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Host Protective Immunity to Fungal Infections-Recent Advances

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Abstract : *Fungi cause different disease types, from common superficial infections to invasive or deep-seated severe infections. Host defense mechanisms determine the clinical outcome of fungal infections, either being inadequate and failing to control infection, being too exuberant and contributing to tissue damage or failing to resolve properly leading to persistent inflammation and fibrosis. The recognition pathways of the innate immune systems, the phagocytes and other immune effector cells, cytokines and other molecules work together to control and contain fungal infections. Recently discovered intracellular receptors are the NLR- NLRP3 inflammasomes and Damage-associated molecular patterns (DAMPs). It has been shown of recent that Neutrophils extracellular traps (NETS) aid in the killing of fungi and Macrophage migration inhibition factor (MIF) plays a role in resistance to fungal infection. In the past, protective immunity to fungi has been known to be by Th- 1 response driven by the 1L-12-IFNγ axis. Recently, other pathways of cytokines and T-cells have been implicated in the immunity to fungal infections; these are Th-17 cells and IL-17, IL23, and IL22. Central to the formation of different T-cell subsets and cytokines, is the discovery that Dendritic cells exhibit plasticity on exposure to different forms of fungi, using different recognition receptors.*

Keywords – *Cytokines,Fungi,Phagocytes,Toll-like receptors,T-Lymphocytes.*

I. Introduction

Fungal infections are becoming more prevalent now with associated increased mortality. This is as a result of increase in immunodeficiency disorders such as acquired immunodeficiency disorders (AIDS), cancer and cancer treatment, and immunosuppressive drugs following transplantations. Fungi exist in different morphologic forms such as yeasts, moulds or dimorphic forms. They are ubiquitous and cause infections when the spores are inhaled, e.g. *Aspergillus fumigatus*; by direct skin contact e.g. *Trichophyton rubrum*, or by commensals when there are changes in the host's normal flora or breech in mucosal barrier as seen with *Candida albicans*. For most immunocompetent individuals, host immune mechanisms are able to control and contain fungal infections though fungi also have evasion mechanisms to survive in the host. Thus host defense mechanisms may be protective or may determine the clinical outcome of fungal infections. The innate immune system comprising the recognition pathways, the phagocytes and other effector cells and molecules work together with the adaptive immune system to provide immunity to fungal infections. Protective immunity has been known to be Th-1 mediated while Th-2 is associated with susceptibility to disease [1, 2]. Research in the area of fungal immunity has increased over the years and in the past decade, a number of advances have been made. These recent advances in the immunity to fungal infections would be the discussed in this review.

II. Pathogenesis And Types Of Fungal Infections

Fungi can be endemic in which case they cause primary pulmonary infections by inhalation of conidia in the environment which are later converted to pathogenic form, e.g. *Coccidiodes immitis*. Other types of endemic mycoses are *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. Opportunistic mycoses are either commensals, e.g. *C. albicans* or saprophytes such as *A .fumigatus*, *Cryptococcus neoformans* which cause disease in immunocompromised individuals. Different opportunistic fungi are associated with different types of immunosuppression; for example, *Candida* infections are associated with HIV/AIDS and hereditary immunodeficiency syndromes while *A. fumigatus* infections are associated with immunodeficiency due to iartrogenic causes [3].The pathogenesis of fungi depends on their virulence factors. These factors include structures which enable them to adhere to host tissues, production of enzymes such as phospholipase which degrades host's tissues causing damage, ability to switch from one form to the other (dimorphism), thermo tolerance (which helps dissemination), capsule and melanin formation(*C.neoformans*), production of pigments (*Aspergillus spp*) [4, 5] and ability to switch metabolic pathways[6].

