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Role of Pathogens in Pulmonary Fungal Infection – A Review

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ABSTRACT

Respiratory fungal infection is a serious clinical issue, particularly in individuals with weakened immune systems. Major pulmonary fungal infections such as *Aspergillus, Cryptococcus, Pneumocystis,* and endemic fungus can cause life-threatening invasive illnesses. Multiple cells and chemicals coordinate the host's response to a fungal infection in the lung, according to a research. Innate myeloid cells, such as macrophages, dendritic cells (DC), and recruited neutrophils, constitute the initial line of defence against fungal infection via phagocytosis and cytokine release. Natural killer cells suppress fungal growth in the lungs by killing invading organisms directly or indirectly. Adaptive immune cells (such as Th1 and Th17 cells) produce the antifungal cytokines interferon-γ and IL-17, which are produced by their characteristic cytokines. Internalization, inflammatory cytokine production, and antimicrobial peptide release are all ways in which lung epithelial cells (LEC) contribute to fungal infection resistance. Several substances with different activities regulate immune defence signals in the host cells stated previously: Fungal recognition is mediated by pattern recognition receptors (PRRs) such as dectin-1 on the cell surface, adaptor proteins, such as MyD88 and TRAF6, are required for signal transduction to the nucleus for transcriptional regulation; and inflammasomes are important in the host's defence against a fungal infection in the lungs. Furthermore, transcriptional factors control the expression of a number of genes, including those encoding cytokines and chemokines, which are important regulators in the infectious milieu and mediate cellular and molecular immune responses to a fungal infection in the lungs.

Keywords: Pulmonary Fungal Infection, Pattern Recognition Receptor, Inflammasome, Cytokine, Chemokine

INTRODUCTION

Fungal infections continue to pose a significant hazard to public health, especially as the number of immunocompromised people rises. The principal causes of fungal infections in humans' lungs are opportunistic fungi, such as *Aspergillus* with invasive aspergillosis (1–3), *Cryptococcus* with cryptococcosis (4–6), *Pneumocystis* with pneumonia (7), and endemic fungi (8, 9). Although these infections are uncommon in healthy persons, they can cause life-threatening invasive illnesses in patients who have a compromised immune system. Patients with immunodeficiency illnesses, such as HIV/AIDS and cancer patients undergoing chemotherapy, as well as those who receive immunosuppressive medication, such as in bone marrow/stem cell transplantation, fall into this category. Invasive mycoses have increased in frequency and infectious mortality as a result of pathogenic fungal infections in the lungs, particularly in individuals with severe immune system abnormalities (10, 11). As previously indicated, several fungal infections begin infection via surface proteins from pathogen-host contact, eventually leading to mycosis with numerous tissue lesions in immunocompromised individuals. For example, *Cryptococcus* primarily infects the lungs before spreading to the brain through circulation, resulting in deadly cryptococcal meningitis. About 1 million AIDS patients are infected with cryptococcosis, which can lead to life-threatening Cryptococcal meningoencephalitis (12). *Cryptococcosis* kills about 600,000 people worldwide every year. The human body has evolved a series of unique and complex defence systems to reduce the harm caused by fungal infections, in which host innate immunity plays a critical role. In order to stop the spread of the fungal infection, two types of innate immune cells, macrophages and dendritic

cells (DC), act as defence soldiers in numerous organs. Furthermore, these innate cells can bridge the gap between innate and adaptive immunity by acting as specialised antigen-presenting cells (APCs) to prepare naive T cells with fungal antigens. Innate immune cells are triggered by pathogen associated molecular patterns (PAMPs) via specialised pattern recognition receptors (PRRs) on the surface upon detection of fungal pathogens, allowing for additional intracellular signalling transduction. Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs) have all been identified as PRRs involved in fungus detection (13, 14). Despite advances in the field of host response to mycobiota, novel cellular and molecular mechanisms of antifungal immunity for the management of fungal infection and related organ damage remain to be discovered. Despite the fact that antifungal medications provide protection against lung fungal infection (15, 16), drug resistance remains a serious issue. To minimise the incidence and mortality rate of pulmonary mycoses, further research into the processes of lung fungal infection is needed from both a scientific and clinical standpoint. We will cover real scientific developments on mycobiota in relation to respiratory tract infections, such as *Aspergillus*, *Cryptococcus*, *Pneumocystis*, and endemic mycoses in this review.

PATHOGENS

Role of *Aspergillus* and *Cryptococcus* in the Lung Infection

One of the most frequent fungal species capable of sporulation with released airborne conidia is *Aspergillus* mould. The generated conidia in the air are tiny enough (2 to 3 μm) to enter human airways and pulmonary alveoli, causing a variety of illnesses, including deadly infections in immunocompromised people and asthmatic patients (1, 17). Inhaled conidia are absorbed by alveolar macrophages and destroyed in a phagocyte oxidase-dependent manner in healthy people (18–20). In immunocompromised people, inadequate death of inhaled fungal conidia leads to germination and fungal hyphae tissue invasion (21).

Cryptococcosis is caused by *Cryptococcus* infection of the lungs after inhalation of the airborne organisms. *Cryptococcus neoformans* is a *Cryptococcus* subspecies that may be found in a variety of environments. Cryptococcal meningitis is the most serious complication of *Cryptococcus* infection. Because *C. neoformans* and *Cryptococcus gattii* can disperse from the lung and cross the blood-brain barrier (BBB), the fungal cells adopt a "Trojan horse" technique to directly infiltrate the BBB via endothelial cells on the blood arteries of the brain (5). Counting yeast cell counts in the brain in animal tests revealed that, *C. neoformans* stayed in the CNS, where large-scale colonisation and tissue harm might occur despite the host's defence systems (22).

