International Journal of Microbiological Research 10 (3): 134-138, 2019
ISSN 2079-2093

DOI: 10.5829/idosi.ijmr.2019.134.138

Review on Immunity to Fungal Infection

Mihretu Ayele

Addis Ababa University, College of Veterinary Medicine and Agriculture,
Department of Microbiology, Immunology and Veterinary Public Health Addis Ababa, Ethiopia

Abstract: The immune mechanisms of defense against fungal infections are numerous and range from protective mechanisms that were present early in evolution (innate immunity) to sophisticated adaptive mechanisms that are induced specifically during infection and disease (adaptive immunity). The first-line innate mechanism is the presence of physical barriers in the form of skin and mucous membranes, which is complemented by cell membranes, cellular receptors and humoral factors. The host response is the outcome of interplay between innate immunity, adaptive immunity (T_{h1}, T_{h2}, T regulatory cells, B cells and antibodies) and fungal virulence factors. Dendritic cells are the gatekeepers between innate and adaptive immunity and have been the intense focus of recent studies on innate immunity to fungi because of their ability to distinguish between different forms of a fungal species, to drive T_{h1} versus T_{h2} versus T regulatory responses and potentially be modulated by fungal products. New mechanisms have been described by which anti-fungal antibodies can modulate infection and augment T cell immunity. T_{h1} responses are central to limiting infection with many fungi; thus, a great deal of attention has been focused recently on the antigen(s) that trigger such a response.

Key words: Fungal · Adaptive · Innate · Immunity

INTRODUCTION

Fungal diseases represent an important paradigm in immunology, as they can result from either a lack of recognition by the immune system or over activation of the inflammatory response. Research in this field is entering an exciting period of transition from studying the molecular and cellular bases of fungal virulence to determining the cellular and molecular mechanisms that maintain immune homeostasis with fungi. Understanding the nature and function of the immune response to fungi is an exciting challenge that might set the stage for new approaches to the treatment of fungal diseases, fromimmuno therapy to vaccines. The past decade has witnessed the development of a wide range of new approaches to elucidate events that occur at the host-fungus interface [1].

It is known that the host defense mechanisms against fungi are numerous and range from protective mechanisms that were present early in the evolution of multi cellular organisms ('innate immunity') to sophisticated adaptive mechanisms, which are specifically induced during infection and disease ('adaptive immunity'). Protective immunity against fungal pathogens is achieved by the integration of two distinct arms of the immune system, the innate and adaptive responses. Innate and adaptive immune responses are intimately linked and controlled by sets of molecules and receptors that act to generate the most effective form of immunity for protection against fungal pathogens. The decision of how to respond will still be primarily determined by interactions between pathogens and cells of the innate immune system. Regulatory T cells in their capacity to inhibit aspects of innate and adaptive antifungal immunity have become an integral component of immune resistance to fungi and provide the host with immune defense mechanisms adequate for protection [2].

Adaptive immunity has long been regarded as the major player in protection against most fungal infections. Mounting evidence suggest however, that both innate and adaptive responses intricately collaborate to produce effective antifungal protection [3].

Corresponding Author: Mihretu Ayele, Addis Ababa University, College of Veterinary Medicine and Agriculture, Department of Microbiology, Immunology and Veterinary Public Health Addis Ababa, Ethiopia.

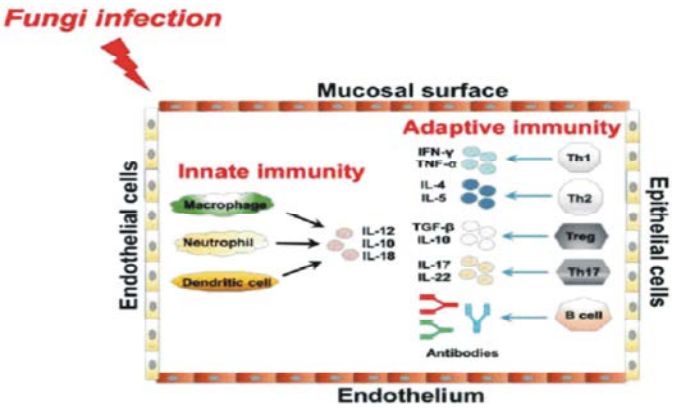

Fig. 1: Immunity against fungal pathogens

The objective of this review therefore is:

- To explain in detail how both the innate and adaptive immune responses get involved either separately or in unison in the control of fungal infections.

