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Immunity to Fungal Infections: Review

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Abstract: Fungal diseases are among 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. Fungi interact with plants, animals or humans in multiple ways, which might induce establish symbiotic, commensal or pathogenic relationships. The immune mechanisms of defense against fungal infections are numerous and range from protective to adaptive mechanisms that are induced particularly during infections. Phagocytosis and killing by phagocytic cells and mucociliary clearance constitute essential innate defense functions of the airways against micro-organisms. Fungi are recognized by cells of the innate immune system which bind components of fungal cell walls using pattern recognition receptors (PRRs) on their surface. Host cells express PRRs such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), mannose receptors and nod like receptors (NLRs). Mammalian PRRs recognize PAMPs and damaged host cell components, such as nucleic acids and alarmins, commonly known as damage associated molecular patterns (DAMPs). Signaling results in generation of Th1/17 adaptive immune responses and activation of innate effector cells up on recognition of fungi through these receptors. In cell mediated adaptive immunity, the immune-regulatory CD4+ T helper cellsare of key importance. The immunological significance humoral immunity to fungal infectionsis not yet completely understood, although recent data strongly support the existence of protective antibodies against certain fungal infections. During infection with fungi, the immune response must eliminate the infectious agent while limiting collateral damage to tissues and restoring a homeostatic environment. Fungi secrete several factors that are potent regulators of the host inflammatory response.

Key words: Adaptive Immunity · Fungi Infection · Innate Immunity

INTRODUCTION

Fungi are heterotrophic eukaryotes that are morphologically classified into yeast and filamentous forms. They are very proficient at sensing their surroundings and responding to signals that promote their survival in changing environments. Fungi can interact with animals, humans or plants in different ways, establishing symbiotic, commensal, latent or pathogenic relationships. Their ability to colonize almost every niche within the body involves specific reprogramming events that enable them to adapt to environmental conditions, fight for nutrient acquisition and deal with or even exploit ‘stresses’ generated by host defense mechanisms [1, 2].

Physical barriersare first-line of innate defenses which are further supplemented by circulating and tissue-associated cells and humoral factors. Fungi are recognized by cells of the innate immune system on their surface. Indeed, the innate immune response can be followed by an adaptive response, which is initiated by cells that present antigen of the fungus. Dendritic cells which can be rapidly differentiate from monocytes transport ingested fungi to draining lymph nodes where they prime and expand fungal-specific T helper cells. Memory T cells and naive T cells will be recruited and activated and the cytokines profile present in the micro-environment will polarize the T helper lymphocytes response towards a predominant Th1, Th2 or Th17 response. Monocytes can

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also increase the innate neutrophil conidiacidal activity and play a crucial role in controlling disseminated fungal infection [3].

Many fungal species have co-evolved with their mammalian hosts over millions of years. This suggests the existence of complex mechanisms of immune surveillance in the host and of sophisticated fungal strategies to antagonize immunity. Since the immune system does not ignore the commensal fungi, a fine balance between pro- and anti-inflammatory signals is crucial to maintain a stable host-fungus relationship, the disruption of which can have pathological consequences [4]. The objective of this paper is to highlight the immunity of hosts to fungal infections.

Innate Immunity to Fungal Infections

Recognition of Fungi by the Innate Immune System

Pathogen Associated Molecular Patterns (PAMPs): The constitutive mechanisms of innate immune response are present at sites of continuous interaction with fungi and include the barrier function of the skin and the mucosal epithelial cell surfaces. Microbial antagonism, defensins, collectins and the complement system also provide constitutive defense mechanisms and opsonic recognition of fungi. A complement receptor 3 (CR3) recognizes complement deposited on β-(1, 6) glucans on the fungus surface. Moreover, host cells express pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and the galectin family proteins that sense PAMPs in fungi. PRRs on phagocytes initiate downstream intracellular events that promote the activation of the immune system and the clearance of fungi, with the specific immune response generated depending on the cell type involved. Monocytes, macrophages and neutrophils, as well as some cells that are normally non-phagocytic such as epithelial and endothelial cells, mostly contribute to the antifungal innate immune response through phagocytosis and direct pathogen killing [5].

