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Review Article

A Review on Antifungal Innate and Adaptive Immune Responses

Sanam Nami[1], Mahta Hashemzadeh Mohtasham[2#], Saba Pourmahmoud[2#], Sana Baradari[2#], Ainaz Zamani[3], Hamid Morovati[1*]

[1]Department of Parasitology and Mycology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Maragheh University of Medical Sciences, Maragheh, Iran

[#]These authors have contributed equally to this work.

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***Corresponding Author:**
Hamid Morovati,
Email: morovatihamid1989@gmail.com

Abstract
Yeast and filamentous forms are typical morphological classifications for fungi, which are heterotrophic eukaryotes. Inhaling spores or tiny yeast cells exposes individuals to most of the fungi found in the environment. Fungi are highly skilled in detecting their environment and reacting to signals that help them survive in shifting conditions. Therefore, they can form symbiotic, commensal, latent, or harmful partnerships with humans, animals, or plants in various ways. Fungal diseases are an essential paradigm in immunology since they can be due to either an overactive inflammatory response or a lack of detection by the immune system. The degree of cellular localization and receptor cooperativity, in addition to the relative degree of activation of each particular receptor, will determine the immunological response. Moreover, fungi produce numerous substances that are powerful modulators of the host inflammatory response. The ability of fungi to evade inflammation by disguising or manipulating the host's detection systems also facilitates fungal adaptation and opportunism. In addition, the fungal cell wall is a dynamic structure that shapes immune recognition and is remodeled during growth and morphological changes. Accordingly, this review integrates current progress in fungal immunology with evolving perspectives on host-directed immunotherapy and immune dysregulation.
Keywords: Innate immunity, Fungal infections, Adaptive, Antifungal host defense

Introduction

Fungal infections pose a serious health risk, particularly for individuals with compromised immune systems.[1] In addition, fungi are responsible for a wide range of diseases in humans and animals, from mild, self-limiting conditions in healthy individuals to severe, potentially life-threatening infections and allergic reactions in immunocompromised patients.[2]

Despite tremendous advancements in antifungal therapy, the human immune system remains the primary line of defense against fungal invasion. Both innate and adaptive systems work in harmony during the immune response to a fungus. Innate immunity constitutes the initial defense mechanism, employing physical and chemical barriers, pattern recognition receptors (PRRs), and effector cells. Conversely, adaptive immunity facilitates antigen-specific responses and immunological memory. The intricate interaction between these two immune branches is essential for the effective elimination of fungi and the mitigation of immune-mediated tissue injury.[3] The increasing prevalence of opportunistic mycoses, typically caused by fungal species that are normally harmless colonizers to hosts with healthy immune systems, is largely due to medical advances and the increasing number of patients with congenital or acquired immunodeficiencies.[4]

This review aims to analyze innate and adaptive immune responses to fungal infections, focusing on host recognition, effector pathways, and immune regulation. It is believed that a deeper understanding of these processes may lead to new immunotherapies and host-directed strategies to prevent and treat invasive and opportunistic fungal diseases.

Innate Immunity

The innate immune system is triggered minutes after a pathogenic microbe invades the host, coordinating the host's defense during the initial hours and days of the illness.[5] Innate immunity, once regarded as non-specific, is now believed to possess a degree of specificity and functional memory (trained immunity or innate immune memory), thereby facilitating effective responses against most invasive pathogens.[2]

Similarly, innate immunity is triggered when PRRs

identify microbial ligands. First, a direct anti-fungal response is started, leading to either phagocytosis or the secretion of microbicidal chemicals. Moreover, proinflammatory mediators (e.g., cytokines and chemokines) are produced, which have a facilitative effect. Ultimately, the adaptive immune system is activated by the absorption and presentation of antigens.[3]

Functionally, the innate immune system comprises four major components as follows:

Physical and Chemical Barriers

Epithelial surfaces, mucus layers, surfactants, and antimicrobial peptides serve as the first line of defense by inhibiting fungal adherence and invasion.[6] Beyond their barrier function, epithelial cells possess the capacity to recognize fungi and distinguish varying degrees of fungal virulence, subsequently initiating an immunological cascade. It is worth mentioning that the recognition of fungi at cutaneous and mucosal surfaces is essential for the induction of an effective antifungal immune response. This process is facilitated by different PRRs produced on myeloid and epithelial cells that detect conserved fungal cell shapes.[7]