Fungi cause different disease types; this can be trivial such as superficial infections, e.g. ring worm infection caused by the *dermatophytes-T.rubrum*. They can also cause invasive or deep seated infections which could be life threatening such as meningitis or pneumonia caused by *C. immitis* or *C. neoformans*. Thirdly, fungal infections may result in allergic diseases in atopic hosts, e.g. allergic bronchopulmonary aspergillosis caused by *A. fumigatus*[7].

III. Host Immune Responses To Fungal Infections.

The mechanisms of resistance to fungal infections are numerous, both the innate and adaptive immune systems with the different mechanisms work interdependently.

3.1 Innate Immunity

The innate mechanisms have been known to include barrier functions of epithelial surfaces and microbicidal products such as defensins and collectins[8].Surfactant protein-A (SP-A) and surfactant protein-D (SP-D) are pulmonary collectins recently implicated in the host defense to fungi. SP-A and SP-D deficient mice show increased susceptibility to fungal infections and humans with gene polymorphisms are prone to fungal infections [9]. The innate immune system includes the recognition system which is the Pathogen recognition Receptor/Pathogen Associated Molecular Pattern (PRR/PAMP), phagocytes, cytokines and other chemical mediators

3.1.1 PRR/PAMP Recognition System

The recognition of PAMP by PRR is the first step in immunity against fungi. These PRRs are expressed by phagocytes and dendritic cells [7]. The PRR for fungi includes the Toll-Like Receptor (TLR) and C-type Lectin Receptor (CLR). The fungal cell wall contains polymers such as glucan, chitins and mannoproteins which are recognised by the PRR [10]. The mannoproteins in fungi are recognised as foreign because mammalian glycoproteins are not mannosylated [10]. The PRRs initiate a stereotyped immune response with intracellular signalling events that would result in inflammation and clearance of the pathogen [11, 12, 15]. The different TLRs activate different programmes which may depend on the MYD88 pathway [13, 14] and influences the activity of neutrophils against fungi. They also play a role in antigen processing and presentation by DCs and modulate T-cell responses [13, 14]

TLR-2, -4 and -9 are mostly involved in the recognition of fungal pathogens [13]. TLR-2 leads to the production of pro-inflammatory cytokines such as TNF and IL-1B [11, 12, 13]. TLR-2 and -4 dependent mechanisms are used for the production of IL-1A, TNF-α and IL-1β by the conidia of *Aspergillus*; however, TLR-2 mechanisms also stimulate the anti-inflammatory cytokine IL-10 by *Aspergillus* hyphae, TLR-2 can also lead to tolerance by induction of Tregs and TGF-β [15,16,17]. Antibodies to TLR-2 have been shown to block production of TNF-α and MIP-2 by macrophages [12]. It has been recently shown that recognition of mannan by TLR-2 and production of cytokines is in collaboration with dectin-1 which is a β-glucan receptor [18]. TLR-2 and TLR-4 negative mice were shown to have reduced survival and increased mortality with cryptococcal infections [19]. Macrophages from TLR-4-mutant mice C3H/HeJ mice also have impaired expression and neutrophil recruitment in *Candida* infections; these mice are more susceptible to *Candida* infections than the wild type [12]. In humans, polymorphisms in TLR-4 are associated with increased susceptibility to pulmonary aspergillosis and systemic candidiasis [20, 21], and polymorphism in TLR-9 with allergic bronchopulmonary aspergillosis [20].

TLRs are regulated by protease activated receptors (PARS). These are activated after stimulation of TLRs and help to modulate TLRs by mediating pro-inflammatory (PAR-1) or anti-inflammatory effects (PAR-2) [22].

The C-type lectins (CLRs) initially thought to be involved only in fungal immunity ,are a family of non-TLRs PRRs and include about 8 receptors which are Dectin-1 (CLEC7A), Dectin-2(CLEC6A), mincle (CLEC4E) DC-SIGN (DC-specific ICAM 3-grabbing non-integrin), mannose receptor (macrophage mannose receptor 1) , Langerin (CLEC4K) [23], Mannan binding Lectin and RegIIIg(HIP/PAP) which has affinity for chitin[24]. They are involved in fungal recognition and stimulate the innate and adaptive immune responses to fungi.

