invasive cryptococcosis [109,110]. Thus, T helper 2 cell responses do not simply fail to eliminate fungi from the respiratory tree but directly contribute to immunopathology associated with uncontrolled pulmonary fungal infection. This concept can be exploited for therapeutic purposes, as illustrated in a recent case of a 4-year-old child with disseminated coccidioidomycosis [111]. This patient suffered from a primary immune deficiency disorder caused by abnormal expression of a short, nonfunctional isoform of the IL-12 receptor, resulting in insufficient type 1 immunity and augmented type 2 immunity. The boy responded clinically to dupilumab, a mAb directed against IL-4 that suppresses type 2 immunity, and recombinant IFN-γ which enhances type 1 immunity.

Third, $ROR\gamma t^+$ T helper 17 cells combat extracellular fungi by secreting IL-17 that can stimulate epithelial cells in the oral and respiratory tract to release neutrophil chemokines and to produce antifungal peptides [112]. Tissue-resident γδ T, natural T helper 17, and type 3 ILCs represent additional lymphocyte subsets that contribute to rapid IL-17-dependent host defense in murine models of oropharyngeal candidiasis and pulmonary blastomycosis [53,113–115]. Recent human data indicates that fungus-specific T helper 17 cells may drive pathologic allergenic inflammation as well, as discussed in the ensuing section [116].

T helper cell responses to respiratory fungal infection are typically mixed in character. Innate and adaptive lymphocytes respond to fungal infection and coordinate recruitment of neutrophilic and eosinophilic granulocytes. During cryptococcosis, the granulocyte response can be experimentally manipulated and polarized by interfering with lymphocyte differentiation [117]. Mice with highly polarized eosinophil or neutrophil responses due to lymphocyte subset impairments succumbed more rapidly to infection than wild type mice with a mixture of lymphocytes and a more balanced granulocyte population. With the exception of *Histoplasma* [118], most fungi can survive and replicate outside of myeloid phagocytes. Thus, balanced T cell responses that target the free-ranging lifestyle of most lung fungal pathogens are likely to be most advantageous to the host.

The development of T helper cell receptor transgenic (TCR-tg) mice has advanced our understanding of T helper cell priming, activation, and memory formation by allowing for the precise tracking of fungal antigen-specific CD4 T cells at various stages of activation, differentiation, and trafficking [119,120]. Following fungal trafficking to lung-draining mediastinal lymph nodes by monocytes and Mo-DCs [121], *Aspergillus*-specific Af3.16 TCR-tg T helper cells proliferated rapidly, migrated to the infected lung and differentiated primarily into IFN-γ-producing T helper 1 cells independently of TLR/MyD88-mediated signals and into a smaller subset of IL-17-producing T helper 17 cells [119]. Dectin-1-mediated signals modulated T-bet expression in Af3.16 TCR-tg cells and controlled the balance of T helper 1 and T helper 17 differentiation [122]. Intriguingly, Mo-DCs are required for the sustained expression of T-bet and maintenance of T helper 1 differentiation during *Aspergillus* and *Blastomyces* lung infection [122,123].

The use of *Blastomyces*-specific 1807 TCR-tg cells allowed for the identification of broadly protective T helper cells that, following adoptive transfer, controlled infections by multiple dimorphic fungi, including *Histoplasma* and *Coccidioides* [120,124]. 1807 TCR-tg cells recognize fungal calnexin, a broadly conserved antigen expressed by fungi that belong to the Ascomycetes family [125]. This finding provides proof-of-principle evidence that a cross-reactive vaccine based on this antigen may protect against multiple fungi via the stimulation of broadly protective T helper cells [126]. The use of TCR-tg cells in these models and in other fungal infections [127] will undoubtedly continue to help advance our mechanistic understanding of critical factors that shape pulmonary antifungal immunity against fungal pathogens.

Despite the potency of cell-mediated immunity and the induction of T cell memory, a select number of fungi cause disease in immunocompetent individuals. Consequently, there is tremendous interest in developing vaccines to primary fungal pathogens, such as *Blastomyces*, *Coccidioides*, *Histoplasma*, and *Cryptococcus gattii*. While there are currently no approved fungal vaccines, experimental candidates against pulmonary fungal pathogens are summarized in the following review [108]. For pulmonary fungal pathogens, an effective vaccine would prime a robust T cell response, which was largely unachievable prior to the development of encapsulated mRNA-based vaccines for SARS-CoV2 [128]. Due to safety concerns with attenuated live fungal vaccine candidates, significant research effort is directed at the development of protein- or peptide-based subunit vaccines. This approach must overcome the challenge of delivering T cell epitopes that accommodate the enormous human MHC allelic diversity and must be formulated with an adjuvant that provokes strong T helper cell memory responses.