Role of *Pneumocystis* and Endemic Mycoses in causing Lung infection

Pneumocystis pneumonia (PCP), caused by the fungal pathogen *Pneumocystis*, such as *Pneumocystis jirovecii*, is the most common AIDS-defining disease. It can also occur in non-HIV immunocompromised patients with a deficiency in adaptive immunity, or people who take long-term high-dose systemic glucocorticoids (11). Primary surface glycoprotein (Msg or glycoprotein A) (23) and *Pneumocystis* protease, kexin, are *Pneumocystis* antigens (Kex1, Prt1). Kex is thought to be involved in the proteolytic processing of *Pneumocystis* surface antigens, making it a potential therapeutic target (24, 25). Mycoses that are endemic to a certain geographic location are more likely to cause severe and deadly complications during hospitalizations (26, 27). Encemic mycoses can potentially produce more severe and widespread illness in immunocompromised individuals, leading to a greater fatality rate (28). In many areas, an increase in the prevalence of endemic mycoses is linked to an increase in the number of immunocompromised people (29). Surprisingly, non-immunocompromised hosts also have a significant death rate (27). Coccidioidomycosis, histoplasmosis, and blastomycosis are three primary endemic mycoses in North America that can appear as community acquired pneumonias (CAP) (27). Half of those infected with coccidioidomycosis in southwest endemic areas are asymptomatic, as an acute infection mimics respiratory symptoms like pneumonia and bronchitis, as well as a fever, which then goes through a self-limited process with only a few cases progressing to disseminated infection; histoplasmosis, caused by the infectious agent *Histoplasma capsulatum*, is considered a community acquired infection to patients with a history of exposure to bat or bird droppings have pneumonia symptoms defined as acute and chronic pulmonary histoplasmosis, which can lead to respiratory failure and death in extreme cases. On the other hand, blastomycosis is less prevalent than histoplasmosis and coccidioidomycosis. Antifungal medication is critical in the management of endemic mycoses-caused community acquired pneumonia, and azole therapy, such as oral fluconazole, is preferable (30). Furthermore, paracoccidioidomycosis is mostly found in Latin America, with Brazil accounting for the majority of reported cases (31)

Human Response to Fungal Infection

German doctors were the first to describe a clinical case of human cryptococcosis in a young lady with inflammatory signs of tibia (32). The lungs and brain are the main targets for the cryptococcus organism that causes human cryptococcosis: pulmonary cryptococcosis is caused by the entry of pathogenic airborne spores (conidia) or dried yeast

cells into the airway and lungs; cryptococcal meningitis (CM) is caused by infection from spores (preferentially from the lungs or elsewhere such as the skin, liver, etc.) disseminating during the early phase via circulation into other parts of the body especially to the central nervous system (CNS) (33–35). According to Charlier et al. (36) and Kim (37) Cryptococci can use parasitized phagocytes (monocytes or macrophages) as a Trojan horse to smuggle germs over the BBB into the brain. The outcome of fungal colonisation in the lungs can be either clearance of fungi by the host immune system or the development of a virtual local inflammation characterised by pulmonary nodules and pneumonia, or the development of a subsequent dissemination into the systemic organs, preferentially into the CNS through the BBB. As a result, cryptococci could only be discovered in lung tissue/bronchoalveolar lavage/sputum, cerebrospinal fluid, or blood, and CM was thought to be a severe and life-threatening mycosis with a high death rate due to cryptococcosis. The encapsulated cryptococcus could be classified into four serotypes (from A to D) based on the immune response to a diverse polysaccharide capsule, and two major species are responsible for opportunistic cryptococcosis: *C. neoformans* (serotypes A and D) and *C. gattii* (serotypes B and C), which are infectious in immunocompromised hosts and immunocompetent or immunological normal individuals, respectively (32, 38–40). $CD4^+$ T lymphocyte depletion makes HIV/AIDS patients more susceptible to cryptococci, therefore despite the discovery of antiretroviral treatment; the rise in incidence of human cryptococcosis was accompanied by an increase in HIV/AIDS diagnosis and morbidity (6, 41, 42). In HIV/AIDS patients, the lung is a target organ, but once infected, the risk of meningitis is significant, presumably because the spread of cryptococcosis into the brain is dependent on the state of pulmonary immune responses (43). On the other hand, highly encapsulated cryptococci are more commonly found in the respiratory tracts than in the CNS, where they resist phagocytes and lower the incidence of systemic dissemination (44). In a preliminary investigation, severe combined immunodeficiency (SCID) mice infected intravenously (i.v.) with live *C. neoformans* cells were able to replicate systemic cryptococcosis in immunocompromised hosts (45). Notably, cryptococcosis in HIV-negative patients is not as uncommon as previously thought (46); these individuals have no obvious immune deficiency but are subjected to immunosuppressive conditions such as immunosuppressive drug treatment (glucocorticoids or other immunosuppressants), malignancies or hematologic disorders (chronic leukaemia, lymphoma), the presence of systemic lupus erythematosus patients receiving immunosuppressive agents, and Interestingly, despite limited immune system development in children, pulmonary cryptococcosis in children is uncommon, although it can be a deadly condition (47). An opportunistic mycosis, invasive pulmonary aspergillosis (IPA), is caused by a pathogenic Aspergillus infection in the lungs. Immunocompromised persons, such as cancer or haematological illnesses (acute leukaemia, neutropenia), patients with chronic granulomatous diseases, and immunosuppressed bone marrow/organ transplant recipients, are also susceptible to Aspergillus (48–51). On the other hand, in immunocompetent hosts inhaled infectious propagules have no further importance due to the fungus's great resistance to killing and clearance by pulmonary immune system cells. Amphotericin B (AMB), fluconazole, and echinocandins are the best antifungal agents for treating mycoses (52–54), however due to antifungal drug resistance, toxicity, and side effects, current antifungal medicines may not be able to cure these illnesses in some cases, posing a danger to patients (55). As a result, innovative techniques are focusing on host defence, which is an important factor in fungal pathogenesis. The ineffectiveness of antifungal medications is now the main issue in the treatment of invasive mycoses, and novel therapeutic immunomodulators are urgently needed. Furthermore, the severe CM in the brain is linked to a bad prognosis. As a result, treatment options that improve pathogen clearance while also preventing pathogen spread into the CNS are still needed.

