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The role of *Aspergillus fumigatus* polysaccharides in host–pathogen interactions

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Aspergillus fumigatus is a saprophytic mold that can cause infection in patients with impaired immunity or chronic lung diseases. The polysaccharide-rich cell wall of this fungus is a key point of contact with the host immune system. The availability of purified cell wall polysaccharides and mutant strains deficient in the production of these glycans has revealed that these glycans play an important role in the pathogenesis of *A. fumigatus* infections. Herein, we review our current understanding of the key polysaccharides present within the *A. fumigatus* cell wall, and their interactions with host cells and secreted factors during infection.

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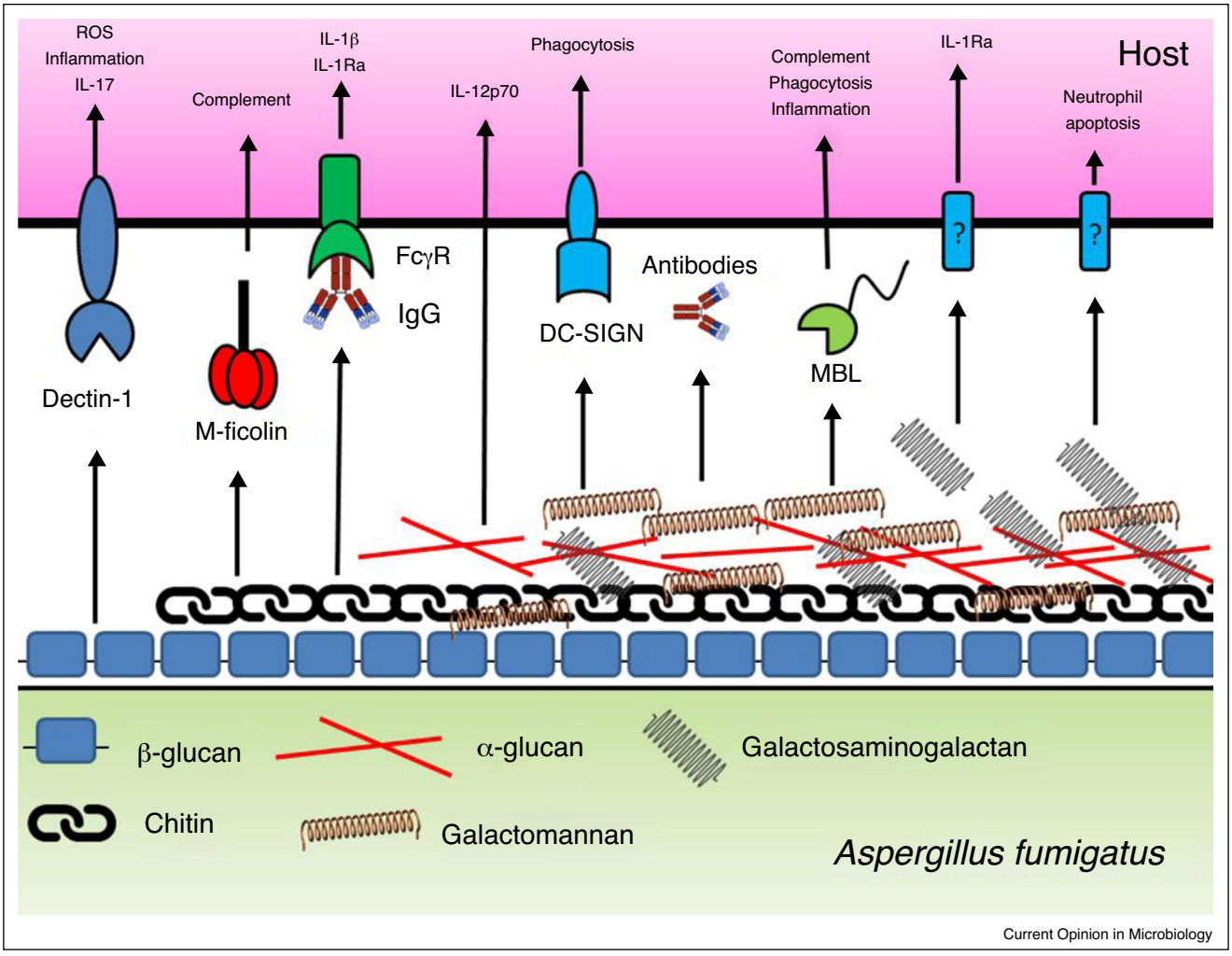
Introduction