Dectin-1 is an NK- like CLR which functions primarily in fungal immunity by recognition of β-glucan, and is the best characterised of the CLRs [25]. It is expressed by myeloid cells and its binding to fungi results in internalisation of the fungal cells and resultant intracellular signalling that is independent of calcum.Intracellular signalling is via its ITAM-like motif and involves the SYK-CARD9 (SYK-dependent) pathway and the serine-threonine kinase RAF (non-SYK dependent) pathway[26,27,28]. The SYK-pathway involves the Calcineurin which is why patients on Calcineurin inhibitors such as cyclosporine A are prone to increased fungal infections [29]. Dectin-1 recognition of zymosan in fungal pathogens such as *C. albicans* results in the production of cytokines (TNF-α, IL-1β,-6, 23) and chemokines (CCL2 and CCL3)[25]. It also influences adaptive responses; it drives cytotoxic T-cell responses [30] and humoral antibody responses [31]. Dectin-1 induces TH-17 associated cytokines (discussed below) [31, 32]. Cellular responses triggered by dectin-1 also include DC maturation, ligand uptake by endocytosis and phagocytosis, respiratory burst and production of Arachidonic acid metabolites [25]. It has also been shown that activation of DC by dectin-1 drives the conversion of Tregs to TH-17 cells [32]. Dectin-1 has also been shown to act synergistically with other PRRs for the production of cytokines and optimal response to fungal infections [33, 34], for example, Dectin-1 collaborates with TLR-2 to

stimulate the production of TNF-α by macrophages [25]. It also interacts with other proteins such as SIGN R1 and DC-SIGN [35, 36]. Dectin-1 may be involved in the induction of NETS (discussed below) which inhibits fungal growth [37, 38].

Mice deficient for dectin-1 have higher mortality rate with infections as a result of impaired cytokine and chemokine production and impaired killing by neutrophils [39]. In humans, Single nucleotide polymorphisms (SNPs) in Dectin1 increase the risk for mucocutaneous candidiasis [40].

Dectin-2 recognises hyphae forms of fungi; it binds FcγR and initiates proinflammatory cytokines and release of leukotrienes [41, 42]. Dectin-2 deficient mice have also been shown to be susceptible to Candida infections [42].

Mincle is also an FcγR associated receptor; it uses the syk-CARD-9 signalling and is important in fungal recognition of *Candida* and *Mallessezia*[43, 44].

Mannose receptor and DC-SIGN are important in antigen presentation and processing. They direct fungal pathogens into the dendritic cell endocytic pathways. They collaborate with Dectin-1 and TLR in the production of cytokines and help in the phagocytosis of unopsonised fungi. It is also involved in the stimulation of Th17 responses [36]

Nod-Like Receptors And NLRP3 Inflammasomes

The NLR are recently discovered intracellular receptors involved in pathogen sensing and recognition. Some of these NLRs, e.g. NLRP3 form inflammasomes which are multiprotein complexes that activate caspase-1. Two signals have been shown to be involved in the regulation of IL-1β. The first signal triggers the expression and synthesis of IL-1β, while the second signal induces the activation of NLRP3 inflammasomes. *Candida* and *Aspergillus* have been shown to activate this via the syk kinase pathway, with the production of ROS and K+ efflux [45, 46]. Inflammasomes are important in fungal recognition, and IL-1β is said to mediate strong protective Th-1 response [47]. Polymorphisms in the gene encoding NLRP3 increase the susceptibility to recurrent vulvovaginal candidiasis [47].

DAMPS

Damage-associated molecular patterns are PRRs that recognise damage in tissue. An example is S100B also known as alarmin. It integrates signals from TLRs and receptors advanced glycation end-products (RAGE), acting as a regulatory mechanisms for inflammation. S100B binds to TLR-2 in fungal infections and inhibits the inflammation induced by it. This is particularly important in *Aspergillus* infection. While the TLR recognition of fungal pathogen and activation of inflammation helps to protect the host, S100B acts to limit the inflammation [48, 49].