Researchers have made advances to overcome these challenges. In a murine model of cryptococcosis, researchers recently identified fungal peptides from in silico MHC II binding algorithms on the basis of their ability to prime protective T cell responses to lethal pulmonary infection with *Cryptococcus* [129]. Several peptides successfully protected Balb/c mice in vaccine formulations, but only one provided comparable protection in C57BL/6 mice. Although these studies represent a step forward in identifying protective peptide T cell epitopes, they highlight the challenges and limitations of peptide-based subunit vaccines. Glucan particles have been used as an experimental preclinical vaccine

adjuvant that was effective when co-formulated with candidate fungal vaccine strains that protect against lethal *Blastomyces*, *Coccidioides,* and *Histoplasma* challenge [130–132]. As discussed earlier, the *Blastomyces* mannoprotein endoglucanase-1 acts a Dectin-2 agonist by virtue of C-terminal O-linked mannans and exhibits adjuvant properties to promote experimental vaccine resistance to *Blastomyces* and *Cryptococcus* [36]. Thus, the co-development of novel adjuvant and peptide- or protein-based candidates appears to represent the most promising avenue to generate robust vaccine immunity against lung fungal pathogens.

An alternative approach, tested in animal models, is the use of heat-killed, whole cell preparations that contain a complex mixture of immunogenic antigens as well as fungal PAMPs for the activation of innate receptors and the effective programming of protective, antifungal T helper 1 and T helper 17 cells. Several laboratories have shown proof-of-principle data that demonstrate the effective use of heat-killed, mutant *Cryptococcus* strains as vaccine formulations for the activation of potent protection [133–136] that can operate even in the context of CD4 deficiency [133,135]. Importantly, some *Cryptococcus* whole cell formulations confer heterologous vaccine-induced protection [134,135, 137]. In the case of the HK-fbp1 vaccine, heterologous protection was observed not only against *C. gattii* but also against *Aspergillus* in a drug-induced model of susceptibility [135]. These findings provide support for the development of vaccine formulations capable of protecting against multiple fungal pathogens, even in the context of defined immune deficiency. Unfortunately, a lack of investment in this field by vaccine manufacturers remains a major impediment to the development of a fungal vaccine. The most promising candidate to date, a formulation of the *Candida albicans* invasin Als3 conjugated with alum demonstrated therapeutic and preventative effects in a phase II trial in vaginal candidiasis [138].

9. Role of fungi in allergenic disease in the lung

Over half of all individuals with allergic asthma are sensitized to fungi or fungal components [139–142]. T helper cells represent central mediators of allergic inflammation; however, unlike anti-fungal immunity that requires balanced T helper 1 and T helper 17 cells, pathologic T helper 2 or T helper 17 cells dominate the response in allergic asthma. In the ensuing section, we discuss recent advances in our understanding of how fungi and the proteolytic activity of common fungal aeroallergens contribute to allergic airway inflammation. A comprehensive review highlighted the multifaceted role of pulmonary macrophages and dendritic cells in allergenic airway inflammation [143].

Common household molds such as *Alternaria*, *Aspergillus*, *Cladosporium* and *Penicillium* account for a large proportion of the fungal allergens that sensitize asthma [144]. Determining how these allergens interact with the host to instigate allergic inflammation has been the focus of intense investigation, starting with the key insight that many fungal allergens are proteases [145]. *Aspergillus* and *Penicillium* secrete the clinically important allergen, alkaline protease 1 (also known as Asp f 13, Pen c 13). The respiratory epithelium is an early target of these inhaled aeroallergens and generates inflammatory signals that recruit and activate allergy- and wound healing-promoting immune cells to diseased airways [146] (Fig. 3). The proteolytic activity of Asp f 13 disrupts bronchiolar epithelial cell

junctions, and club cells that line the bronchioles respond to this damage by releasing calcium fluxes [147]. The phosphatase calcineurin responds to the rise in cytosolic calcium and indirectly activates proinflammatory cytokine secretion that supports T helper 2 cell priming and the ensuing eosinophilia. The mechano-sensitive calcium channel, TRPV4, functions in epistasis with calcineurin, suggesting that club cells detect junctional injury as mechanical force. The homologous protease, Pen n 13, also disrupts epithelial cell junctions, triggering a potent allergic response, likely by analogous mechanisms [148]. Finally, Asp f 13 exerts inflammation-independent airway hyperreactivity and bronchoconstriction by disrupting the interaction of extracellular matrix and smooth muscle cells subjacent to bronchioles. Protease-damaged smooth muscle cells signal via RhoA and ROCK, suggesting transduction of mechanical forces in this cascade as well [149]. A central theme of these studies that fungal protease-dependent tissue injury triggers and aggravates allergic responses.