The saprophytic mold *Aspergillus fumigatus* is found throughout the environment, where it plays an important role in decomposition and nutrient recycling [1]. *A. fumigatus* produces copious amounts of airborne conidia, which are easily dispersed by air currents. It has been estimated that the average human inhales hundreds of these conidia daily [1]. Both the relatively small size of *A. fumigatus* conidia (approximately 2 μm in diameter), as well as their strongly hydrophobic surface, enhance the ability of these particles to reach the terminal airways of the human host [1,2]. In healthy individuals, conidia are rapidly eliminated by the action of the mucociliary escalator or phagocytosed, and killed by resident alveolar macrophages and pulmonary epithelial cells [2,3]. Conidia that evade eradication by these mechanisms can swell and germinate, leading to the induction of a robust inflammatory response involving the recruitment and activation of neutrophils. These cells mediate the killing of germinating hyphae by the release of reactive oxygen species (ROS) and antimicrobial peptides [3,4]. However, in immunocompromised hosts or those with abnormal lung function, *A. fumigatus* hyphae can persist within the pulmonary system to establish an acute invasive or chronic airway infection, respectively [3]. In immunocompromised patients, such as those receiving cytotoxic chemotherapy, the innate immune response is unable to restrict fungal growth and hyphae that invade the lung parenchyma, causing tissue injury, and if unchecked, systemic dissemination [3]. Mortality rates for this disease can reach 90% in disseminated disease [5•]. In patients with chronic pulmonary disease, such as those with cystic fibrosis, the conidia are poorly cleared by the dysfunctional pulmonary mucociliary elevator. These conidia can then germinate and grow within the airways and pulmonary mucus layer. Hyphae remain largely contained to the airways due to the presence of a functional systemic immune system, although chronic, slowly progressive cavitary disease can develop [3,6]. Chronic pulmonary aspergillosis syndromes can lead to debilitating pulmonary and systemic inflammation as well as worsening of pulmonary function [6].

The *A. fumigatus* cell wall is a key point of contact between *A. fumigatus* and the host [7,8] (Figure 1). The majority of the fungal cell wall is composed of polysaccharides, and, as a result, there has been great interest in elucidating the role that these macromolecules play in host-fungal interactions. While recent studies with purified polysaccharides and mutant strains with altered polysaccharides have begun to shed light on the role of these molecules during infection, it is important to acknowledge the limitations of both experimental approaches. Purified polysaccharides may vary in size and composition from their native forms, and the immune response to soluble or microparticular polysaccharides may be different from the response to polysaccharides presented in their natural context where they immobilized within the cell wall and linked to other glycans and proteins. These effects have been best illustrated in studies of interactions with the cell wall polysaccharide chitin in which both particle size and the presence of co-stimulatory pattern recognition receptor ligands have a dramatic effect on the type of host response to this glycan (detailed below) [9,10••]. The use of synthetic oligosaccharides of defined length and composition may be helpful in this regard, but

Figure 1



Graphical overview of interactions between fungal polysaccharides and host elements.

few studies have used this approach. Studies of mutants lacking specific polysaccharides must also consider the secondary effects that loss of a given polysaccharide may have on cell wall structure and organization. Further, loss of one cell wall polysaccharide can lead to compensatory effects on the production of other polysaccharides. This phenomenon has been well described in *Candida albicans* and other fungi, in which the inhibition of β-glucan synthesis leads to an increase in fungal cell wall chitin content [11,12].

β-Glucan

β-Glucan is a linear polymer composed of β-(1,3)-linked glucose that is synthesized at the plasma membrane [13]. It is a major component of the inner cell wall where it is involved in maintaining cellular structural integrity, and acts as a scaffold for the anchoring of other polymers in the cell wall. *A. fumigatus* strains lacking β-glucan are extremely susceptible to cell wall-destabilizing agents, and exhibit massive shedding of galactomannan [14]. The level of β-glucan exposure on the surface of *A. fumigatus* varies depending on the developmental stage of the organism. In resting conidia, the β-glucan is concealed by the hydrophobic rodlet layer [15]. As germinating conidia swell and shed this rodlet layer the underlying β-glucan is transiently exposed; however, it is once again masked in hyphae by a layer of the exopolysaccharide galactosaminogalactan [16,17••]. Stage-specific β-glucan exposure is thought to be a major signal for the activation of pulmonary leukocyte recruitment in response to early *A. fumigatus* infection. Resting conidia, in which β-glucans remain hidden by the rodlet layer, are phagocytosed by alveolar macrophages or epithelial cells without inducing the production of pro-inflammatory cytokines or chemokines [15]. However, if conidia escape this first line of defense, they undergo germination, resulting in exposure