Innate Immunity: Neutrophils, macrophages and DCs are all critical to the antifungal response [4]. Upon infection, these innate immune cells are rapidly recruited to sites of infection by virtue of their production of inflammatory cytokines, chemokines and/or complement units [5]. The release of inflammatory cytokines, as well as reactive oxygen intermediates and antimicrobial peptides, can then clear the fungi in target organs. Neutrophils, a class of professional phagocyte, can also engulf and/or kill invading fungi [6]. One of its more recently discovered antifungal mechanisms is the neutrophil extracellular trap, which, together with an oxidative burst and the release of antimicrobials, constitutes a potent antifungal response [7]. Activated neutrophils release the cytokines IL-12 and IL-18 (Fig. 1) and mediate antifungal responses via their expression of receptors such as Toll-like receptor 4 (TLR4) and/or the complement receptors e.g., CR1 [8].

Fungi usually infect their host via epithelial or endothelial cells, invading both the mucosal and endothelial surfaces. Cells in both the innate and adaptive wings of the immune system are activated by fungal infection, which subsequently generate different antifungal effectors. Upon initial fungal infection, innate immune cells (including macrophages, neutrophils and DCs) release cytokines such as IL-12, IL-10 and IL-18. Cellular players in the adaptive immune response then secrete various cytokines against fungal infection: Th1 cells produce IFN-γ and TNF-α; Th2 cells produce IL-4 and IL-5; Th17 cells generate IL-17 and IL-22; and T_{Reg} cells produce TGF-β and IL-10. B-cells also secrete antibodies to target fungal pathogens [8].

Macrophages have long been appreciated for their role in balancing the effectors cytokine species required for neutrophils recruitment and activation, as well as enhancing or inhibiting innate immunity [9]. For example, following infection by *A. conidia*, macrophages can produce pro-inflammatory cytokines, including TNF-α and IL-1β However, they can also stimulate IL-10 production, which is a typical anti-inflammatory cytokine [10]. The strength of either response may be dialed up by TLR signaling, inclusive of TLR4 and TLR2 which would suggest that different TLR signaling pathways contribute to dissimilar biological responses upon fungal infection. The administration of corticosteroids suppresses the production of IL-1α, TNF-α and MIP-1α in macrophages, all of which are protective against aspergillosis [11]. Aspergillus species are saprophytic fungi widely distributed in nature and are associated with a number of human disease [12].

Dendritic Cells (DCs) are particularly potent players in the immune response as they initiate both innate and adaptive immune responses to various fungi including *Cryptococcus neoformans, Aspergillus fumigatus* and *C. albicans* [12]. The signaling pathways triggered by DCs largely depend on the infectious agent. DCs also capture and process antigens, express lymphocyte co stimulatory molecules and migrate to lymphoid organs and secrete cytokines to initiate immune responses including IL-12 and IL-10. Similar to macrophages, DCs can access the TLR system for antifungal host defense [13]. However, DCs largely mediate antifungal immunity by initiating and buffering T-cell responses [14].

NK cells show capacity against multiple types of fungi, including *C. albicans* and *A. fumigatus in vitro*. NK cells produce interferon gamma (IFN-γ) and play a fungicidal role in fighting against *C. neoformans* [15]. Furthermore, other innate immune cells including mast cells, basophils and eosinophils contribute to the fungal protection as well.

Epithelial cells are also very important to the antifungal role. For instance, mucosal epithelial surface is the initial site of *C. albicans* for contacting with host and up regulate TLR4 and subsequently protect against tissue damage caused by *C. albicans*. Furthermore, endothelial cells can also interact with fungi, however, its mechanism might involve complex processes, which would be potentially great for both bench work and clinical research in future [16].

Adaptive Immunity: In general, allergens can be recognized by the cellular immune system through 3 major mechanisms: (1) engagement of pattern recognition receptors (PRRs), (2) molecular mimicry of Toll-like receptor (TLR) signaling complex molecules and (3) recognition of the allergen's biological activities, such as proteases Recognition of fungi and fungal allergens likely occurs through the first and third mechanisms. Several families of PRRs have been shown to be involved in interactions with fungi [17].