3.1.2. Innate Effector Mechanisms

Phagocytes such as neutrophils and macrophages protect the host by killing the fungi or inhibiting growth. The mechanisms used involve oxidative means where reactive oxygen species produced by respiratory burst damage fungi by lipid peroxidation and nucleic acid breaks [50, 51, 52]. Non- oxidative mechanisms involve release of molecules such as cationic peptides [51]. The protective effects of neutrophils is best observed in patients with chronic granulomatous disease who have increased incidence of fungal infections especially aspergillosis [53].

As discussed earlier, phagocytes and dendritic cells induce the release of cytokines which help in the immunity against fungi. Pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-12 and IFN-γ are important in the clearance of fungal pathogens [54]. IFN-γ has been shown to restore resistance to fungi in patients with chronic granulomatous disease, it induces recruitment of neutrophils and macrophages and help in their function of phagocytosis and oxidative killing [55]. IL-10 and transforming growth factor B (TGF-β) have both beneficial and detrimental effects on anti-fungal immunity, they control and resolve inflammation caused by pro-inflammatory cytokines thus limiting tissue damage [55]. However, IL-10 also impairs the functions of phagocytes and protective cell mediated immunity. IL-10 secreted by Tregs is said to favour fungal latency and persistence [56].

Dendritic cell Plasticity

It was recently shown that DCs exhibit plasticity on exposure to different forms of fungi, using different receptors. This also results in functionally opposing Th cell responses; exploitation of Mannose receptor results in IL-12 production and Th-1 cell activation while ligation of FcγR may result in Th-2 response and IL-10 secretion which is associated with pathology [57, 58, 59]. Fig. 1 illustrates this.

Neutrophil extracellular traps (NETs)

NETS are extracellular fibres of granule proteins and chromatin formed by activated neutrophils found to be effective in immunity against bacteria. It has been shown of recent that *Candida* infection also induces NETS formation. *Candida* yeast and hyphae forms are susceptible to killing by NETS. NETS are said to be formed by IL-8 neutrophils and are maintained by DNA, they are said to kill pathogens which neutrophils cannot phagocytose [37, 38]. However, some other study showed a conflicting result about NETS entrapping but not killing microbes [60].

The role of Macrophage migration inhibition factor (MIF)

Studies in mice have shown that MIF contributes to resistance against invasive *A. fumigatus* .It controls the pro-inflammatory and anti-inflammatory cytokines and also increases the release of adhesion molecules. It promotes expression of TLR and other metabolites involved in inflammation. Mice deficient for MIF were shown to be more susceptible to disseminated aspergillosis than the wild type mice [61, 62].

3.2 Adaptive Immunity

3.2.1 Cell Mediated Immunity

In the past, protective immunity to fungi has been known to be by Th-1 response driven by the 1L-12-IFNY axis. Th-1 response is required for protective immunity, while Th-2 response impairs Th-1 protective responses and favours fungal growth [1, 2, 63]. Disseminated infections are associated with low levels of IFN-γ and impaired delayed type hypersensitivity (DTH), while Th- 2 cytokines such as IL-4 and -5 are increased alongside with IgE, IgG4 and IgA[54,63]. However, patients with defects in the IL-12/IFN-γ pathway are prone to mycobacterial infections but not fungal infections [64]. Recently, other pathways of cytokines and T-cells have been implicated in the immunity to fungal infections. These are discussed below.