Pathogen-Host Communication

Understanding the connection between the host and the fungal pathogens might aid in the diagnosis and treatment of infection. However, although considerable scientific progress has been achieved in this respect, the signalling processes for fungal pathogens and mammalian host cell interactions remain poorly known (56). Chitin, modified glycoproteins, and glucans make up the majority of the fungal surface. Mannose-containing polysaccharides are frequently covalently linked to proteins in most yeast. *C. neoformans* is a rare pathogenic fungus that uses a particular polysaccharide component (glucuronoxylomannan, GXM) as an anti-phagocytosis capsule outside the cell wall (57). The presence of GXM in the *C. neoformans* capsule is required for the pathogen's pathogenicity. In fact, GXM is found in the cerebral fluid and serum of cryptococcal patients, where it has various immunomodulatory effects. The principal PAMPs detected by host cells are fungal surface polysaccharides or glycans, whereas the surface proteins on various fungi are critical for their virulence and intracellular survival. Phagocytosis by host cells is a well-known early process in the host-microbe relationship (58). The specific processes by which mammalian host cells influence fungal phagocytosis and reproduction in concert remain a mystery. The phagocytosis process, which involves reactive oxygen species (ROS), allows professional phagocytes, such as macrophages, to absorb and destroy big particulate material (59). The phagocytosis of pathogenic particles and the development of phagosomes would arise from the binding of pathogenic particles to cell surface receptors, as well as a remodelling of the membrane and intracellular components. In the *C. neoformans* infection, engulfment of the fungal pathogens activates the host autophagy initiation complex (AIC) and upstream kinases, which can mediate autophagy (60).

Cell Populations in Host Defense Against Pulmonary Fungal Infections

Despite the fact that mounting signal mechanisms driving the initiation and progression of fungal infection have been clearly revealed by independent groups, we still have a poor understanding of the integrated cellular and molecular systems involved in the process of distinct fungal infection in the lung. As a result, there are few viable treatment methods for pulmonary fungal infection and inflammation. Multiple cell types and several chemicals, including receptors, adaptors, kinases, and transcriptional factors, contribute to the host processes of fungal infection in the lung. We focus on *Aspergillus*, *Cryptococcus*, and other pulmonary fungus, and highlight typical components in the host response from cell biology and molecular biology. Innate immunity is critical for the host's defence against fungal infection. Patients with certain immune deficiency deficiencies, such as chemotherapy-induced extended neutropenia or functional faults in NADPH oxidase, might develop invasive pulmonary aspergillosis (IPA), candidiasis, and other mycoses. Neutrophils and macrophages are recruited as first line immune cells to infected and inflammatory regions once pattern recognition receptors (PRRs) detect fungus. They eliminate fungal infections at an early stage of infection. DCs can deliver fungal antigens, bridging the gap between innate and adaptive immunity. In reality, the initial line of defence against fungal infection in the lungs is orchestrated by the innate immune system.

Phagocytic and Myeloid Derived Innate Cells: Alveolar Macrophages and Neutrophils, and Dendritic Cells

A precise network of innate immune cells as well as adaptive $CD4^+$ Th1 type cells protects the host from pulmonary fungal infections (61, 62), Lung phagocytic leukocytes, such as resident alveolar macrophages (AM), DC, and neutrophils, typically regulate the early immune response to pulmonary infection, acting as a first line of defence against pulmonary fungal infections (63). According to one research, the $CD11c^+$ AM population is prevalent in uninfected lungs as well as in the early days after *C. neoformans* infection. Following that, accumulating pulmonary DCs are blamed for the fast proliferation of $CD11c^+$ cells. AM ($CD11c^+$CD11bmin) and normal DC ($CD11c^+CD11b^+$) are distinguished using CD11b expression. *C. neoformans* infected mice with AM/DC population depletion showed fast deterioration, according to the findings (63). TNF-α, interleukin-1α/β, interleukin-6, macrophage inflammatory proteins, and granulocyte-colony stimulating factor are all produced by alveolar macrophages in response to fungal infections, and these responses are mostly dependent on signalling from identified fungal glucan via host PRR dectin-1 (64). Neutrophils, particularly polymorphonuclear neutrophils (PMN), play an important role in the infectious process. These cells may quickly infiltrate the lungs and arrive to inflammatory areas, where they aid in the elimination of infections and the promotion of tissue healing. In the early stages of *Aspergillus fumigatus* infection, AM and neutrophil work together to shape the host's defence and survival. AM is thought to destroy conidia, while neutrophil is thought to limit hyphae tissue penetration (61). To assess the temporal demand for neutrophils in the host defence, a well-established approach of temporary neutrophil depletion using antibody RB6-8C5 (anti-Ly6G/Ly6C) can be utilised (65). RB6-8C5 caused neutropenia in both circulation and single cell lung suspensions while having no effect on $CD11b^+Ly6C^+Ly6G^-$ monocytes, resulting in invasive aspergillosis and tissue destruction (66). Mice given RB6-8C5 before or within 3 hours of infection were aggravated, as seen by greater susceptibility and mortality rates, in contrast to depletion at later time periods, when survival rates are practically normal. In various mice infection models, neutrophils, a form of IL-17, produce cells. Eric Pearlman revealed that in the presence of *A. fumigatus*, $Ly6G^+Ly6C^+$ neutrophils are activated through IL-17A-IL-17RC interactions involving several molecules such as dectin-2 and IL-17 signalling related IL-6, IL-23, and RORgt (67). In addition, TLRs may regulate neutrophil activity in Aspergillosis (10). The integrin CD11b/CD18 and PI3K are involved in non-oxidative intracellular death of *A. fumigatus* conidia. The extracellular death of the Aspergillus hyphae involves antibody mediated opsonization with the participation of Fcγ receptors recognition and kinase signalling for downstream ROS related metabolites generation via MPO and NADPH oxidase when the conidia germinate by evading early killing (68). When *Aspergillus* or *Cryptococcus* is inhaled, phagocytic leukocytes such as AM, DC, and recruited neutrophils provide the initial line of defence by phagocytosing pathogens with yeast lysis. As a result, the local AM and DC play a role in the early innate immune response as well as the control of adaptive immunity later on. Dendritic cells (DCs) are a kind of innate immune cell that may initiate and govern adaptive immunity, which is mediated mostly by T and B lymphocytes (69, 70). By regulating T cell proliferation and boosting the protective Th1 response within the lung, pulmonary DCs also coordinate adaptive immune responses to *A. fumigatus* (71–73). Immature DCs' pro-inflammatory responses following exposure to *A. fumigatus* are mediated by Dectin-1 (74). Interestingly, neutrophils can mediate lung DC maturation and efflux (75), whereas DCs can drive neutrophil/Th1 lymphocyte recruitment via secreted chemokines (76), implying cellular interactions between neutrophils, DCs and T lymphocytes.