It is generally acknowledged that activation of the adaptive arm of the immune system is critical for resolution of fungal infection in the host. Immune-regulatory $CD4^+$ T helper cells are of key importance, which can be functionally categorized as one of the five groups: T_{h1}, T_{h2}, T_{h9}, T_{h17} and T_{Reg} cells. The transition from innate to adaptive immunity is facilitated primarily by DCs, although macrophages contribute. These phagocytes process and present fungal Ag to naïve $CD4^+$ T cells in the context of class II MHC. This interaction initiates the commitment to effectors T_h subsets. DCs also activate $CD8^+$ T cells by Ag presentation via MHCI. For antigens that enter through the exogenous pathway, engagement of $CD8^+$ proceeds through a mechanism termed cross-presentation in which antigens are shuttled into the class I MHC pathway. In contrast to the requirement of Antigen processing for activation of T cells, B cells directly react to fungal antigens and secrete immunoglobulin's that may influence the outcome of infection [18]. There is marked plasticity in the T-cell response to fungi. The heterogeneity of the CD4+ and $CD8^+$ T-cell repertoire might account for the multiplicity and redundancy of effectors mechanisms through which T cells participate in the control of fungal infections. These include direct antifungal activity, release of antimicrobial peptides from $CD8^+$ T cells, lysis of fungus-containing phagocytes and effectors functions resulting from dynamic interactions with T cells that express selected members of the Vβ families of the T-cell receptor [19]. This functional plasticity indicates the potential of vaccines in conditions of immunod eficiency, as highlighted by the ability of $CD8^+$ T cells to compensate for $CD4^+$ T-cell deficiency in experimental models of vaccine-induced resistance to endemic fungi. The flexible program of T cells leads to the production of many mediators, including cytokines. Due to their action on circulating leukocytes, the cytokines produced by fungus-specific T cells are instrumental in mobilizing and activating antifungal effectors, so providing prompt and effective control of infectivity after the fungus has established itself in tissues or spread to internal organs. Therefore, host resistance to fungi seems to depend on the induction of cellular immunity, mediated by T cells, cytokines and effectors phagocytes (Fig. 2). The clinical circumstances in which fungal infections occur are associated with impaired cell-mediated immunity. AIDS and severe hematological malignancies are examples of acquired defects in T-cell function that predispose to severe fungal infections. Experimental data have shown the deleterious effects of IL-12 or IFN-γ ablation on the course and outcome of fungal infections [20]. Through production of the signature cytokine IFN-γ and providing help for opsonizing antibodies, the activation of T_{h1} cells is instrumental in the optimal activation of phagocytes at sites of infection. Therefore, the failure to deliver activating signals to effectors phagocytes might predispose patients to overwhelming infections, limit the therapeutic efficacy of anti-fungal and antibodies and favor persistency and/or commensalism.

Most fungi are detected and destroyed within hours by innate defense mechanisms mediated by phagocytes and opsonin's through the involvement of distinct pattern-recognition receptors (PRRs). These mechanisms act immediately and are followed some hours later by an early induced inflammatory response, which must be activated by infection but does not generate lasting protective immunity. These early phases help to keep infection under control. In vertebrates, however, if the infectious organism can breach these early lines of defense, an adaptive immune response will ensue, with the generation of antigen-specific T helper (T_H) effectors cells, regulatory T (T_{Reg}) cells and B cells that specifically target the pathogen and induce memory cells that prevent