The uptake of fungi by dendritic cells (DCs) induces DC maturation and this promotes the differentiation of naive T cells into effector T helper (TH) cell subtypes. To achieve optimal activation of antigen-specific adaptive immune responses, it is first necessary to activate the pathogen-detection mechanisms of the innate immune system. The fungal cell wall varies in composition depending on the morphotype, growth stage and environment of the fungal species and is the main source of PAMPs that are recognized by PRRs on mammalian cells. The three major cell wall components, found in all pathogenic fungi are: β-glucans, especially β-(1, 3)-glucans with varying numbers of β-(1, 6) branches; chitin (a polymer of N-acetylglucosamine); and mannans (which are chains of several hundred mannose molecules that are added to fungal proteins via N- or O-linkages). B-(1, 2)-linked oligomannosides are also PAMPs and these molecules are recognized by galectin 3, which allows phagocytes to discriminate between pathogenic and non-pathogenic yeasts [6].

C-Type Lectin Receptors (CLRs): CLRs comprise proteins that can recognize diverse self and non-self-molecules and thus regulate a wide range of physiological and pathological processes. They are constituted of soluble and membrane-bound proteins characterized by the presence of at least 1 C-type lectin domain (CTLD), some of which act as carbohydrate recognition domains (CRD). Conserved residues in the CRD allow recognition of diverse sugar structures, including theGlu-Pro-Asn andGln-Pro-Asp motifs which confer specificity for mannose and galactose, respectively [7]

CLR family members include dectin 1, dectin 2, mincle, DC-specific ICAM3-grabbing non-integrin, the mannose receptor (macrophage mannose receptor 1), langerin and mannose-binding lectin. Dectin 1 is the main PRR that recognizes β-glucans and, following ligation, it induces the production of both pro- and anti-inflammatory cytokines and chemokines. This is achieved through the activation of two distinct signaling pathways downstream of dectin 1, the spleen tyrosine kinase -caspase recruitment domain- containing protein 9 pathways and the RAF pathway [8].

The genes encoding dectin-2 Cluster receptors are located near dectin-1, on chromosome 6 in mice and chromosome 12 in humans and members of this family include clec6a (dectin-2), clec4d (MCL) and clec4e (macrophage-inducible C-type lectin or mincle). Their expression appears to be primarily restricted to myeloid cells, including monocytes, macrophages, neutrophils and DCs [9].

Dectin 2 recognizes high-mannose structures that are common to many fungi and binds hyphal forms with higher affinity than yeast forms. It selectively pairs with the Fc receptor γ-chain (FcRγ) to induce pro-inflammatory cytokine and leukotriene release Mincle is mainly expressed by macrophages and is also FcRγ-associated activating receptor and induces NF-κB-mediated inflammatory responses through SYK-CARD9 signaling.