NK Cells and T Lymphocytes

Through granule-mediated killing and effector IFN-γ release, natural killer (NK) cells in the innate immune system provide basic immunological protection against tumours and harmful microorganisms (77, 78). During *Pneumocystis* infection, adoptive transfer of $CD4^+$ T cells was discovered to be responsible for an increase in NK cells with the activation marker NKG2D and the production of gamma interferon, granzyme B, and perforin (79). Furthermore,

human NK cells detect *A. fumigatus* hyphae but not conidia in a direct reaction (80). NK cells, unlike other innate immune cells, do not actively fight the fungus by phagocytosis, but instead appear to modulate their antifungal activity by producing inflammatory IFN-γ (81). Similarly, murine NK cells destroy *C. neoformans* directly, making them antifungal (82). Natural killer cells' mediated defence against respiratory fungal infections and their interaction with other immune cells during infection are yet unknown and further research is needed.

After innate immunity, the homeostasis of numerous adaptive T cell subtypes (usually the CD4 positive subtype, which includes Th1/Th2/Th17/Treg cells) is involved in the defence against the fungal infection. Although the relevance of initial innate immunity in the host-pathogen interaction has been extensively documented, the roles of adaptive immunity with representative T cell responses are equally important for the host's defence. The clearance of *C. neoformans* yeast frequently necessitates a Th1 adaptive immune response involving Th1 cytokines such as IFN-γ. H99-gamma animals infected with an IFN-gamma-producing *C. neoformans* strain were resistant to a second infection in the lung by a deadly strain, according to prior research. Increased granulomatous development, fast inflammatory infiltration, and Th1-mediated adaptive immunity were all linked to protection against cryptococcosis in the respiratory tract (83). IL-12 therapy protected mice against a deadly infection by shifting the host immunological balance toward the Th1-state; whereas the mRNA expression patterns of pulmonary cytokines in infected animals were Th2-type (84). Excessive inflammation caused by IL-17 amplification and deduced Tregs with anti-inflammatory activity, which led to a greater vulnerability to *A. fumigatus* in mice, are shown in Tregs and Th17 cells with IL-17 production (85). Furthermore, the role of $CD8^+$ T cells in fungal infection and the molecular processes underpinning fungal clearance are infrequently discussed. TLR3, according to one research, promotes the protective and antifungal memory of $CD8^+$ T cell responses, suggesting that it might be a potential therapeutic target for aspergillosis in high-risk individuals (86).

Lung Epithelial Cell

Multiple hematopoietic cells, such as macrophages and DCs, play critical roles in anti-fungal immune resistance and fungus tolerance by maintaining a balance between immunopathology and protective immunity. However, mounting data suggests that the release of surfactant proteins and antimicrobial peptides by epithelial cells plays an important role in infection and inflammation (87). To begin with, epithelial and endothelial cells have the ability to internalise *A. fumigatus* conidia (88). By connecting innate and adaptive immunity, lung epithelial cells (LEC) play an important role in the interaction between fungal infection and mucosal immunity at the pulmonary mucosa. Indoleamine 2,3-dioxygenase (IDO) signalling is thought to be responsible for LECs' protective tolerance to *A. fumigatus* (89).

KEY MOLECULES REGULATING HOST IMMUNE RESPONSES TO FUNGAL INFECTIONS IN THE LUNG

Receptors

PRRs Including CLRs and TLRs - In an infection, signalling transductions through host receptors are reasonably well-studied. During fungal infection, some host-encoded molecules, such as damage-associated molecular patterns (DAMPs), are produced in addition to fungi-derived PAMPs (13, 14, 90). CLRs and TLRs/IL-1R are the most common PRRs involved in fungal pathogen identification. Dectin-1/2, MCL (Macrophage C-type lectin, Clec4d), Mincle (macrophage inducible C-type lectin, Clec4e), and MR (mannose receptor) are all significant C-type lectin receptors involved in fungus recognition (91–94). Dectin-1 expressed on resident alveolar macrophages and polymorphonuclear neutrophils is necessary for the onset of a host response in an *A. fumigatus* lung infection, but the involvement of dectin-2 is unknown (95). The Gordon D. Brown group (96) recently developed a C-type lectin receptor, the melanin-sensing C-type lectin receptor (MelLec), which was fungicidal by sensing the unit of DHN-melanin in *A. fumigatus* conidia. MelLec protected the host against *A. fumigatus* in animal models. In humans, a single nucleotide polymorphism in MelLec was discovered to suppress myeloid cell inflammatory responses and increase the risk of *A. fumigatus* infection in stem cell transplant patients.

C. neoformans is a kind of Candida albicans. Mannoproteins can bind to a variety of lectin receptors, including the mannose receptor and DC-specific non-ICAM3 grabbing nonintergrin (DC-SIGN) (97, 98). Pathogen phagocytosis by myeloid cells in response to PRRs identification or exposure to soluble glycoantigens and cryptococcal DNA would result in the generation of cytokines and chemokines, as well as yeast lysis. Furthermore, different TLRs are dispersed on distinct immune cells; TLR2, TLR4, and TLR7 are substantially expressed in resident alveolar macrophages, and immunosuppressed animals with TLR2 or TLR4 loss are more vulnerable to invasive aspergillosis (99–102).

Cytokine Receptors Such as IL-1R and TNFR

In terms of signal transduction, IL-1R and TLRs are quite similar (103), and TLR/IL-1R signalling is crucial in the response to fungal infections (104). On both innate and adaptive immunity, the complex group of TNF ligands and the

receptor superfamily provide a rich supply of therapeutic targets. The T cell produced glucocorticoid-induced TNFR-related protein (GITR, TNFRSF18), a member of the tumour necrosis factor receptor superfamily, regulates both natural and acquired immunological responses through its ligand GITRL expressed on APC. GITR-GITRL was found to impact TLR2 and TLR4 expression on DC, which was linked to T cell response during candidiasis (105). During aspergillusis and cryptococcosis the impact of GITRL-GITR on DC and its connection with Treg is unknown (106).

Adaptor Molecules

For the host immune response against fungal infections, TLR-mediated signalling pathways for downstream NF-κB activation events are critical. Multiple adaptor proteins, including as MyD88, TRAF6, TRIF, and others might be used in TLR or IL-1R signalling for downstream signal cascades transduction.

