The interaction between *Histoplasma capsulatum* cell wall carbohydrates and host components: relevance in the immunomodulatory role of histoplasmosis

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Histoplasma capsulatum *is an intracellular fungal pathogen that causes respiratory and systemic disease by proliferating within phagocytic cells. The binding of* H. capsulatum *to phagocytes may be mediated by the pathogen's cell wall carbohydrates, glucans, which consist of glucose homo and hetero-polymers and whose glycosydic linkage types differ between the yeast and mycelial phases. The* α*-1,3-glucan is considered relevant for* H. capsulatum *virulence, whereas the* β*-1,3-glucan is antigenic and participates in the modulation of the host immune response.* H. capsulatum *cell wall components with lectin-like activity seem to interact with the host cell surface, while host membrane lectin-like receptors can recognize a particular fungal carbohydrate ligand. This review emphasizes the relevance of the main* H. capsulatum *and host carbohydrate-driven interactions that allow for binding and internalization of the fungal cell into phagocytes and its subsequent avoidance of intracellular elimination.*

Key words: *Histoplasma capsulatum* - carbohydrates - glucans - polysaccharides - immunomodulation

Histoplasma capsulatum is an ubiquitous dimorphic intracellular fungal pathogen which exists in either a mycelial (saprobe-infective form) or a yeast (parasitic-virulent form) phase. The characterization of outer carbohydrates specific to these phases may lead to a better understanding of their pathogenic fungal-host interactions, such as fungal adhesion, internalization and host immune evasion mechanisms. Therefore, this review focuses on specific fungal saccharidic structures that may be involved in the aforementioned mechanisms.

The chemical characteristics and the functions of *H. capsulatum* cell wall carbohydrates

The cell wall is essential to almost every aspect of *H. capsulatum* biology and pathogenicity. In general, 80% of the fungal cell wall's dry weight is composed of saccharides (Bernard & Latgé 2001). Glucose (Glc), followed by mannose (Man) and galactose (Gal), is the most abundant monosaccharide found in *H. capsulatum* cell walls during the mycelial and yeast phases. It has been reported that polymers of Glc (glucans) and N-acetyl-glucosamine (GlcNAc) called chitin are the major components of the *H. capsulatum* cell wall (Kanetsuna et al. 1974). The concentration of saccharides can vary depending on culture medium composition, environmental conditions, strain type and the extraction method used (Domer et al. 1967, Kanetsuna et al. 1974, Reiss et al. 1977).

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It has been proposed that glucans play an important role in fungal host-cell interactions. There are differences between the glucan glycosydic linkages in the cell walls of the *H. capsulatum* yeast and mycelial phases. The α and β-glucans present in the cell walls of these morphological phases have different biological roles (Domer et al. 1967, Domer 1971, Gómez et al. 1991). An α-glucan contains α-1,3-glucosyl linear residues, while β-glucan consists of a linear β-1,3-glucosyl-linked backbone with β-1,6-glucosyl-linked side chains that vary in length and distribution, while forming a complex tertiary structure stabilized by interchain hydrogen bonding (Kanetsuna et al. 1974). The yeast cell wall contains an inner layer of chitin, a polysaccharide composed of β-1,4-GlcNAc residues, and an outer fibrous-layer of α-1,3-glucan (Kanetsuna et al. 1974). Topographically, the α-1,3-glucan overlaps the β-glucan polymer in the yeast cell wall. The yeast and mycelia phases of *H. capsulatum* contain different chitin fibril arrangements within their cell walls (Kanetsuna 1981).

Based on the α-1,3-glucan concentration in the yeast cell wall, *H. capsulatum* is classified as chemotype I and II (Domer et al. 1967, Domer 1971). A chemotype II cell wall contains of a mixture of α and β-glucans, with glucan predominantly linked in the α-configuration, while chemotype I is entirely β-linked (Davis et al. 1977). Moreover, the cell walls of *H. capsulatum* chemotype I strains contain more chitin and less glucan than chemotype II (Domer et al. 1967, Domer 1971).

In general, fungal chitin is considered to play both a structural role in maintaining cell wall rigidity, as well as in resisting the environment (Ruiz-Herrera 1992). It is also possible that chitin has a dual immunomodulatory effect on macrophages by immunosuppressing or

activating anti-microbial mechanisms by increasing nitric oxide production, an activity previously described in *Candida albicans* (Rementeria et al. 1997).