Interleukin-33, a prototypical alarmin and ST2 ligand, was recently proposed to act as a soluble protease sensor. In this model, protease sensing enables host cells to react to the threat of tissue injury. Uncharacterized *Aspergillus* and *Alternaria* proteases cleave IL-33 into a highly active form that activates group 2 ILCs via the ST2 receptor to produce type 2 cytokines and drive IL-5-dependent eosinophil recruitment to the lungs [150] (Fig. 3). However, IL-33 signaling does not affect the generation of T helper 2 responses to the main protease constituent of *Aspergillus* extract, Asp f 13 [146]. It is possible to reconcile these seemingly contradictory observations since type 2 cytokine responses may be beneficial in the context of wound repair [151]. Thus, protease sensors may serve a beneficial function by signaling innate immune cells to coordinate transient and moderated wound repair while a more substantial barrier injury may prime a permanent and anamnestic T cell response which contributes to lifelong allergenic disease.

Beyond direct injury to epithelial cells, fungal proteases have also been implicated in host fibrinogen cleavage to generate fibrin split products. Fibrin split products activate macrophage-dependent fungistatic activity via an integrin receptor Mac-1 (CD11b/CD18) and TLR4 signaling-dependent pathway to boost epithelial cell responsiveness to T helper 2-derived cytokines, such as IL-13, and to promote mucin production. This pathway does not appear to influence the formation of T helper 2 cells [152]. Although *Candida* species are not a cause of invasive disease in the lung, patients with cystic fibrosis can harbor *Candida* within diseased airways; this finding has been associated with long-term declines in pulmonary function [153,154]. *C. albicans* and *C. dubliniensis* pseudohyphae secrete a 31 amino acid cytolytic peptide toxin, candidalysin, that mediates mucosal infection [155]. Candidalysin, a product of the *Ece1* gene, damages epithelial cells and triggers protective immune responses by inducing mitogen-activated protein kinase and NF-κB signaling [156]. In a murine model of allergic airway inflammation, candidalysin-secreting *C. albicans* strains induced platelet activation in the lung via a direct candidalysin-von Willebrand factor glycoprotein 1ba interaction that stimulates the release of the Wnt agonist Dickkopf-1 (Dkk-1) which in turn promoted T helper 2 and T helper 17 responses [157] (Fig. 3). Surprisingly, these signaling events reduced the lung fungal burden and promoted platelet-dependent hemostasis and tissue protection, a critical property to prevent lethal hemorrhage during invasive fungal disease in the lung [157,158].

Beyond local effects on allergenic airway disease, fungi can exert long range effects by promoting pathologic T helper cell subsets at distant sites. A seminal study revealed that the intestinal- and mucosal tissue-resident fungus *C. albicans* can prime and induce the majority of human T helper 17 cells [116], while other fungal constituents of the microbiota and human fungal pathogens only induce small and variable fractions of IL-17-producing T helper cells, the majority of which are cross-reactive with *Candida* antigens and can respond to homologous peptides expressed by other ascomycetes. In patients with inflammatory bowel disease, the frequency of *Candida*-reactive T helper cells was increased compared to healthy controls; this finding correlates with a parallel increase in *Aspergillus*-reactive T helper 17 cells. In patients with allergic bronchopulmonary aspergillosis, these *Candida*-induced, and *Aspergillus* cross-reactive T helper 17 cells were expanded and mediated pathologic inflammation prior to receipt of antifungal drugs and corticosteroid therapy. This study supports the concept that fungal antigen exposure at extrapulmonary sites can generate cross-reactive, pathologic Th17 cells that respond to heterologous fungi in the lung.

Further evidence for the concept of a fungal gut-lung axis that regulates extraintestinal inflammation comes from studies in murine models of house dust mite-induced allergy. Prolonged oral administration of the antifungal drug fluconazole (which targets most yeasts, but not molds) led to an outgrowth of three drug-resistant filamentous fungal taxa, *Aspergillus amstelodami*, *Epicoccum nigrum* and *Wallemia sebi* in the murine intestinal tract, leading to fungal dysbiosis. Drug therapy was associated with exacerbated colitis and heightened pulmonary house dust mite-triggered allergenic responses. This finding was recapitulated in germ-free mice reconstituted with the three identified taxa [159,160]. In this model, the induction of heightened allergenic responses in the lung depended on Syk and CARD9 signaling in intestinal $CX3CR1^{+}$ mononuclear phagocytes; these mononuclear phagocytes represent the major subset of fungus-responsive sentinels in the intestinal tract [161].