MyD88

Previous research on innate immunological processes demonstrated remarkable conservation of molecular components of host defence signalling pathways, one of which is the Toll-IL-1R homology (TIR) domain, which is provided by adaptor protein MyD88 and is required for signal transmission. Adaptor MyD88 might activate NF-κB downstream via the human TLR/IL-1R transduction pathway, which involves IRAK and TRAF6 (107). Overexpression of MyD88 was functional enough to induce the fungicidal peptide Drosomycin in vitro under the conditions of fungal infection. According to a recent research, MyD88 plays a significant role in host defence during a respiratory fungal infection, particularly during the early stages of illness. Adaptors such as MyD88 and CARD9 might be activated via host receptors such as the C-type lectin receptor, TLR, and IL-1R for immunological signalling transduction as well as fungal clearance in the case of ubiquitous airborne conidia generated by *A. fumigatus* and breathed by people on a daily basis. MyD88 deletion slowed neutrophil lung trafficking and chemokine production at the outset of respiratory fungal infection, resulting in lung damage. Through the IL-1R, MyD88 which was expressed on lung epithelial cells was responsible for fast neutrophil recruitment and chemokine synthesis. In MyD88-deficient mice, exogenous CXCL1 therapy similarly reduced mortality. Overall, host MyD88- NF-κB signalling is important in early responses to *A. fumigatus* in the lung, and fungal PAMPs to host PRRs activated MyD88-NF-κB signalling, which is a key route in the pathogen-host interaction (100, 108).

TRAF Family Proteins

TRAF family proteins, particularly TRAF3 and TRAF6, have an important role in regulating innate and adaptive immune responses, in addition to MyD88. TRAF6 is reliant on MyD88 rather than TRIF in TLR signalling, and it controls MyD88- and IRAK-1-induced NF-κB activation differentially (109, 110). Although TRAF6 and TAK1 have been linked to candida infection (111), their functions in CLR-initiated signalling have yet to be investigated. TRAF6-TAK1 connection and spleen tyrosine kinase (Syk) phosphorylation are both early stages in CARD9-Bcl10-MALT1 complex and downstream MAPK and NF-κB activation in conventional CLR signalling. Adaptor Syk-coupled CLRs like as Dectin1/2 and Mincle promote innate defence against fungal infection (92, 93, 112). Another study found that Dectin-1-Syk and autophagy both helped the *A. fumigatus* phagosome mature (113).

The Inflammasome Complex

Inflammasomes

Inflammasomes, which are made up of many intracellular proteins, are required for the proper control of innate immune responses. These complexes are closely linked to infectious pathogens such as fungi, viruses, and bacteria, and are triggered by PAMPs-PRRs or host-derived DAMPs signalling, notably in respiratory infections (114, 115).

NLRP3 and AIM2

NLRP3 and AIM2 are two common inflammasomes that play important roles in innate immunity through different mechanisms: The activation of the NLRP3 inflammasome is controlled by two primary signalling pathways. The priming stage involves PAMPs such as TLR agonists (LPS is an example) or important cytokines such as TNF-α and IL-1β inducing NLRP3 and pro-IL-1β expression in an NF-κB dependent way. The second stage involves various stimuli, such as ATP/nigericin, activating NLRP3 assembly. Further research revealed that phagocytosis of particulate matter activates NLRP3 and promotes K^+ efflux (116, 117), but a K^+-independent activation method was recently reported by targeting mitochondria with small molecules (118). In terms of the NLRP3 inflammasome's biological activity in the field of infection, it protects against certain lung fungi that can cause aspergillosis and cryptococcosis (90). Notably, fungal polysaccharides such as curdlan (119, 120) identify NLRP3 inflammasome-mediated signalling in the host immunological system, and *A. fumigatus* activates the NLRP3 inflammasome via syk kinase activity and reactive oxygen species (121). Furthermore, fungal zymosan and mannan activated the NLRP3 inflammasome, resulting in macrophage and DC caspase-1 activity as well as IL-1β secretion, suggesting that conserved cell wall components are involved for ASC and NLRP3 inflammasome activation during fungal infection (122). The acapsular

mutant strain of *C. neoformans* (Cap59), but not the encapsulated wild type strain (H99), activates the inflammasome in cellular and animal models (123). Furthermore, germline NLRP3 knock-out mice infected with biofilm of clinical *C. neoformans* strain HS1101 had a more severe infection and inflammation in the lungs, as did Casp1 and ASC knock-out animals. These findings highlight the relevance of NLRP3 inflammasome components in the host's response to a fungal lung assault (124). AIM2 (Absence in Melanoma 2) is a one of a kind DNA-sensing receptor. Mice lacking AIM2 alone showed equivalent susceptibility to wild type mice when infected with Aspergillus, however mice lacking both AIM2 and NLRP3 failed to limit Aspergillus hyphae spread, succumbing to the fungal assault more quickly than wild type mice or mice without either AIM2 or NLRP3 (125). Other new host inflammasomes, such as NLRP1, NLRC6, and NLRP7 have yet to be discovered and their activities and methods in suppressing fungal infection are unknown.

NF-κB and MAPK

It was discovered that the macrophage dectin-1, TLR2, and TLR4 could identify the mature hyphal forms of *Aspergillus* but not spores, resulting in NF-κB dependent inflammatory cytokine release and antimicrobial ROS generation (126). Dectin-2-Syk signalling was also found to be involved in IκBα (inhibitor of the kappa B protein) phosphorylation and NF-κB activation in response to *A. fumigatus* stimulation (127). Interestingly, gliotoxin, a poisonous metabolite produced by *A. fumigatus*, inhibits NF-κB activity and promotes death in cells (128). Another study indicated that ERK, but not p38, was required for defence against *A. fumigatus* on alveolar macrophages, with NF-κB activation playing a secondary role. MAPKs translocated to the nucleus after being phosphorylated by upstream molecules to phosphorylate downstream target molecules that transcriptionally controlled cytokine genes (129). Unlike macrophages that detect *Aspergillus* via TLR2/4 to trigger TLR-MyD88-NF-κB-dependent synthesis of inflammation-related molecules, pulmonary epithelial cells could detect sprouting but not resting *Aspergillus fumigatus* spores to induce the synthesis of interleukin (IL)-8 via p38 MAPK, ERK1/2, and PI3 kinase, implying that MAPK is important in both on phagocytes and epithelial cells (130). TLR4 and CD14 may also play a role in the host response against the *C. neoformans* capsular polysaccharide glucuronoxylomannan (GXM), promoting nuclear translocation of NF-κB in macrophages without MAPK activation and TNF-α production (131).