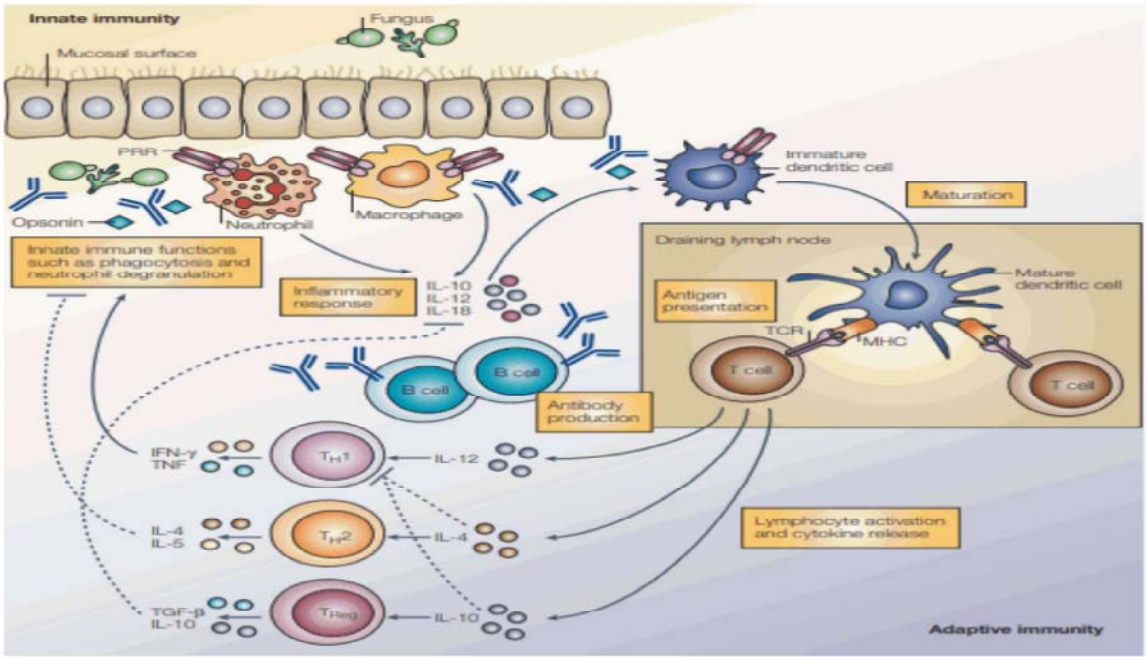

Fig. 2: Balancing protection and immunopathology in fungal infections: a cooperative effort of the innate and adaptive immune systems

subsequent infection with the same microorganism. Dendritic cells sample fungi at the site of colonization/infection, transport them to the draining lymph nodes and activate disparate TH and T_{Reg} cells in a morphotype and tissue-dependent manner. As the different TH-cell subsets release a distinct panel of cytokines, capable of delivering activating and inhibitory feedback signals to effectors phagocytes, the activation of the appropriate T_H-cell subset is instrumental in the generation of a successful immune response to fungi. Counter regulatory T_{Reg} cells might serve to dampen the excessive inflammatory reactions and contribute to the development of memory antifungal immunity [20].

Plant extracts can be used as natural fungicides to control pathogenic fungi, thus reducing the dependence on the synthetic fungicides [21].

CONCLUSIONS

Host defense against fungal infection relies on an integrated immune response; the innate and adaptive arms of the immune system respond differently to specific morphologic states of the fungal pathogen. Differences in innate and adaptive immune responses to different morphologic states reflect, in part, differences in fungal cell wall composition and might represent a host adaptation tailored to the severity of an invasive threat and to the risk of excessive tissue damage caused by inflammation. An area of immense promise is the development of cell and antibody-based therapies as adjuncts to antifungal agents. Invasive mycoses are an increasing problem in patients that have primary immune deficiencies, pharmacologic or disease-induced immune or myelo-suppression and are associated with high mortality rates. Greater understanding of the molecular and cellular mechanisms of fungal recognition and eradication is likely to lead to improved therapeutic interventions.

REFERENCES

1. Romani, L., 2011. Immunity to fungal infections. Nature Reviews Immunology [Internet]. Mar 11; 11: 275. Available from: https://doi.org/10.1038/ nri2939.
2. Romani, L., 2008. Cell mediated immunity to fungi: a reassessment. Med. Mycol., Sep; 46(6): 515-29.
3. Hamad, M., 2012. Innate and adaptive antifungal immune responses: partners on an equal footing. Mycoses. May; 55(3): 205-17.
4. Brown, G.D., 2011. Innate antifungal immunity: the key role of phagocytes. Annual Review of Immunology, 29: 1-21.