of β-glucan, which can be bound by the C-type lectin receptor Dectin-1 on the surface of alveolar macrophages [3]. In addition to alveolar macrophages, Dectin-1 is also expressed on an array of immune cells, such as dendritic cells (DCs), neutrophils, monocytes, and some T cells [18,19]. In conjunction with toll-like receptor (TLR) 2, Dectin-1 binding to β-glucan leads to Syk recruitment and NF-κB translocation to the nucleus resulting in the expression and release of a multitude of pro-inflammatory cytokines and chemokines including chemokine ligand 1 (CXCL1), interleukin (IL)-1β, tumor necrosis factor (TNF)-α, CXCL2, IL-1α, IL-6, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage (GM)-CSF, and IFNγ [20]. Recognition of β-glucan by DCs exposed to zymosan can also lead to production of the anti-inflammatory cytokine IL-10 through the Syk pathway [21]. The net effect of this chemokine and cytokine signalling recruits neutrophils to the site of infection and stimulates a T helper type-1 mediated immune response [16]. β-Glucan binding to neutrophil Dectin-1 is required for neutrophil production of IL-17 [22] and also leads to activation of protein kinase C (PKC)-δ, which is necessary for ROS generation [20]. Dectin-1 mediated activation of the PKC pathway is also found in macrophages, although it is not necessary for fungal killing in this context [20]. TLR9 may also participate in the recognition of β-glucan, as it is recruited to phagosomes in macrophages containing β-glucan [23•]. Consistent with these observations, Dectin-1-deficient mice are more susceptible to *A. fumigatus* challenge in a high-dose infection model of pulmonary invasive aspergillosis [18].

α-Glucan

The most abundant cell wall polysaccharide in *A. fumigatus* is α-(1,3)-glucan, which comprises approximately 40% of the mycelial cell wall [24••]. While no host receptor is known for α-(1,3)-glucan is known, purified α-(1,3)-glucan can induce dendritic cell activation, as measured by IL-12 p70 expression [25]. Mice vaccinated with purified α-(1,3)-glucan in combination with CpG, or dendritic cells pulsed with α-(1,3)-glucan developed a mixed Th1/Treg response, and exhibited increased survival following fungal challenge [25]. Studies of a mutant lacking α-(1,3)-glucan have revealed that of loss α-(1,3)-glucan synthesis was associated with dramatic alterations in the cell wall of conidia. These changes include the exposure of inner cell wall polysaccharides, increased chitin and β-glucan levels within the cell wall and the cloaking of the rodlets in an amorphous layer of pro-inflammatory glycoproteins. These alterations in the conidial cell wall resulted in enhanced phagocytosis and TNF-α production by alveolar macrophages. Mutants deficient in α-(1,3)-glucan have been found to be hypovirulent in both an immunocompetent and immunocompromised mouse model of *A. fumigatus* infection, likely as a consequence of an enhanced early immune response that limits fungal growth [24••].

Chitin

Chitin is a highly insoluble polymer of β-(1,4)-linked *N*-acetyl glucosamine that is covalently linked to β-(1,3)-glucan in the inner cell wall [7,26,27]. Chitin plays an important role in cell wall structure and integrity [7]. Experiments using purified polysaccharide have established that chitin activates macrophages; however, the size of the chitin particle plays an important role in governing on the type of immune response that is elicited [9]. Exposure of macrophages to larger chitin particles (40–70 μm in diameter), more representative of intact fungal hyphae, induces the release of pro-inflammatory TNF-α and IL-17 whereas smaller particles (2–10 μm) induce IL-10 production [28,9]. Stimulation of human peripheral blood mononuclear cells (PBMCs) with small chitin particles (<0.5 μm) was also reported to induce the secretion of immunosuppressive interleukin-1 receptor antagonist (IL-1Ra) [10••]. Intriguingly, co-stimulation of PBMCs with the combination of chitin and other non-fungal pattern recognition receptor ligands (lipopolysaccharide, Pam3Cys, or muramyl dipeptide) induced the production of pro-inflammatory produce IL-1β and TNF-α [10••]. The production of both immunosuppressive and pro-inflammatory cytokines by PBMCs was dependent on immunoglobulin opsonization of chitin particles followed by Fc-γ-receptor recognition and phagocytosis and was dependent on activation of Syk and phosphatidylinositol 3-kinase (PI3K) [10••]. Collectively these studies emphasize that the context of glycan presentation (particle size and co-stimulation with other ligands) plays a critical role in determining the character of the host response.