10. Fungal co-infections in the context of severe viral disease

Viral infections can increase the susceptibility of patients to fungal co-infections, even in the absence of pre-existing immune deficits. For example, influenza-associated pulmonary aspergillosis (IAPA) and COVID-19-associated pulmonary aspergillosis (CAPA) have emerged as distinct entities of post-viral respiratory fungal infections that can manifest in previously healthy patients [162–167]. In transplant patients, cytomegalovirus (CMV) disease or a discordant serostatus (CMV-seropositive donor and CMV seronegative recipient) increases the risk of fatal invasive fungal infections, including respiratory infections by *Aspergillus*, *Pneumocystis*, and *Cryptococcus* [168,169].

There are several proposed mechanisms by which these viruses may predispose patients to fungal infections in the lungs. This topic has recently been comprehensively reviewed [170], so we highlight some key concepts and findings here. As respiratory pathogens themselves, influenza virus and SARS-CoV2, the causative agent of COVID-19, can directly damage the respiratory epithelium and endothelium, which may lead to disruption of these physical barriers along with their roles in coordinating pulmonary antifungal responses [171–173]. These viruses may also alter the presence and effector functions of immune cells

in the lungs that are important for fungal recognition and clearance. In a murine model of IAPA, influenza suppressed neutrophil recruitment to the lungs through the induction of IFN-STAT1 signaling, leading to increased susceptibility to invasive pulmonary aspergillosis [174]. CMV-infected human monocytes have reduced expression of genes encoding fungal pattern recognition receptors CD36, mannose receptor, complement receptor 3, and TLR6, as well as impaired phagocytosis of fungal organisms, including *Cryptococcus* [175]. SARS-CoV2 causes a dysregulation in monocyte and neutrophil responses, including an overwhelming influx of these cells into the lungs during severe disease [176,177]. This excessive inflammatory response contributes to significant immunopathology in the lungs during severe COVID-19 disease, which in turn may facilitate the development of CAPA [176,177]. However, this mechanism and other correlative observations have not yet been directly studied.

Therapies used to treat viral infections have also been investigated for their potential role in increasing the risk for fungal co-infections. Oseltamivir, a neuraminidase inhibitor that is used to treat influenza, has been found to impair the anti-fungal activity of mouse splenocytes and human peripheral blood mononuclear cells (PBMC) against *Aspergillus* through the inhibition of host neuraminidase activity and prevention of sialic acid recognition by immune receptors [178]. Frontline treatments that emerged during the COVID-19 pandemic included corticosteroids and the IL-6R inhibitor tocilizumab, both of which can increase susceptibility to fungal infections when given at high doses and/or for prolonged periods of time [179–183]. Notably, short courses of these drugs are recommended for COVID-19 treatment [184]. Tocilizumab has not clearly been shown to increase the risk for CAPA [185]. Studies on the contribution of corticosteroids to CAPA have had conflicting results [186–191]. However, a recent study suggests that dexamethasone increases the risk for CAPA three-fold [192].

Other fungal co-infections have been described, including COVID-19-associated mucormycosis (CAM), which came to prominence in India [193,194]. The incidence of cryptococcosis after COVID-19 has been studied, but the data suggest these patients already have typical risk factors for cryptococcosis [195]. Further studies are needed to determine if additional pathogens can increase the risk for respiratory fungal infections and to investigate the potential immune mechanisms that mediate this increased susceptibility.

11. Conclusions and future perspectives

The past decade has witnessed substantial advances in deciphering the molecular and cellular components of antifungal immunity in the lung, notably with respect to integrating parenchymal, innate, and adaptive immune cells into cooperative models of organ-specific immunity and fungus-associated allergenic disease. Preclinical vaccine studies have identified complex mixtures of fungal-derived antigens and novel adjuvant combinations that confer vaccine-mediated protection, and in individual cases, sterilizing immunity. The stubborn remaining hurdles in fungal vaccine studies relate to advancing these studies into the clinical realm, harnessing mRNA-based vaccine platforms, and harnessing broader interest and support from the biotechnology sector. Important and substantial knowledge gaps remain. For example, the sensory nervous system is a key contributor to cutaneous