5. Dan, J.M., R.M. Kelly, C.K. Lee and S.M. Levitz, 2008. Role of the mannose receptor in a murine model of Cryptococcus neoformans infection. Infection and Immunity 76(6): 2362-7.
6. Ermert, D., A. Zychlinsky and C. Urban, 2009. Fungal and bacterial killing by neutrophils. In: Host-Pathogen Interactions. Springer, pp: 293-312.
7. Byrd, A.S., X.M. O'Brien, C.M. Johnson, L.M. Lavigne and J.S. Reichner, 2013. An extracellular matrix-based mechanism of rapid neutrophil extracellular trap formation in response to Candida albicans. The Journal of Immunology, 190(8): 4136-48.
8. Nicola, A.M., A. Casadevall and D.L. Goldman, 2008. Fungal killing by mammalian phagocytic cells. Current Opinion in Microbiology, 11(4): 313-7.
9. Fromtling, R.A. and H.J. Shadomy, 1986. An overview of macrophage-fungal interactions. Mycopathologia, 93(2): 77-93.
10. Cyktor, J.C. and J. Turner, 2011. Interleukin-10 and immunity against prokaryotic and eukaryotic intracellular pathogens. Infection and Immunity, 79(8): 2964-73.
11. Lewis, L.E., J.M. Bain, C. Lowes, N.A. Gow and L.P. Erwig, 2012. Candida albicans infection inhibits macrophage cell division and proliferation. Fungal Genetics and Biology, 49(9): 679-80.
12. Leila, S., S. Azar, K. Alireza, B. Mansour and B. Amir, 2010. Determining protein patterns for three fungus species Aspergillus fumigatus, Asp. flavus and Asp. niger, obtained from outdoor air in Iran. Glo. Vet., 4(2): 130-4.
13. Ramirez-Ortiz, Z.G. and T.K. Means, 2012. The role of dendritic cells in the innate recognition of pathogenic fungi (*A. fumigatus*, *C. neoformans* and *C. albicans*). Virulence, 3(7): 635-46.
14. Mogensen, T.H., 2009. Pathogen recognition and inflammatory signaling in innate immune defenses. Clinical Microbiology Reviews, 22(2): 240-73.
15. Lin, J.S., C.W. Yang, D.W. Wang and B.A. Wu-Hsieh, 2005. Dendritic cells cross-present exogenous fungal antigens to stimulate a protective CD8 T cell response in infection by Histoplasma capsulatum. The Journal of Immunology, 174(10): 6282-91.
16. Bouzani, M., M. Ok, A. McCormick, F. Ebel, O. Kurzai and C.O. Morton, 2011. Human NK cells display important antifungal activity against Aspergillus fumigatus, which is directly mediated by IFN-γ release. The Journal of Immunology, 187(3): 1369-76.
17. Naglik, J.R. and D. Moyes, 2011. Epithelial cell innate response to Candida albicans. Advances in Dental Research, 23(1): 50-5.
18. Wills-Karp, M., A. Nathan, K. Page and C.L. Karp, 2010. New insights into innate immune mechanisms underlying allergenicity. Mucosal Immunology, 3(2): 104.
19. Moraes-Vasconcelos De, D., A.S. Grumach, A. Yamaguti, M.E.B. Andrade, C. Fieschi and De L. Beaucoudrey, 2005. Paracoccidioides brasiliensis disseminated disease in a patient with inherited deficiency in the beta1 subunit of the interleukin (IL)-12/IL-23 receptor. Clin Infect Dis. Aug 15; 41(4): e31-37.
20. Deepe Jr, G.S. and R.S. Gibbons, 2002. Functional properties of the T cell receptor repertoire in responding to the protective domain of heat-shock protein 60 from Histoplasma capsulatum. The Journal of Infectious Diseases, 186(6): 815-22.
21. Romani, L., P. Puccetti and F. Bistoni, 1997. Interleukin-12 in infectious diseases. Clinical Microbiology Reviews [Internet], 10(4): 611-36. Available from: https://cmr.asm.org/content/cmr/10/4/611.full.pdf.
22. Hailu, G., M. Bitew and M. Temesgen, 2017. Studies on Antifungal Effects of Some Plant Extracts on Fungal Isolates of Candidia albicans and Trichophyton menthagrophytes in Jimma Town, Ethiopia. Intl. J., 8(3): 79-85.