Although no chitin-deficient strain of *A. fumigatus* has been constructed, an environmental isolate that exhibits increased chitin exposure at the surface of the cell wall at all stages of growth has been studied in animal models [27,29]. In a model of repeated pulmonary exposure, mice exposed to the environmental isolate exhibited increased eosinophilia of the airways, lower levels of interferon (IFN)-γ producing CD4+ T cells and increased IL-4 and CCL11 (eotaxin) expression as compared with mice exposed to wild-type conidia [27]. Consistent with this report, recent studies of acidic mammalian chitinase, a chitinolytic enzyme, suggest that chitin oligosaccharides released by host enzymatic degradation of chitin may contribute to the activation of the non-protective pulmonary Th2 responses to *A. fumigatus* [30••]. Chitinase-deficient mice exhibited lower levels of IL-33 production and lower pulmonary fungal burden after *A. fumigatus* challenge, as well as improved lung function following chronic fungal exposure [30••].

The cellular receptor(s) that recognizes chitin has yet to be identified; however, interaction of chitin with members of the ficolin family of soluble proteins has been reported [31,32••]. The ficolins are a class of innate pattern recognition molecules that belong to the

fibrinogen related-domain superfamily [31]. M-ficolin is found in the lung, where it is produced by type-II alveolar epithelial cells, monocytes and neutrophils [31]. Strong staining of M-ficolin has been observed in human tissue samples proximal to aspergilloma lesions [32••]. Studies *in vitro* demonstrated that M-ficolin binds purified chitin, and co-localized with chitin-rich parts of the cell wall [32••]. This binding could be inhibited by soluble *N*-acetyl glucosamine [32••]. M-ficolin binding to chitin-poor regions of the cell wall was also noted, however, suggesting that this protein may bind multiple fungal polysaccharides [32••]. M-ficolin binding of chitin was found to mediate complement activation, and M-ficolin opsonization of the chitin-containing alkali-insoluble cell fraction of *A. fumigatus* resulted in increased IL-18 secretion by A549 epithelial cells as compared to either component alone [32••,33]. The role of M-ficolin binding to *A. fumigatus* chitin has not yet been investigated in animal models of disease.

Galactomannan

Galactomannan is composed of an α-(1,2)(1,6)-mannopyranose backbone with short branches of β-(1,5)-oligogalactofuranose connected by β-(1,3) and β-(1,6) linkages [34]. Galactomannan (GM) is found in both the inner and outer cell wall of *A. fumigatus* hyphae, and is copiously shed by growing hyphae [33,36]. Recently, a second form of galactomannan characterized by longer galactofuranose side chains with 6-*O* substitutions, produced through the action of a unique set of mannosyltransferases, has been identified in the conidial cell wall [37,38].

Both the galactofuranose and mannan components of GM are recognized by the host immune system. The galactofuranose side chains of GM are antigenic and naturally occurring antibodies in humans recognize these structures [36]. The mannan component of *A. fumigatus* GM is an important pathogen-associated molecular pattern molecule that is likely recognized by host mannose receptors including DC-specific ICAM 3-grabbing nonintegrin (DC-SIGN), Dectin-2, and mannose-binding lectin [15].

DC-SIGN is a type II membrane C-type lectin found on the surface of macrophages and dendritic cells [35•]. Studies of the interaction of conidia and human monocyte-derived dendritic cells (MDDCs) have demonstrated that binding of conidia by MDDCs and IL-10 release is inhibited by both soluble galactomannan and antibodies to DC-SIGN. [35•]. Similar findings were observed with alveolar macrophage-like bone-marrow derived macrophages [35•]. In contrast, knockdown of DC-SIGN had no effect on TNF-α and interleukin-12 expression in immature dendritic cells exposed to *A. fumigatus* germ tubes [39]. These findings may reflect differences in dendritic cell derivation methods, or alternately indicate that there are important differences between the mechanisms by which innate cells recognize hyphal and conidial GM.

Dectin-2 is a C-type lectin receptor found on the surface of alveolar macrophages which recognizes α-mannans of several fungi [14,40]. Indirect evidence suggests that Dectin-2 likely recognizes the α-mannan backbone of GM [41•]. Binding of germinating conidia and young hyphae to the THP-1 macrophage cell-line, and subsequent activation of NF-KB was Dectin-2 dependent [42]. Similarly, antibodies to Dectin-2 reduced the ability of plasmacytoid dendritic cells (pDCs) to bind Aspergillus hyphae [43]. Direct binding or inhibition studies to confirm that the α-mannnan chain is the Dectin-2 ligand responsible for these phenotypes have yet to be performed.