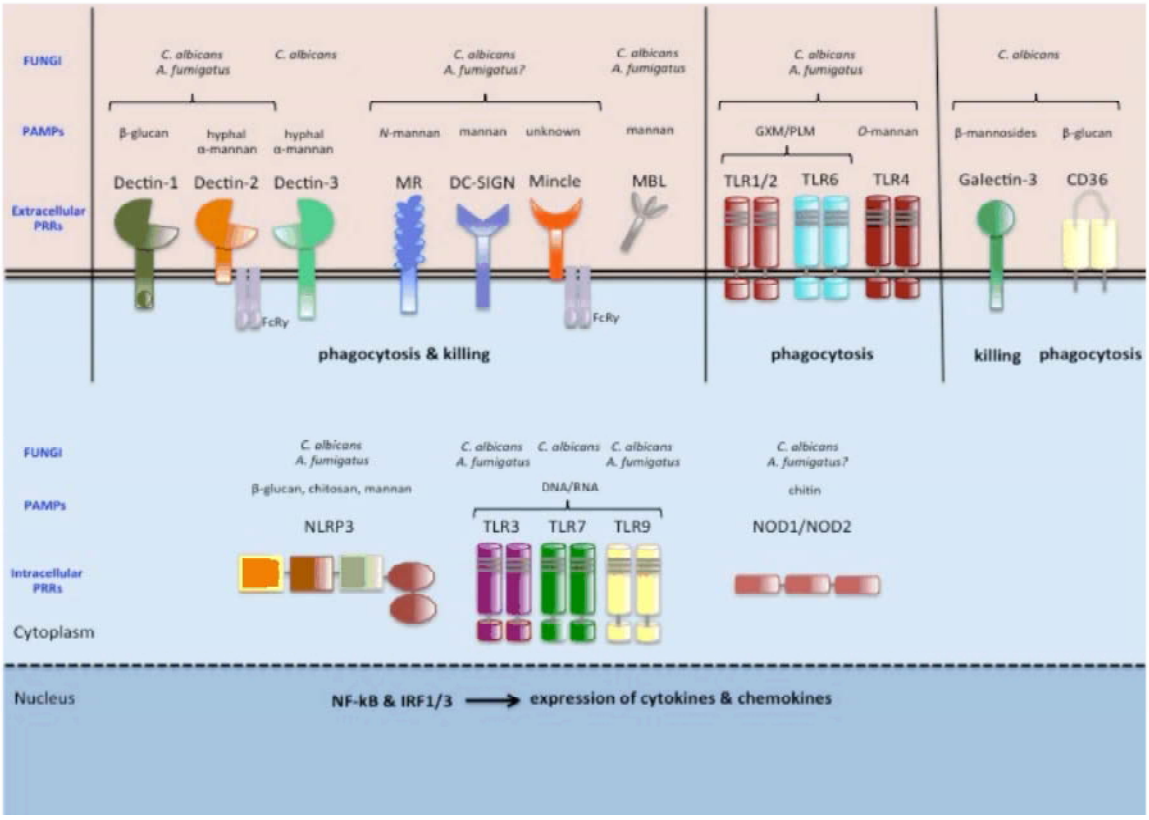

Fig. 1: Pattern recognition receptors and immuneresponses to major fungal infections
Source: (Becker *et al*. [14])

The mannose receptor and DC-SIGN recognize branched N-linked mannans and both receptors can direct mannosylated fungal antigens into the DC endocytic pathway, thereby promoting antigen processing and presentation to T cells. Indeed, the mannose receptor has been shown to be involved in the promotion of antifungal TH17 cell responses [10].

Toll-Like Receptors (TLRs): TLR2, TLR4 and TLR9 are the main TLRs that are involved in sensing fungal components, such as zymosan, phospholipomannan, O-linked mannans and fungal DNA (Fig. 1). The physiological roles of individual TLRs in fungal infections are still unclear. The contribution of individual TLRs may vary depending on the fungal species, fungal morphotypes, route of infection and receptor cooperativity. Similar to CLRs, TLRs facilitate the presentation of fungal antigens by DCs and tailor T cell responses. The stimulation of TLRs by fungi unmasks the divergent roles of PAR1 and PAR2 in downstream signaling and inflammation. After fungal recognition by TLRs, PARs become activated to sense proteolytic virulence factors and tissue injury, to mediate pro-inflammatory (PAR1) or anti-inflammatory (PAR2) responses and to modulate the activity of TLRs. Thus, TLRs regulate PAR signaling and vice versa [11].

NOD-Like Receptors (NLRs): NLRs are implicated in sensing fungi and, once activated; these receptors induce the production of IL-1β and IL-18 through the formation of inflammasomes. Mice lacking IL-1 receptor type I (IL-1RI) signaling, IL-18 or caspase 1 have disparate patterns of susceptibility to fungal infections; however, mice lacking NLRP3 consistently show enhanced susceptibility to candidiasis [12].