Th-17 CELLS AND IL-17

Th-17 cells are the new lineage of T-cells thought to be responsible for most of the effector mechanisms attributed to Th-1 cells in the immunopathogenesis of fungal infections[65], though the role of Th-17 cells in fungal immunity is still controversial [66]. Naïve CD4 cells in the presence of IL-6 and TGF-β, and transcription factor RORγT differentiates to TH17 cells [65]. Th- cells are induced in fungal infections via TLR and non-TLR dependent mechanisms [67], and produce IL-17, IL-22 and IL-26 in humans [68]. On one hand, IL-17 promotes inflammation by the recruitment of neutrophils which is important in immunity to fungal pathogens [69]. IL-17R is said to be important for immunity to mucosa candidiasis in the oral cavity and skin [70, 71]. People with hyper immunoglobulin E syndrome who have mutations in STAT-3 with defects in Th-17 pathway are prone to candidiasis [72]. Patients with APS 1 have recurrent mucocutaneous candidiasis, it is suggested that this may be due to the presence of antibodies to Th-17 cytokines [73]. On the other hand, uncontrolled inflammation caused by IL-17 and Th-17 cells causes defective clearance of fungal pathogens and impaired protective immunity to candidiasis and aspergillosis [63]. This explains why fungal persistence occurs in the face of chronic inflammation. It was shown that neutralization of IL-17 increased fungal clearance, while ameliorating inflammation and restoring the protective function of the Th-1 immunity [74].

IL-23

IL-23 is a pro-inflammatory cytokine that shares the same p40 subunit with IL-12 [75]. It works with IL-17 in the Th-17 pathway to negatively regulate the Th-1 mediated protective immunity, causing the inflammatory pathology previously attributed to Th-1. IL-23 stabilises Th-17 cells thus maintaining the effector functions of IL-17[63, 76]. Results from recent studies showed that though IL-23/Th-17 pathway may offer some protective role and antifungal resistance in the setting of IFN-γ or IL-12 deficiencies, IL-23 also causes chronic inflammation by continuous activation of Th-17 cells [76]. This lack of resolution of inflammation creates a condition of fungal growth and resistance.IL-23 was also said to activate Th-2 which is non-protective [76].

IL-22

IL-22 is also produced by Th-17 cells and Th-22 cells; it belongs to the IL-10 family and its production is enhanced by IL-23. Naturally occurring IL-22 cells are abundant at mucosal surfaces which are entry sites for fungal pathogens thus providing a first -line defense against *Candida* by inhibiting fungal growth in the absence of a Th-1 response or Th-17[66, 77].It is said that while IL-22/IL-23 axis provides the resistance to initial fungal growth, Th-1 helps in preventing dissemination of fungi [77]. IL-22 is also implicated in the increased susceptibility to mucocutaneous candidiasis seen in hyper immunoglobulin E syndrome as STAT-3 deficiency also affects IL-22[78]. IL-22 can also be produced by the gut dendritic cells where they are involved

in the release of S100A8 and S100A9 peptides which are said to have anti-fungal and anti-inflammatory properties [66]. Inhibition of IL-22 may impair protective immunity to fungi as autoantibodies to IL-22 are seen in patients susceptible to mucocutaneous candidiasis [73].

The role Regulatory T-cells

Regulatory T-cells are known for their function of controlling immune responses and limiting inflammation. The limitation of inflammation is to limit damage to host, but this on the other hand, may cause fungal persistence [69, 79]. An inverse relationship has been observed between IFN-γ and IL-10 produced by Tregs in patients with fungal infections, with high levels of IL-10 in people with chronic candidiasis [80, 81]. Indoleamine- 2, 3 dioxygenase (IDO), produced by Dendritic cells also controls inflammation and fungal infection. It induces tolerance by affecting the balance between Tregs and Th-17 cells [80, 69].