Cytokines and Chemokines

The most common modulators released by the host in response to fungal pathogen infections are cytokines and chemokines. Infectious disorders may be exacerbated by an imbalance of pro- and anti-inflammatory cytokines, resulting in weakened host defence.

IL-1 Family Cytokines IL-1β/IL-18/IL-33/IL-36

IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ are all proinflammatory cytokines, whereas IL-1Ra, IL-36Ra, IL-37, and IL-38 are antiinflammatory cytokines (132). Through reduced autophagy and enhanced inflammasome activation, IL-1α and IL-1β are considered to be the principal causes of inflammation in chronic granulomatous illness (133). In vitro, both lung homogenates and alveolar macrophages generated from Dectin-1 KO mice showed lower IL-1α/IL-1β, TNF, MIP, and KC, suggesting that IL-1α and IL-1β production is derived from Dectin-1 signalling during invasive pulmonary aspergillusis (IPA) (134). According to a recent research, IL-1R is essential for protection since IL-1α is necessary for lymphocyte recruitment and confers resistance to fungal spread (135). In immunological response against the opportunistic mould *A. fumigatus*, members of the IL-1 family frequently play a protective role. IL-18, in addition to IL-1β, protects against *C. neoformans* by generating IFN-γ. As previously stated, IL-1β/IL-18 is largely secreted in an NLRP3 inflammasome-dependent way. The IL-1 family member IL-33 was shown to perform regulatory functions in lung infection defence against *A. fumigatus* in a recent research. In the absence of Dectin-1, IL-33 expression was identified in the lungs and increased following exposure to the fungus. Mice without the IL-33 receptor ($Il1rl1^{-/-}$) showed surprisingly improved fungal pathogen lung clearance, but IL-33 treatment to normal mice blocked fungal-induced IL-17A and IL-22 through PGE2. Because normal mice generated less PGE2 after fungal exposure when given IL-33, but PGE2 was dramatically enhanced in fungal-exposed $Il1rl1^{-/-}$ animals, this suggests that IL-33-mediated regulation of IL-17A and IL-22 took place at the PGE2 level. Inhibition of cyclooxygenase 2 or PGE2 decreased fungal-induced protective IL-17A and IL-22, as well as IL-1α, IL-1β, and IL-6 production, resulting in poor fungal clearance in $Il1rl1^{-/-}$ mice (132). Furthermore, interleukin-36γ (IL-36γ) is a newly discovered inflammatory cytokine of the IL-1 family that is significantly expressed in epithelium and some myeloid cells. In human studies, it was shown that A. fumigatus substantially generates IL-36g and IL-36Ra, but not IL-36α, which are both reliant on dectin-1 and TLR4, and that inhibiting IL-36 signalling prevents the production of protective Th17 and Th1 responses (136).

IL-17 and IL-23

IL-17 (IL-17A) is a pleiotropic cytokine that has been linked to the pathogenesis of autoimmune inflammations such as rheumatoid arthritis (RA) and multiple sclerosis (MS), but it has also been linked to bacterial infection prevention

(137). Because RORγt is present on various cell types, natural killer T cells (NKT cells), γδT cells, and innate lymphoid cells may produce IL-17 more quickly than Th17 cells (138). Recent research has focused on the involvement of IL-17 and IL-23 in the host response to pulmonary fungal infection. Together with IL-23, IL-17 and IL-23 control neutrophil recruitment and homeostasis in airway lesions (139, 140). Intriguingly, IL-17 and IL-23 are emphasised with a regulatory function in the *A. fumigatus* model of pulmonary fungal infection via the intranasal route, inhibiting the IL-12-IFN-γ mediated Th1 protective response or perhaps weakening antifungal immune resistance (141). Thus, the multi faceted activities of host inflammation include not only important antifungal immunity, but also adversely controlling appropriate immune responses or even worsening fungal illnesses when the balance between protection and pathogenesis is disrupted in a given environment.

Type I and Type II Interferons

IFN-α/β, or type I interferons, are generated by a variety of cell types in response to a variety of stimuli, including viruses. Downstream IFN-α/βstimulated genes (ISGs) can be triggered by binding to a particular IFN-α/β receptor called IFNAR (IFN-α/βR). There are two subtypes of IFNAR: IFNAR1 and IFNAR2. ISG gene expression is induced by canonical type I IFN signalling, which activates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway (142). There currently little understands regarding their functions in non-viral illnesses such pulmonary fungal infections (143). Nonetheless, a recent research looked at the role of type I interferons in the host resistance against *C. neoformans*. The scientists discovered that IFNAR1 knockout mice (IFNAR1 KO) had higher fungal clearance and better Th2 and Th17 responses following infection than control mice. In addition, MUC5AC expression in broncho-epithelial cells was considerably greater in IFNAR1 knockout animals. As a result, type I interferons may inhibit the early host response against a fungal infection (144).

After an intratracheal or i.v. challenge with *C. neoformans*, mice lacking either the IFNAR or IFN-β succumbed to unrestrained pneumonia and encephalitis, with increased Th2 cytokines IL-4/IL-10/IL-13 but decreased TNF-α, IFN-γ, iNOS, and CXCL10, suggesting that type I IFN signalling is associated with type I cytokine polarisation (145). When *Aspergillus* infects a person, the conidia mostly stimulate IFN-β signalling in respiratory epithelial cells. Differentiated human bronchial epithelial cells (HBECs) may detect resting conidia, resulting in the expression of IFN-β-inducible genes such IP-10 (CXCL10). IP-10 has the potential to control activated T cells even more (146). Resveratrol may lower IFN-β/IP-10 expression by inhibiting IFN-β signaling mediators such as RIP-1 (Receptor-interacting protein 1) and TBK-1 (TANK-binding kinase-1) (147). The Th1 cytokine IFN-γ, on the other hand, has been shown to be effective in eradicating *C. neoformans* infection. The injection of recombinant IFN-γ lowers fungal load and boosts survival rates, enhancing the efficacy of fungicidal amphotericin B (148, 149). In mice challenged with the IFN-γ releasing *C. neoformans* strain, pulmonary cytokine analyses revealed a Th1-type pro-inflammatory cytokine bias, rather than Th2-type cytokines production, as compared to wild-type strain-treated animals (150).