The presence of α-1,3-glucans in *H. capsulatum* has previously been associated with strain virulence (Kügler et al. 2000, Rappleye et al. 2007). Alternatively, β-glucan, which is predominant in the fungal mycelial phase, participates in both leukocyte recruitment and the upregulation of inflammatory mediators, such as leukotrienes (Medeiros et al. 1999).

A temperature-induced phase transition may modify the biosynthesis of glucans, i.e., the synthesis of α-1,3-glucan is a special attribute of *H. capsulatum* yeast phase (Kanetsuna et al. 1974, Klimpel & Goldman 1988). In recent studies, α-1,4-amylase has been involved in both the synthesis of α-1,3-glucan and the virulence of *H. capsulatum* (Marion et al. 2006). Virulent *H. capsulatum* strains contain up to 1,000-fold more α-1,3-glucan than avirulent strains do. Some *H. capsulatum* strains spontaneously produce avirulent variants lacking α-1,3-glucan. These can persist for several weeks inside macrophages and adopt an unusual morphology, similar to those variants reported in tissues of chronically infected humans and other mammals (Klimpel & Goldman 1988). The α-1,3-glucans may contribute to the establishment of intracellular latency (Eissenberg et al. 1996, 1997), regulate yeast proliferation inside a host macrophage (Kügler et al. 2000) and protect yeast within phagolysosomes (Eissenberg & Goldman 1991). Moreover, the low TNF-α produced by infected host cells provides indirect evidence for an α-1,3-glucan-mediated effect on the host-parasite relationship (Rappleye et al. 2004, 2007). It has also been suggested that α-1,3-glucan can block innate immune recognition of *H. capsulatum* by a particular β-glucan receptor (Rappleye et al. 2007).

Cell wall mannans (Man-containing polysaccharides) and mannosylated proteins are important fungal antigens and have been implicated in host tissue adherence (Ross 2002). Galactomannan-protein complexes from the mycelial phase cell wall of *H. capsulatum* have antigenic properties; they can induce delayed-type hypersensitivity in guinea pigs and inhibit macrophage migration factor release (Azuma et al. 1974, Reiss et al. 1974). A deproteinized polysaccharide-protein complex isolated from *H. capsulatum*, which immunolocalized mainly to the mycelial phase cell wall by colloidal gold labelling (Taylor & Bojalil 1977, Taylor et al. 1980, Pereira-Morales et al. 1998), shares common characteristics with the galactomannan-protein complex reported by Reiss et al. (1974). Fungal galactomannan complexes may be involved in a mechanism to protect the organism against its own serine-thiol protease, an enzyme associated with pathogen dissemination through the extracellular matrix, as described in paracoccidioidomycosis (Matsuo et al. 2006).

The fungal cell wall contains a low proportion of lipids, of which several are linked to carbohydrates and illustrate structural heterogeneity. In *H. capsulatum*, sphingolipid modifications may be functionally relevant for their growth, life cycle, morphogenesis, and host-pathogen interactions (Dickson & Lester 1999). Adherence to the membrane of host cells by *H. capsulatum* seems to be mediated by lactosylceramide (Galβ1-4Glcβ1-1Cer) (Jiménez-Lucho et al. 1990). Lactosylceramide is the major glycosphingolipid in the host cell and seems to be an important component of some receptor moieties participating in yeast adherence to phagocytes and other host cells, an event that probably favours fungal dissemination (Obei et al. 2002). The glycosylinositol phosphorylceramides present in the mycelial and yeast phases of *H. capsulatum* (Barr et al. 1984, Barr & Lester 1984) seem to be required for fungal survival (Dickson & Lester 1999).

The interactions between *H. capsulatum* cell wall carbohydrates and host cells

The molecular interactions between host cells and *H. capsulatum* are critical events in the intracellular fate of this fungus, as well as in the pathogenesis of histoplasmosis. Microorganisms initially trigger the immune system by activating the innate immune response, which is based on recognition of pathogen-associated molecular patterns (PAMPs). β-Glucans possess many of the characteristics attributed to PAMPs and are known to be potent triggers of innate immunity (Brown 2006).