3.2.2 Humoral Immunity-The Role of Antibodies

Antibodies have not been known to offer any protective immunity to fungal infection [82]. However, antibodies can enhance protective innate immunity by enhancing phagocytosis via opsonisation in *C. neoformans* [83] and may have direct anti-microbial effect by inhibiting *Candida* morphogenesis [84]. Following research into the effectiveness of monoclonal antibodies, some monoclonal antibodies were found to confer protective immunity in animal models. Monoclonal antibodies which have been developed and are being tried include antibodies to HSP and non-HSP proteins shown to be associated with resolution of infection[85,86], anti-idiotypic antibodies which also have antifungal effects[87], and antibodies to laminarin(a β-glucan) shown to protect against *Candida* and *Aspergillus* infections in mice[88].

3.2.3 The Place of Vaccines

Although there is no vaccine currently in used now for fungal infections, there are quite a number at experimental stage and some are on clinical trials. Vaccines are being developed for some fungal infections as exposure to some dimorphic fungi was associated with lifelong immunity. The vaccines being tried include Agglutinin (Als 1p) for *Candida* which improves survival after an intravenous challenge [89, 90] and HYR1, a virulence factor being used as a recombinant vaccine (Hyr1p) which protects mice against haematogenous spread of *Candida* [91]. The type of protection provided by these vaccines is Th-1 mediated [90]. Th-17 requirements are also essential for protective immunity in experimental vaccines [68].

IV. Immune Evasion Mechanisms Of Fungi

Some fungi are able to survive as commensals in the host. They do this by evading the immune mechanisms of the host. *C.albicans* is able to establish itself as a commensal by inducing tolerance in gut macrophages and dendritic cells via Tregs[17, 80, 92]. *Mallassezia* also down regulates inflammatory responses in the skin by inducing TGF-β and IL-10[93].

V. Figures And Tables

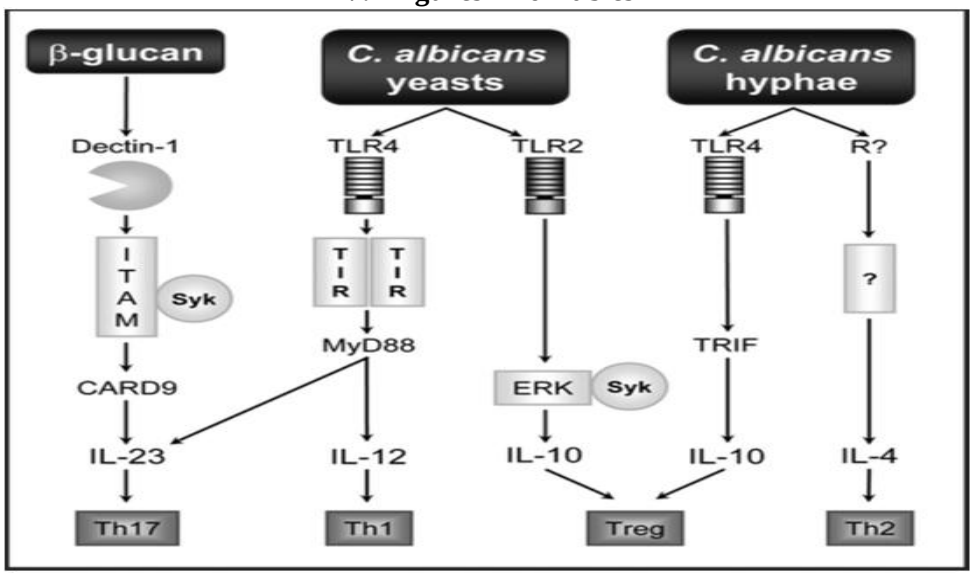

Figure 1 Dendritic cells plasticity. Different PRRs and forms of fungi activation of DCs result in different subset of cells.[Reproduced from Reference 63]

VI. Conclusion

The immune response to fungal infections depends on collaboration of the innate and adaptive systems. The recognition system, the phagocytes, and effector molecules with the adaptive responses work together to protect the host. However, the problem lies with maintaining a balance between pro--inflammation which causes pathology to the host but restricts infection, and anti-inflammation which restricts host pathology but may favour fungal persistence.

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