Classical Cytokines and Chemokines: IL-6, IL-8 (KC), TNF-α, GM-CSF

Innate immunity relies heavily on pro-inflammatory cytokines such IL-6, IL-8 (KC), TNF-α, and GM-CSF. Interleukin (IL)-6 and IL-8 levels are raised in both serum and bronchoalveolar lavage fluid (BALF) in haematological patients receiving IPA (151). With its anti-inflammatory effect, circulating IL-6 can stimulate acute phase responses to regulate local or systemic acute inflammation (152). In healthy and haematological controls, IL-6 promotes *Aspergillus*-induced IL-17 production, but not in IPA patients with reduced T cell response to IL-6 (153). When *Aspergillus* infection occurs, respiratory epithelial cells produce interleukin (IL)-8 as a CXC chemokine (CXCL8) via the PI3K and MAPK pathways, rather than the TLR-MyD88 pathway (130), similar to other CXC chemokines such as KC (keratinocyte-derived chemokine, CXCL1, specific for mice; it is the counter chemokine for IL-8 in humans) and When animals were transiently depleted of neutrophils and challenged with AF, significantly greater levels of KC and MIP-2 were seen in their lungs; and lung-specific overexpression of KC enhanced the outcome of mice in IPA by enhancing the host defence against *Aspergillus fumigatus* (154, 155). Proteases produced from *A. fumigatus* increase the levels of IL-6 and IL-8 mRNA in human alveolar type II epithelium-like cells, eliciting cytokine production (156).

However, another study found that after encountering *A. fumigatus*, A549 cells produce only low amounts of these cytokines (IL-6 and IL-8), resulting in reduced leukocyte recruitment to the lesion sites and pathogen escape from immune response (157). During the peak of infection in the lung *A. fumigatus* induced an acute inflammation regulated by neutrophils with pro-inflammatory cytokines (TNF-α, GM-CSF, and IL-1β), as well as chemokines (MIP-1a, MCP-1, and MIP-2). Neutralizing TNF-α or GM-CSF decreased neutrophil influx and delayed fungal clearance, according to a study (158). TNF-α increases host responses to A. fumigatus, and inhibiting its activity may increase aspergillosis susceptibility (159). Endogenous TNF-α, IFN-γ, IL-18, and IL-12 are immunoreactive with antifungal activity in response to inhaled *A. fumigatus* in a cytokine network experiment in the lungs of immunocompetent mice (160). GM-CSF, a pleiotropic hematopoietic cytokine that regulates the myeloid cell host response, is also a pleiotropic

hematopoietic cytokine. The GM-CSF receptor (GM-CSFR/Csf2r) is made up of two parts: GM-CSFR/Csf2ra and GM-CSFR/Csf2rb (161). Mice missing the GM-CSF receptor β chain (GM-CSFRβ) were more vulnerable to *A. fumigatus* conidia infection in the lungs, demonstrating the importance of GM-CSFR signalling in the fight against inhaled *A. fumigatus* conidia (162). Human polymorphonuclear leukocytes from healthy people can produce inflammatory cytokines in response to *C. neoformans* yeast cells or the principal capsular polysaccharide-glucuronoxylomannan (GXM) (163). The polarisation state of macrophages is important for the management of *C. neoformans* infection, and IFN-γ and IL-4 are responsible for the fungicidal action associated with M1/2 polarisation. This suggests that cell-mediated immunity and cytokine-mediated immunity are in communication (164). Targeting cytokines might be a viable intervention technique for antifungal treatment, considering clinical applications and translational medicine. To this purpose, the fluoroquinolone medication moxifloxacin protected human monocytes infected with *A. fumigatus* by suppressing the generation of inflammatory cytokines via NF-κB and MAPK inactivation (165).

Secreted Soluble Proteins in the Lung

In addition to the cytokines and chemokines released by infected immune cells, when fungal infections are inhaled, the innate immune system can build a second barrier on the airway surface. This barrier contains several soluble peptides and proteins that have antibacterial action. Lysozyme, lactoferrin, secretory leukocyte proteases, secretory phospholipase A2, defensins, and cathelicidins, which are mostly released by cells in the airway submucosal glands or epithelial cells, meet this need. These soluble effector molecules have been found to remove a variety of pathogens with neutralising, opsonization, antibiotic, or direct killing properties, similar to antimicrobial peptides (AMPs) in the gut (166, 167).

Collectin

MBL (Mannan binding lectin) and pulmonary surfactant proteins A through D are essential innate immune mediators for antifungal defence and belong to the human collectin family (collagen-like or C-type lectin) (168). Opsonization, inflammatory control, and pathogen direct clearance are all roles of collectins (169). MBL was found to be protective in a mouse model of aspergillosis in a prior study (170). Surfactant proteins protect the airways from fungus buildup and phagocytosis clearance (171). SP-A binds to *C. neoformans* in the respiratory tract but does not improve phagocytosis, whereas SP-D may play an important role in the early stages of infection by increasing uptake and phagocytosis. As a result, wild-type mice showed a higher number of phagocytosed *C. neoformans* cells than SP-D KO animals. SP-D boosts fungal survival in macrophages in vitro and protects animals missing SP-D in vivo (171, 172).

The cause for these contradictory findings will have to be investigated further. Collectins, ficolins, and pentraxins are circulating proteins that have the potential to act as opsonins (173). H-Ficolin might be secreted by type II alveolar epithelial cells as an innate immunological opsonin to aid in lung defences against fungal infection. H-ficolin was discovered to be engaged in *A. fumigatus* defence via activation of the lectin complement pathway, demonstrating the relationship between host and fungus as well as ficolin's control of the immune response (174). In addition, the bronchoalveolar lavage (BAL) fluid from individuals with a fungal infection included another human serum opsonin, L-ficolin. L-ficolin opsonization boosted IL-8 synthesis in A549 cells, as well as conidial uptake and *A. fumigatus* death by macrophages and neutrophils, with less inflammatory cytokine release (175).