Soluble Mediators

Factors such as pentraxins, collectins, and complement proteins improve fungal clearance and aid in opsonization.[8] The complement system has three biochemical pathways (the classical, alternative, and lectin activating pathways) that involve serum proteins in complex cascades that provide antimicrobial actions by opsonophagocytosis and inflammatory cell recruitment. It is believed that the lectin pathway has a negligible role against pathogenic fungi.[3]

Pattern Recognition Receptors

Immune sensing is the initial stage of optimized immunity to fungal pathogens. It is triggered by PRRs, which identify microbial pathogen-associated molecular patterns (PAMPs) and host-derived damage associated molecular patterns (DAMPs) on cell surfaces or within cells.[9] PRR activation sets off signaling pathways (mainly TLR-MyD88 and CLR-SYK-CARD9) that produce cytokines and chemokines and antimicrobial effector molecules. Each of the four main PRR families, namely, toll-like receptors (TLRs), C-type lectin receptors (CLRs), nod-like receptors, and RIG-I-like receptors, recognizes unique molecular patterns.[10] While overstimulation can result in excessive inflammation and tissue damage, proper PRR activation is necessary to start optimized adaptive immune responses. In addition, increased vulnerability to fungal infections is linked to genetic abnormalities, particularly PRRs and signaling pathways. To avoid detrimental inflammatory overactivation, PRR systems, such as TLRs, CLRs (dectin-1 and dectin-2), and inflammasomes, should be strictly regulated.[11]

Fungal Pathogen-Associated Molecular Patterns

As a cellular-cytokine system, the immune system interprets molecular patterns and tissue damage.

The cell wall is thought to be the most common source of fungal PAMPs (e.g., β-1,3-glucans and mannans) due to its intrinsic dynamic composition and varying cellular localization of the many constitutive components throughout contact with the host.[12]

Main Fungal Pathogen-Associated Molecular Patterns

Fungal β-1,3/1,6-glucans (located in the inner layer of the cell wall) are potent inducers of dectin-1, stimulating the T helper 17 (Th17) response and neutrophil recruitment.[13] Additionally, mannans/mannoproteins are located in the outer layer of the cell wall that can be detected by the mannose receptor, Dectin-2, and Mincle, which induce Th1/Th17 responses. Mannan is the most potent immunogenic unit of the fungal pathogen.[14] In addition, chitin is a structural polysaccharide in the inner layer of the cell wall, which has a variable immunogenicity depending on its size. It causes eosinophilia and stimulates interleukin 10 (IL-10) or inflammatory responses. Furthermore, glycosylphosphatidylinositol-anchored proteins are surface proteins that can connect the host's receptors and stimulate TLRs and CLRs. Moreover, galactomannan (GM) is located in the cell wall of *Aspergillus*. It can be recognized by the immune system of the host and is widely used as a diagnostic biomarker (GM test).[15] Further, capsular glucuronoxylomannan and galactoxylomannan in the *Cryptococcus neoformans* capsule can have an anti-inflammatory effect, dampening immune responses and impairing antigen presentation [16].

Damage-Associated Molecular Patterns

DAMPs are critical danger signals that alert the immune system to tissue damage during fungal infections. Their activation can amplify pro-inflammatory responses, potentially leading to chronic inflammation and immunopathology. A thorough understanding of DAMP-mediated pathways may facilitate the development of targeted immunomodulatory strategies that selectively enhance protective antifungal immunity while limiting tissue damage.[17]

Effector Cells

Tissue-resident macrophages, circulating neutrophils, and monocytes are the primary cells in the host innate immune system responsible for immunological surveillance against fungal pathogens and early antifungal defense. In addition, dendritic cells (DCs) are critical in bridging innate and adaptive immunity by mediating antigen uptake, processing, and presentation.[3]

Dendritic Cells

These cells are capable of absorbing and digesting antigens for presentation to naive T lymphocytes by major histocompatibility complex class I or II molecules and have strong fungicidal actions.[18]

DCs are particularly skilled at deciphering information

related to fungal pathogens and converting it into qualitatively distinct adaptive T cell immune responses. Fungi have taken advantage of common pathways to enter DCs, such as opsonin-dependent and lectin-like pathways for filamentous and unicellular forms, respectively.[19]

Macrophages

In a similar vein, macrophage clustering may help conceal fungal damage, thereby reducing the pro-inflammatory neutrophil response and avoiding excessive tissue damage.[2]

The respiratory burst pathway generates reactive oxygen species (ROS) that compromise fungal cell viability via a number of enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase and nitric oxide synthase. Moreover, the non-oxidative mechanism involves degranulation and the subsequent release of defensins, neutrophil cationic peptides, and other effector molecules.[20]