antifungal immunity and pulmonary immunity to bacterial pathogens [196–198]. However, the role of neuro-immune interactions in pulmonary anti-fungal immunity remains largely unknown. In the case of concurrent polymicrobial infections with fungi and other non-fungal pathogens and in the case of secondary fungal infections following severe bacterial and viral infections, it is largely unclear how concurrent and antecedent infections with other pathogenic microbes disrupt core features of antifungal immunity. Recent studies have highlighted contributions of intestinal fungi to protective antifungal immunity [199–201] and to invasive disease [202]. *Candida albicans*, a member of the intestinal-resident fungal community, promotes the formation of fungus-specific IgG antibodies [199] and the expansion of fungus-specific T helper 17 cells [200], both which exert protective functions during murine systemic candidiasis. The relationship of endogenous fungal communities in the intestine and at extraintestinal sites with susceptibility to pulmonary fungal infections remains another important question for future investigation. Ongoing progress in these many areas is critical to formulate improved strategies to benefit patients with life-threatening pulmonary fungal infections.

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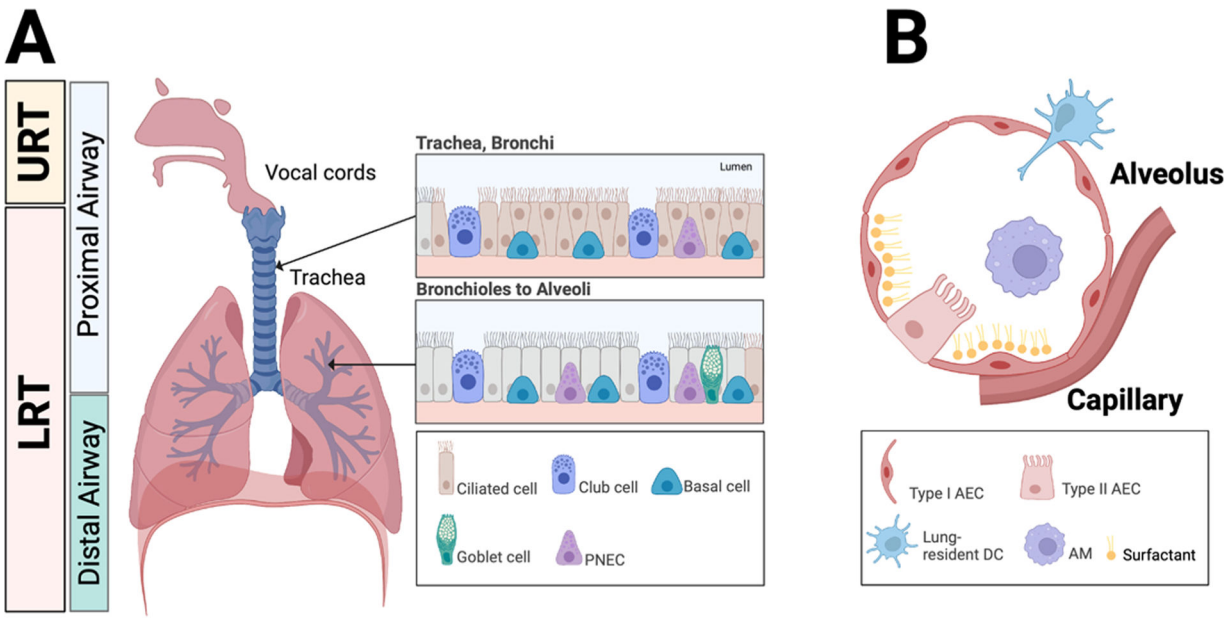

Fig. 1.

Anatomy of the respiratory tract and lung. A. The vocal cords in the human respiratory tract form the boundary between the upper and lower respiratory tracts. Proximal airways function largely to conduct air to the distal airways. Distal airways are comprised of the respiratory bronchioles, alveolar ducts, and alveoli where gas exchange occurs. The inset depicts the epithelial architecture of the trachea and bronchi (upper panel) as well as the bronchioles (lower panel). PNEC, pulmonary neuroendocrine cell. B. The schematic depicts the cellular architecture of alveoli that includes type I and type II alveolar epithelial cells (AEC), alveolar macrophages, surfactant, and lung-resident dendritic cells. Gas exchange occurs via adjacent capillaries.