Damage Associated Molecular Patterns (DAMPs): The relative contributions of PAMPs and DAMPs to inflammation, immune homeostasis and mechanisms of repair during infection were also unclear. However, a mechanism that allows the host to discriminate between PAMP- and DAMP-induced immune responses; the alarmin S100B coordinates this process via the spatiotemporal integration of signals from TLRs and the

receptor for advanced glycation end-products (RAGE). By sequential binding to fungus-derived TLR2 ligands and nucleic acids, S100B first inhibits TLR2-induced inflammation during fungal pneumonia and then subsequently activates intracellular TLR3 and TLR9 to induce its own transcriptional down regulation. Thus, the crosstalk between RAGE and TLRs represents a regulatory circuit in infection, whereby an endogenous danger signal protects the host against pathogen-induced inflammation and a nucleic acid-sensing mechanism terminates the inflammation induced by the endogenous danger signal [13].

Mucus and Mucociliary Clearance: The mucus constitutes a physical, chemical and biological barrier of secretory products from the mucus membrane. The airway fluid contains glycoproteins including mucins, proteoglycans, lipids, secretory IgA, lysozyme, peroxidase and surfactant. Surface liquids provide an efficient biological barrier by interacting with micro-organisms, thereby preventing them from adhering to and migrating through the airway epithelium. Mucociliary clearance is mediated by coordinated ciliary movement that transports the epithelial fluid, together with trapped material, out of the airways into the pharynx [15].

Alveolar Macrophages and Neutrophils: Phagocytosis and killing by phagocytic cells constitute essential innate defense functions of the airways against micro-organisms. Macrophages selectively protect against fungal spores that have escaped mucociliary clearance. The phagocytic cells bear surface receptors that can recognize surface structures of the micro-organisms in a non-adaptive way. A critical surface structure of fungi is fungal mannan, which is recognized by the mannan-binding protein present on phagocytic cells, allowing recognition and efficient phagocytosis even in the absence of opsonizing complement or immunoglobulins [16].

After binding and phagocytosis, alveolar macrophages secrete pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, interferon (IFN)-γ and tumor necrosis factor (TNF)-α, to prime and activate different cells in the environment. These cytokines are able to augment the phagocytic and killing capacity of phagocytes through enhanced oxygen free-radical production. Moreover, IL-1, TNF-α and INF-γ secreted at the site of infection activate epithelial cells, resulting in additional production into the pharynx.Mononuclear cells and polymorphonuclear phagocytes provide selective protection against *A. fumigatus* conidiae and mycelia, respectively. Adhesion by these cells to hyphae too large for phagocytosis, together with the release of toxic oxygen radicals and cationic peptides, appear to be key events that cause hyphal damage [17].

Adaptive Immunity to Fungal Infections

Cell Mediated Immunity: In cell mediated adaptive immunity, immune-regulatory CD4+ T helper cells are of key importance, which can be functionally categorized as one of the five groups: Th1, Th2, Th9, Th17 and TReg cells. Th1 cells can be activated by DCs via TLR signaling, activated in response to the recognition of immutable fungal molecules. Th1 cells can then help to optimize the activation of phagocytes at sites of infection. Th1 cells can also secrete signature pro-inflammatory cytokines such as IFN-γ and TNF-α. Th2 cells, activated by IL-4 and IL-13, generate cytokines including IL-5 that can limit the Th1 response, as well as activating M2 macrophages, which are harmful to patients with severe fungal infections and fungal-related allergic responses. As an indication of the complexity of these issues, Th2-associated antibody responses can also partially increase the Th1 cell response. Th17 cells act principally at mucosal surfaces, including the lungs, where these cells play important roles in protective antifungal immunity. Th17 cells produce IL-17 and IL-22 largely following their activation by signals transduced by the myeloid differentiation primary response 88 (MYD88) pathways (including the key signaling effector SYK-CARD9) and the mannose receptor pathways in DCs and macrophages. Moreover, TReg cells generating anti-inflammatory cytokines including TGF-β and IL-10 have been described in fungal infections. In experimental fungal infections, TReg cells have been shown to regulate both inflammation and immune tolerance in the respiratory and/or gastrointestinal mucosa. Collectively, Th1, Th2, Th17 and TReg cells are essential to the host's susceptibility or resistance to invasive fungal infections. The observation that CD8+ T-cells can provide protection even without the presence of CD4+ T-cells against fungi infection such as *Histoplasma capsulatum*. Furthermore, CD8+ T-cells can produce IFNγ against *Pneumocystis carinii* infection and induce the clearance of the fungal infection. Antibody generation by B-cells is critical for fungal clearance, such as clearing pneumocystis from the lung [18].