Defensin and Lysozyme

The development of protective actions, such as inflammatory cell recruitment and the synthesis of direct antimicrobial agents, requires the release of inflammatory mediators such as AMPs from epithelial cells. Defensins, particularly the b-defensin, are one form of AMP with b-sheets supported by two disulfide links. The expression of b-defensin2 and b-defensin9 (hBD2 and hBD9) genes were increased in HBECs after exposure to *Aspergillus fumigatus*, showing that AMPs from the respiratory epithelium are implicated in the host response during *Aspergillus* infection (176). Furthermore, lysozyme, a tiny enzyme created by epithelium as well as resident macrophages in human lung tissues, contributes to *A. fumigatus* hyphal disruption as one of the most prevalent antimicrobial proteins in the airway (177, 178). Lysozyme P is found on Paneth cells in the small intestine, while lysozyme M is largely expressed on alveolar macrophages, alveolar type II epithelial cells, and bronchoalveolar lavage fluid (BALF) in the lung in mice (179, 180). However, it is unclear if lysozyme M provides protection against pathogenic fungus in the lungs. Previous research suggests that defensins and lysozymes may play a role in the host's defence against respiratory fungal infections.

Calcineurin Signaling

In *A. fumigatus*, calcineurin and associated pathways are thought to be involved in the regulation of hyphal synthesis, morphological character, and virulence. A mutant of *A. fumigatus* with reduced calcineurin is a heterodimer composed of catalytic subunit A and Ca^{2+}/calmodulin binding unit. The morphology of a catalytic component was deficient, and filamentation was reduced (181–183). Meanwhile, a calcineurin mutant with reduced beta-glucan levels increased the

fungicidal effectiveness of cell wall inhibitors, suggesting that targeting calcineurin with other fungicides might be a viable synergistic treatment for *A. fumigatus* (184). *C. neoformans* growth was inhibited by CsA and FK506, which mediates signal transduction on the Ca^{2+} regulated protein phosphatase calcineurin, and Calcineurin mutant strains failed to be infectious in a brain model of cryptococcosis, suggesting that calcineurin is required for *C. neoformans* pathogenicity (185). Furthermore, calcineurin signalling is important for host immune responses to fungal infection. For example, the ability of neutrophils to intervene in *Aspergillus* species germination was inhibited in hematopoietic stem cell transplant (HSCT) recipients, and this impairment was partly attributed to the administration of calcineurin inhibitors (186), suggesting that calcineurin signalling may affect neutrophil activity against *Aspergillus*, especially in immunocompromised individuals. Calcineurin signalling has also been linked to macrophages, in addition to neutrophils.

The calcineurin inhibitor tacrolimus was found to impair macrophage immune responses and clearance of the major mould pathogen *A. fumigatus* from the airway, possibly due to inhibition of *A. fumigatus*-induced phagosomal TLR9-BTK-Calcineurin-NFAT cascades independent of MyD88, and NFAT collaborating with NF-κB contributed to TNF-α production in primary alveolar macrophages (187). Cyclosporine (CsA), which inhibits the protein phosphatase calcineurin, can be employed as both an immunosuppressive medication and an antibacterial agent by targeting host and pathogen calcineurin signalling. CsA can prevent transplant recipients from severe transplant rejection by inhibiting host calcineurin or its downstream calcineurin-NFAT pathway, but it may also enhance host immunological deficiencies, resulting to organ transplant-related invasive aspergillosis. Surprisingly, various immunosuppressants resulted in varying outcomes in transplant patients, although the death rate looked to be lower in those who got calcineurin inhibitors (188). However, the specific mechanisms governing host calcineurin signalling in cryptococcosis remain unknown.

Molecules Mediating Autophagy During Fungal Infection

Extracellular infections can be removed by immune cells by phagocytosis, but pathogens can also trigger autophagy, a lysosomal breakdown process required for host cell survival and homeostasis (189–192). LC3-associated phagocytosis (LAP) in phagocytes is a non-canonical autophagy pattern, and phagosomes with a single-membrane formation followed by clearance of absorbed pathogens are necessary in this process (193, 194). The LAP begins with pathogen detection by PRRs and LC3 recruitment to the phagosomal membrane. This specific xenophagy, also known as LAP, is used to protect the host from invading fungus (195–197). The amount of autophagy in both host and yeast cells is crucial for pathogen control as well as immune cell survival, owing to the fact that autophagy is linked to cell-programmed necrosis and apoptosis (191). In one study, autophagy in macrophages was examined in relation to *C. neoformans* infection, and non-activated bone marrow derived macrophages (BMDMs) from Atg5 (Autophagy-related gene 5) knockout mice restricted *C. neoformans* growth with fungistatic activity; and in vivo, mice with myeloid depletion of Atg5 consistently displayed reduced susceptibility to *C. neoformans* (198).

LAP is required for antifungal responses in the host. LAP may be inhibited by *A. fumigatus* cell wall melanin for pathogenicity amplification, according to new research (199, 200). Canonical autophagy molecules are also important for LAP; for example, once phagocytes internalise zymosan, beclin-1 in the PI3K pathway is recruited to autophagosome. The autophagy protein ATG7 is also crucial for LAP, since its absence would result in the loss of LC3 recruitment and a reduction in the clearance of internalised pathogens and apoptotic cells (201, 202). Rubicon (RUN domain protein as Beclin-1 interacting and cysteine rich containing) was shown to be required for LAP but not autophagy activation in mediating A fumit clearance (203). Furthermore, LC3 activation necessitates NADPH-regulated ROS (200). The Atg genes in *C. neoformans* are also engaged in the pathogenic processes of infection. For example, in mice with a pulmonary infection, *C. neoformans* with an Atg7 mutant imparted decreased survival but increased vulnerability to the killing machinery of distinct host phagocytes (204). In a mouse infection model, it was demonstrated that PI3K signalling with a faulty production of Atg8 tagged vesicles inside *C. neoformans* resulted in a substantial reduction in virulence (205).

PERSPECTIVE AND CONCLUSION

The cellular and molecular processes of the host defence against pathogenic fungal infections in the lung were outlined in this study. In terms of cells, innate immune cells such as macrophages, neutrophils, and DCs are the first line of defence against a fungal invasion; adaptive T lymphocytes are important for limiting fungal expansion; and natural killer cells (NK cells) are responsible for killing fungal pathogens directly through cytotoxicity. When it comes to signalling molecules, the receptors-adaptors-transcriptional factors cascade helps to keep the body in a state of homeostasis after a fungal infection. Cytokine production is important in the micro-environment because it allows cells to communicate with one other via cytokine receptors. However, more mechanisms need to be investigated. In

pathogenic fungal infections, phagocytosis regulation, autophagy, miRNA/lncRNA, and ROS signalling are all still understudied. Furthermore, elucidating the host defensive mechanisms against infectious fungal infections in the lung would need the identification of novel genes and pathways using high throughput screening or sequencing, as well as additional functional research.

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