Neutrophils

Neutrophils facilitate the uptake and destruction of yeasts and inhaled molds through oxidative cytotoxic processes.[21] Furthermore, they are particularly essential for killing fungal hyphae, which are frequently resistant to macrophage-mediated phagocytosis.[22] Nicotinamide adenine dinucleotide phosphate oxidase 2, also known as phagocyte oxidase, is assembled by neutrophils following pattern recognition and phagocytosis. The initial ROS are superoxide radicals, which are created when the cytoplasmic and transmembrane protein subunits of the nicotinamide adenine dinucleotide phosphate oxidase 2 complex assemble. Superoxide radicals further combine with hydrogen peroxide, and then myeloperoxidase transforms into hypochloric acid, or bleach. It should be noted that the elimination of opportunistic fungal infections depends on ROS.[23]

In addition, neutrophil extracellular traps play a major role in trapping and killing pathogen elements, particularly large hyphal structures, by their ability to expel chromatin covered in antimicrobial proteins.[2].

Mast Cells

Mast cells play a double-edged role in immune responses.[24] More precisely, they can enhance host defense against fungal pathogens while also contributing to dysregulated immune responses that may increase disease severity and tissue damage. Through multiple mechanisms, mast cells significantly influence innate immunity. These mechanisms encompass the detection of microbial components via TLRs, the rapid discharge of pre-formed granule mediators (e.g., proteases and cytokines), the orchestration of inflammatory cell recruitment (e.g., neutrophils), and the production of antimicrobial peptides. Moreover, mast cells may directly engage with pathogens (e.g., through the phagocytosis of fungal elements). Depending on the immunological context, these processes can either promote effective pathogen elimination or contribute to heightened, potentially detrimental inflammation.[25]

Natural Killer Cells

These cells are crucial innate immune effectors that directly damage pathogenic fungi (e.g., *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, and *Rhizopus oryzae*) by releasing granzyme B, granulysin, and perforin. In addition to their cytotoxic activity, NK-derived cytokines, such as interferon-gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor, and RANTES/CCL5, enhance the functions of neutrophils, macrophages, and T cells, aiding in the regulation of antifungal immunity. However, some fungi have the ability to inhibit NK-cell responses. For instance, *A. fumigatus* and *C. albicans* weaken host defense mechanisms by decreasing the production of tumor necrosis factor alpha (TNF-α) and IFN-γ through NK cells.[26]

Innate Lymphoid Cells

ILCs are a diverse type of immune cell that are vital for immunological homeostasis, tissue repair, and pathogen defense since they do not have modified antigen-specific receptors. These cells participate in mucosal immunity, tissue repair, and antifungal defense, especially at epithelial interfaces, through the expedited synthesis of cytokines and growth factors.[27]

Adaptive Immunity

In cases where innate immune mechanisms prove inadequate for the clearance of fungal pathogens, the development of adaptive immunity is critical for ensuring robust host defense. It is worth mentioning that adaptive immune responses, distinguished by their antigen specificity, clonal expansion, and immunological memory establishment, rely predominantly on the activation of T and B lymphocytes.

T Cell-Mediated Responses

T cells are essential for the host's fight against fungi. $CD4^+$ Th cells have four functional arms, including Th1, Th2, Th17, and T regulatory (Treg) cells. Th1 and Th17 responses generally support beneficial antifungal defense, but Th2 responses may be associated with disease progression or immune tolerance. In addition, Tregs can be beneficial or detrimental to the host based on how they regulate the immune response, since they play a significant role in coordinating the equilibrium between T-cell subsets. Unlike T CD_4^+cells, T CD_8^+cells have a minor role against pathogenic fungi. Although the exact roles of cytotoxic T cells and gamma delta (γδ) T cells in antifungal host defense remain unclear, evidence suggests their involvement. Notably, γδ T cells likely contribute to the early immune response against fungi at mucosal and epithelial surfaces. Nonetheless, further research is needed to fully define their role in antifungal immunity.[28]

T Helper 1-Mediated Immune Responses: Fungal Clearance

Pathogens may deceive the host by activating an inappropriate Th cell response and suppressing its protective responses; these protective responses are predominantly dependent on Th1 cells.[29] The Th1 cellular immune arm primarily involves CD_4^+Th1 cells, CD_8^+cytotoxic T cells, and NK cells. These cells are activated mainly by IL-12 and subsequently produce IFN-γ and TNF.[30] The Th1 response typically peaks within 3–7 days after infection. Its major functions include macrophage activation, granuloma formation, and intracellular fungal killing, which are vital for controlling intracellular fungal pathogens, such as *Histoplasma* and *Coccidioides*.[31]