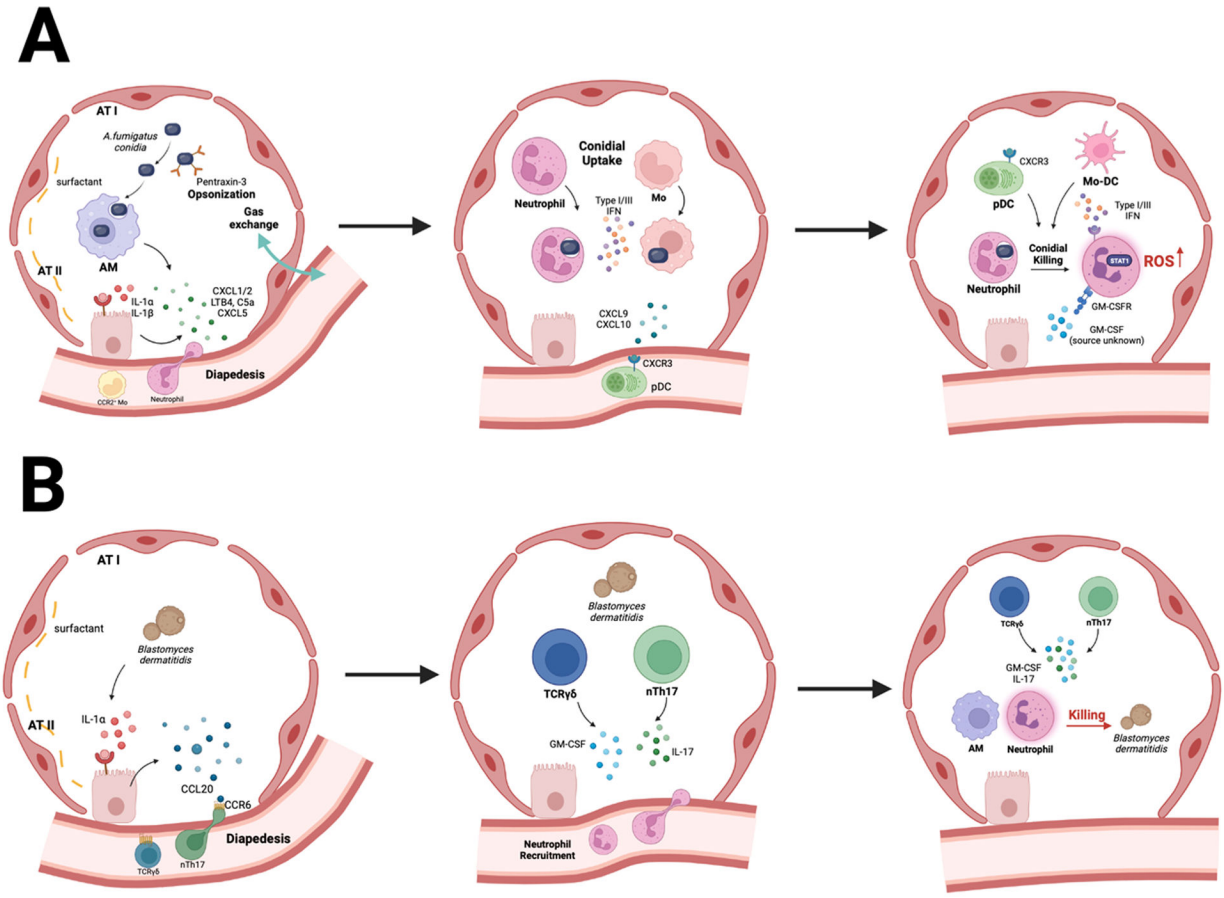

Fig. 2.

Immune crosstalk is a central feature of pulmonary antifungal immunity. A. *Aspergillus* conidia induce the rapid release of IL-1 α/β by lung-resident AMs and DCs. This process activates IL-1R/MyD88 signaling in pulmonary epithelial cells which causes the release of neutrophil chemoattractants, primarily CXCL1 and CXCL5. CXC- chemokines collaborate with LTB_4, C5a, and galectin-3 to mediate neutrophil influx to infected airways. CCL2, –7, and –12 mediate the ensuing influx of $CCR2^+$ monocytes into the lung parenchyma. Neutrophils, monocytes, and monocyte-derived dendritic cells (Mo-DCs) engulf conidia into phagolysosomes and inactivate fungal cells via products of NADPH oxidase. Monocyte-regulated type I and type III IFNs enhance fungal killing. Fungus-engaged neutrophils and Mo-DCs release CXCL9 and CXCL10 which recruits $CXCR3^+$ plasmacytoid DCs from the circulation into the lung. Plasmacytoid DCs (pDC) do not bind conidia but enhance the oxidative burst to boost conidial killing in neutrophils. GM-CSF enhances this process as well. B. During *Blastomyces* infection, early IL-1α/β release triggers epithelial CCL20 production which acts on $CCR6^+$ ILCs and mediates their trafficking to the infected lung. ILCs and natural T helper 17 cells produce IL-17 and GM-CSF which potentiate yeast cell killing by neutrophils and Mo-DCs.