Humoral Immunity to Fungal Infections: The immunological significance of antibodies directed against circulating fungal antigens, as related to the development of protective immunity and/or pathology in fungal infections, is not yet completely understood. It has been shown that the great majority of patients suffering from chronic bronchitis as well healthy individuals develop serum IgG against thermophilic actinomycetes and fungal antigens. Recent data strongly support the existence of protective antibodies against Candida and Cryptococcus, two of the major opportunistic fungal infections. Moreover, inhibition of adhesion to the host's receptor cells, inhibition of germ-tube formation, opsonization and neutralization of virulence enzymes were proposed as key events in the protection. In humans, fungal infections can also be associated with various allergic disorders characterized by high IgE responses. Allergen-specific T-cells from patients with ABPA express a typical Th2-type cytokine pattern, with high IL-4 and little or no IFN-γ [19].

Balancing Resistance and Tolerance to Fungi: During a fungal infection, the immune response must eliminate the fungus while limiting collateral damage to tissues and restoring a homeostatic environment. High levels of IL-10, which negatively affect IFNγ production, are detected in patients with fungal infections. However, given its prominent effect on the resolution of inflammation, IL-10 production may be a consequence, rather than a cause, of the infection. This indicates that, in the case of chronic fungal infections that are dominated by non-resolving inflammation, IL-10 acts as a homeostatic host-driven response to keep inflammation under control. Both inflammation and immune tolerance in the respiratory or gastrointestinal mucosa were controlled by the coordinated activation of different TReg cell subsets [1].

Fungal Evasion of Inflammation: Fungi produce several factors that are potent regulators of the host inflammatory response. By masking or subverting the host detection systems, fungi may avoid inflammation and this contributes to fungal adaptation and opportunism. For example, β-(1, 3)-glucans are exposed in the bud scar of *C. albicans* yeasts but are masked on hyphae, thus favoring fungal escape from recognition by dectin1. Many fungi exploit CR3 to dampen the inflammatory response and allow intracellular fungal parasitism. The most extreme example of evasion of innate immune recognition is mediated by the capsule of *C. neoformans*, which completely covers the fungal cell wall and prevents recognition by PRRs and the induction of inflammation. In addition, *C. neoformans* yeast can escape from macrophages through an expulsive mechanism that does not kill the host cell and avoids inflammation. By continually activating the PRR system, it is possible that fungi contribute to inflammatory processes and promote autoimmunity. Indeed, dectin 1 and fungal β-glucans have been implicated in the induction of autoimmune disease [20].

CONCLUSIONS

The immune mechanisms of defense against fungal infectionsrange from protective to adaptive mechanisms that are induced specifically during infection. Fungi are recognized by cells of the innate immune system which bind components of fungal cell walls using pattern recognition receptors on their surface. Upon recognition of fungi through these receptors, signaling results in generation of Th1/17 adaptive immune responses and activation of innate effector cells. The immune-regulatory CD4+ T helper cells are of key importance in adaptive immunity, while the role antibody against fungal antigens is needs further research.

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