Mannose-binding lectin (MBL) is a soluble circulating collectin-class lectin which binds a variety of fungal mannans [44]. Upon binding to these glycans, MBL induces complement activation via complex formation with MBL-associated serine proteases (MASPs) [44]. As with Dectin-2, direct evidence for MBL binding of Aspergillus GM is lacking; however, MBL binds to the surface of *A. fumigatus* conidia and this binding can be inhibited with soluble mannose [44,40]. Studies in mouse models have yielded somewhat contradictory roles for MBL that may indicate site and disease specific roles for this lectin in the pathogenesis of *Aspergillus* infections and allergy [45–47]. MBL treatment enhances phagocytosis of conidia and killing of hyphae by human PMNs and activates the complement cascade [45]. Treatment of mice with recombinant human MBL enhances survival in a model of invasive pulmonary aspergillosis in association with increased production of pro-inflammatory cytokines (TNF-α and IL-1β) and reduced production of immunosuppressive IL-10 [45]. Conversely, MBL-deficient mice are more resistant to intravenous *A. fumigatus* challenge [46]. MBL-deficiency in mice was associated with decreased Th2 cytokine and increased IFN-γ production upon intratracheal challenge with *A. fumigatus* [47]. These conflicting results could stem from differences in mouse background, or perhaps indicate that pharmacologic levels of intrapulmonary MBL exert unique effects on pulmonary neutrophils. Finally, in a fungal asthma model MBL-deficient mice were found to produce lower levels of type-2 cytokines and develop less airway hyperreactivity early after *A. fumigatus* challenge [47]. Although more work is required to understand these observations, these findings may reflect the relative importance of complement activation versus induction of cytokine production in these different models of disease.

Galactosaminogalactan

Galactosaminogalactan (GAG) is an exopolysaccharide found throughout the cell wall and extracellular matrix of *A. fumigatus* [48]. The quantity of hyphal-associated

GAG produced by other *Aspergillus* species has been correlated with their frequency of isolation from invasive aspergillosis patients, suggesting that this polymer plays an important role in fungal virulence [4]. GAG is a heteropolymer of α-(1,4)-linked galactose and partially de-*N*-acetylated galactosamine that is absent from conidia, but produced at all other stages of growth [48]. GAG plays a number of roles in host-fungal interactions. GAG mediates adherence of *A. fumigatus* to host tissues and other substrates [17••,49]. Cell wall-associated GAG enhances immune evasion through cloaking immunostimulatory polysaccharides found deeper in the cell wall, such as β-glucan, from detection by pattern recognition receptors [17••,49]. Additionally, as GAG is a cationic polysaccharide, cell-associated GAG can act as an electrostatic barrier to intracellular penetration by cationic antimicrobial peptides, such as those found in neutrophil extracellular traps [4].

Studies of purified fractions of secreted GAG suggest that this polysaccharide mediates a variety of direct effects during infection. Soluble GAG induced apoptosis of human neutrophils, via a natural killer cells-dependent mechanism [50,51]. Stimulation of peripheral blood mononuclear cells with soluble GAG induced the release of anti-inflammatory IL-1 receptor antagonist, and suppression of IL-17 and IL-22 production by these cells [52]. Finally, it has been reported that GAG stimulates platelet activation, resulting in increased CD62P, CD63, and Annexin V exposure on their surface [53]. While intravascular thrombosis is a well-described phenomenon in invasive aspergillosis [54], the effects of GAG-mediated platelet activation in thrombosis during pulmonary fungal infection have not yet been studied *in vivo*. Taken as a whole, these studies strongly suggest the presence of a receptor for GAG on host cells; however, attempts to identify a mammalian receptor for GAG have not yet been successful.

Future directions

Although substantial progress has been made in expanding our understanding the role of *A. fumigatus* cell wall polysaccharides in host–pathogen interactions, a number of glycans, including β-(1,6)-glucans and chitosan, remain completely unstudied. In addition, the development of glycomic tools and methods has lagged behind genomics, proteomics and other fields. The development of new reagents and approaches, including synthetic oligosaccharides and probes, robust protocols for polysaccharide purification and visualization, and the generation of antibodies specific for individual glycans will be critical in moving the field forward. Identification of the receptors for GAG, α-glucan, chitin, and other glycans will be critical step in elucidating the role of these glycans in the pathogenesis of Aspergillus disease. Finally, exploring the use of glycoconjugate vaccines that incorporate fungal oligosaccharides or chimeric-T cells that recognize fungal polysaccharides holds promise for the development of new immunotherapies for invasive and chronic aspergillus syndromes.

Author contributions

Caitlin A. Zacharias and Donald C. Sheppard wrote the manuscript.

Conflict of interest statement

Nothing declared.

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