T Helper 2-Mediated Immune Responses: Tolerance

Conversely, the Th2 pathway, which is represented by IL-4, IL-5, and IL-13 cytokines, inhibits Th1-dependent cellular mechanisms through stimulating a humoral response.[3] Th2 cells are responsible for coordinating type 2 immune responses against some infections (e.g., helminths and allergens), and their formation is triggered by DCs in the presence of antigens, resulting in the transcription of key genes. They accomplish this process by generating cytokines, including IL-4, IL-5, and IL-13, which stimulate the generation of B-cell antibodies (particularly immunoglobulin E), activate eosinophils, and promote tissue healing. However, when overactivated, these cytokines can also lead to allergic inflammation.[32]

T Helper 17-Mediated Immune Responses: Inflammation

Th17 plays a major role in mucosal immunity against fungal pathogens. Human T cell memory repertoires specific to fungi contain Th17 cells.[33] Overall, the IL-23/Th17 pathway has a double-edged role in antifungal immunity. This can both promote susceptibility by inhibiting Th1 responses and drive tissue-damaging inflammation. Nevertheless, it may also contribute to protective antifungal defense under specific conditions (e.g., IFN-γ deficiency), indicating the importance of a tightly regulated Th1/Th17 balance for immune homeostasis and effective antifungal immunity.[29]

T Regulatory-Mediated Immune Responses: Immune Regulation

Treg profiles play a crucial role in fine-tuning the immune responses against fungi. The immune system must eradicate the fungal pathogen during a fungal infection while minimizing tissue damage and reestablishing a homeostatic environment.[33] Treg cells often help the host by reducing tissue damage in many chronic infections through controlling excessive immune response. However, the effectiveness of protective immunity may be hampered by the natural Treg cell responses.[34] It should be noted that although Tregs reduce inflammation through transforming growth factor-β and IL-10, they may unintentionally encourage fungal persistence, as in the case of a *Cryptococcus infection*.[35]

Follicular Helper T Cells: A Bridge Between Cellular and Humoral Immunity

Tfh, on the other hand, promote humoral immunity through opsonophagocytosis, antibody class switching (IgM→IgG/IgA), and B-cell activation. When combined, these processes improve extracellular fungal component neutralization and pathogen clearance.[36]

B Cell-Mediated Immunity

Antibodies aid in the removal of fungi, albeit being less significant than cellular systems. The main roles of humoral immunity against fungal pathogens include opsonization, activation of complement, neutralization of fungal virulence factors, initiation of complement activation through IgM secretion, opsonization and antibody-dependent phagocytosis through IgG (specifically IgG1 and IgG3 activation), and optimization of mucosal immunity by IgA.[37]

Concluding Remarks and Perspectives

Innate and adaptive immunity cooperate closely to manage fungal infections. The integrity of PRR signaling, efficient macrophage and neutrophil activation, and balanced T cell responses are necessary for antifungal defense to be effective. It is worth mentioning that dysregulation at any level of this immune network may result in impaired fungal clearance or excessive immunopathology.

A profound understanding of antifungal immunity has also opened new avenues for host-directed immunotherapeutic strategies, including immune modulation, vaccination approaches, and adjunctive immunotherapies. Human susceptibility to fungal infections arises from the interplay of mycology, immunity, and genetics. Accordingly, understanding host immune and genetic factors clarifies severe individual cases and identifies high-risk populations, thereby enabling host-directed immunotherapies, immunosuppression biomarkers, and polygenic risk scores. In addition, integrating these fields helps turn the complexity of fungal diseases into actionable strategies to improve outcomes.

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Authors' Contribution

Conceptualization: H.M., S.N., M.H.H., S.P., and S.B.
Data curation: H.M., S.N., and A.Z.
Formal analysis: H.M.
Investigation: H.M., S.N., M.H.H., S.P., and S.B.
Methodology: H.M., S.N., M.H.H., S.P., and S.B
Project administration: H.M.
Resources: H.M., S.N., and A.Z.
Software: H.M.
Supervision: H.M.

Validation: H.M., S.N., M.H.H., S.P., and S.B.
Visualization: H.M.
Writing–original draft: H.M., S.N., A.Z., M.H.H., S.P., and S.B.
Writing–review & editing: H.M., S.N., A.Z., M.H.H., S.P., and S.B.

Competing Interests
The authors declare no conflict of interests.

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