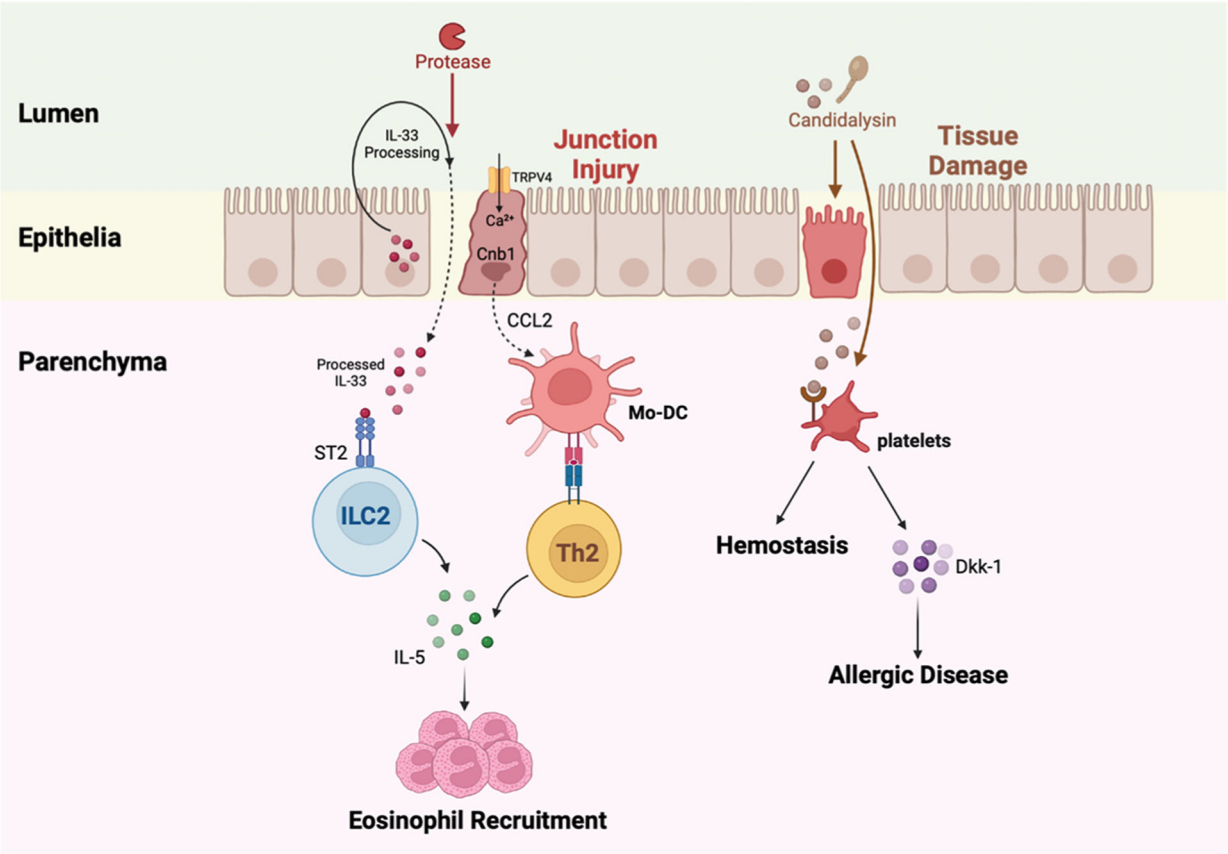

Fig. 3.

Fungal proteases and candidalysin can initiate allergenic inflammation. A fungal protease cleaves IL-33 and disrupts epithelial junctions. Processed IL-33 penetrates the barrier into the lung parenchyma, binds to ST2 receptors on type 2 innate lymphoid cells (ILC2), and drives the production of IL-5 by ILC2. This process drives eosinophil recruitment. Protease injury to the epithelial cell junctions also activates TRPV4 and causes calcium to flux into epithelial cells. Calcium signals through calcineurin and promotes CCL2 release from epithelial cells, resulting in the recruitment of Mo-DCs. Mo-DCs present antigen to T helper 2 cells in the lungs that secrete IL-5 and coordinate eosinophil influx and allergenic disease. Candidalysin, a peptide toxin released by *Candida albicans*, can damage lung epithelial cells in the upper airway. Platelets that arrive to limit hemorrhage interact with candidalysin, release dickkopf-1 (Dkk-1), and Dkk-1 promotes T helper 2-and T helper 17-dependent allergic responses.

Table 1

Common fungal agents, characteristic growth patterns, associated pulmonary clinical syndromes, and risk factors for human pulmonary mycoses.

Agent of Lung Disease and Geographic Range	*Infectious Propagule*	Morphotype	*Pulmonary Clinical Syndromes*	*Common Patient Populations*
Aspergillosis*Aspergillus fumigatus, A. flavus, A. niger, A. terreus, A. versicolor, A. ustus, A. lentulus, A. nidulans* (chronic granulomatous disease) Range: Ubiquitous	**Airborne conidia** (2–3 μm diameter)	**Mold** forms tissue-invasive hyphae	**Pneumonia Tracheobronchitis** (CNS dissemination) **Chronic cavitaryaspergillosis** (hyphae in pre-existing lung cavities) **Allergenic disease** Allergic bronchopulmonary aspergillosis (ABPA), extrinsic allergic alveolitis	Hematologic malignancy or aplastic anemia, hematopoietic cell transplant; lung and heart transplant, patients with severe COVID-19 or severe influenza, chronic granulomatous disease. Patients with structural lung damage, COPD, prior tuberculosis, bronchiectasis, sarcoidosis ABPA occurs primarily in patients with atopic asthma and cystic fibrosis
Mucormycosis*(Rhizopus, Mucor,Rhizomucor, Lichtheimia spp.)* Range: Ubiquitous	**Conidia** (variable size based on species)	**Mold**	**Pneumonia**	Acute hematologic malignancy or bone marrow failure, hematopoietic cell transplant recipients; lung and heart transplant recipients, patients with severe COVID-19, diabetic ketoacidosis.
Cryptococcosis*(Cryptococcus neoformans,C. gattii)* Range: *C. neoformans:* ubiquitous, *C. gattii:* Australia, Papua New Guinea,US Pacific Coast and British Columbia	**Desiccated yeast cells**	**Encapsulated yeast** (variable capsule size, rare Titan cells up to 100 μm diameter)	**Pneumonia (**CNS dissemination)	Patients with HIV/AIDS, patients on lymphodepleting therapies for hematologic malignancies.
Blastomycosis*(Blastomyces dermatitidis)* Range: Eastern US and Canada; emergomycosis in Africa	**Conidia** (2–10 μm)	**Dimorphic,** 8–12 μm yeast with broad-based buds in tissue	**Pneumonia** (self-limiting to life-threatening disease, mucosal disease, skin)	Patients with HIV/AIDS, 50% of cases in immune competent patients; patients of Laotian ancestry in endemic area
Coccidioidomycosis*(Coccidioides immitis, C. posadasii)* Range: CA, OR, WA, AZ, Mexico	**Arthroconidia** (3 × 5 μm, boxcar-shaped)	**Dimorphic,** 20–80 μm thick-walled spherules contain 2–5 μm yeast cells in tissue	**Pneumonia** (self-limiting to life-threatening disease, mucosal disease, CNS, erythema nodosum)	Patients with HIV/AIDS, patients on lymphodepleting therapies. Pregnant women, African-American and Filipino ancestry in endemic area
Histoplasmosis*(Histoplasma capsulatum)* Range: OH and MS Valleys in US, Canada, Central and South America, sub-Saharan Africa, SE Asia, Australia	**Conidia** (microconida & macroconidia)	**Dimorphic,** Intracellular yeasts tissue; Hc var. capsulatum 2–4 μm; Hc var. duboisii 8–15 μm)	**Pneumonia** (self-limiting to life-threatening disease)	Patients with HIV/AIDS, patients on lymphodepleting therapies.
Paracoccidioidomycosis*(Paracoccidioides brasiliensis)* Range: Central and South America (20th parallel north to 35th parallel south of equator)	**Conidia**	**Dimorphic,** yeast cells with multiple buds in tissue	**Pneumonia** (mucosal disease, skin)	Patients with HIV/AIDS, patients on lymphodepleting therapies.
Talaromycosis*(Talaromyces marneffei)* Range: SE Asia	**Conidia**	**Dimorphic,** yeast cells in tissue	**Pneumonia** (mucosal disease)	Patients with HIV/AIDS, patients on lymphodepleting therapies.
Pneumocystosis*(Pneumocystis jirovecii)* Range: Likely ubiquitous, non-culturable, no known reservoir outside of humans	**Unknown**	**Trophozoites, Cysts**	**Pneumonia** (characterized by hypoxemia)	Patients with HIV/AIDS, patients on lymphodepleting therapies.