Different host receptors can interact specifically with fungal carbohydrates, especially the lectin-like receptors, including the Man receptor (CD206); β-glucan receptors, such as Dectin-1 and DC-SIGN (CD209); complement receptor-3 (CR3 or CD11b/CD18); and collectins, such as surfactant factors (SP-A and SP-D) and pentraxin-3. These are considered pattern recognition receptors (PRRs) and are present in both professional and non-professional host phagocytes, including macrophages, dendritic cells (DC) and epithelial cells (Brown 2006, Dennehy & Brown 2007).

Dectin-1, a nonclassical C-type lectin found in neutrophils, natural killer cells, DC and a subset of T cells is important for the detection of glycosylated fungal components (Brown 2006). It is a major nonopsonic β-glucan receptor and one of the first PRRs identified that can mediate its own signalling, as well as being able to act synergistically with Toll-like receptors (TLR) to initiate specific responses to infectious agents. It can also mediate signals to induce inflammatory responses to β-glucans from several fungal pathogens (Brown 2006, Dennehy & Brown 2007). Several PAMPs located in the cell wall or on other fungal cell surfaces have been identified as potential ligands for TLR-2 and TLR-4 and have been implicated in host defence against some pathogenic fungi (Meier et al. 2003, Roeder et al. 2004). However, the participation of TLRs in histoplasmosis has not been confirmed.

It has been suggested that *H. capsulatum* α-1,3-glucans block host Dectin-1 from recognizing β-glucans present during the fungal yeast phase (Rappleye et al. 2007). This implies that the α-1,3-glucans act as "decoy ligands" for the Dectin-1 receptor. However, several membrane components, such as CR3, the scavenger receptor, and Gal β1-4Glcβ1-1Cer, have been shown to interact with β-glucan (Kataoka et al. 2002). Consequently, the abrogation of the host innate immune response by blocking Dectin-1 with α-1,3-glucan may be circumvented by other β-glucan receptors or Gal β1-4Glc β1-1Cer molecules during natural host interactions.

At present, the specific receptors recognizing *H. capsulatum* α-1,3-glucan have not been identified. However, Bittencourt et al. (2006) recently described the participation of cell wall α-1,3-glucan in the phagocytic internalization of *Pseudallescheria boydii*, which stimulated the secretion of inflammatory cytokines through the involvement of TLR2, CD14, and MyD88.

As previously described, *H. capsulatum* β-glucan favours the production of inflammatory mediators (Medeiros et al. 1999). In general, activation of macrophages by several types of soluble β-glucans culminates in the induction of proinflammatory mediators, nitric oxide synthase, TNF-α and macrophage inflammatory protein-2 (Kataoka et al. 2002, Deepe & Gibbons 2006, Deepe 2007).

CR3 is considered the main macrophage lectin-like receptor involved in nonopsonic recognition of *H. capsulatum* yeast (Long et al. 2003). *H. capsulatum* yeast bind to CD18 β2-chains of integrin, CR3 (CD11b/CD18), LFA-1 (CD11a/CD18) and to CR4/p150/95 (CD11c/CD18) on macrophages (Bullock & Wright 1987). Heat shock protein 60 seems to be the major ligand mediating *H. capsulatum* yeast and conidia binding to the CD18 chain of CR3 on macrophages (Long et al. 2003). It has been reported that signalling via CR3 down-regulates IL-12 production in response to *H. capsulatum*. Consequently, the lower production of IL-12 abolishes its protective response against fungi (Marth & Kelsall 1997). It is well known that the CR3 molecule contains a lectin domain with specificity for polysaccharides containing Man, GlcNAc and Glc (Xia et al. 1999, Ross 2002). In addition, lectin-mediated interactions between CR3 and several microbial ligands abrogate the release of toxic oxygen metabolites. Therefore, CR3 functions as a receptor for soluble and particulate polysaccharides and may act as a safe portal for the entry of an intracellular microorganism into macrophages.

Another lectin-mediated interaction between *H. capsulatum* yeast and host cells has been considered, in which lectin activity is associated with a component present on the yeast cell surface. This lectin-like activity is specific to galactosylated surface molecules (mainly β-anomer) on murine macrophages (Taylor et al. 1998, Duarte-Escalante et al. 2003). *H. capsulatum* yeast also has the ability to bind and agglutinate human erythrocytes through this lectin-like component (Taylor et al. 2004). The biological significance of these findings seems to be related to aspects of dissemination and pathogenesis of the associated clinical disease. The *H. capsulatum* lectin recognizes a 68-kDa cell surface protein on murine macrophages (Taylor et al. 1998). This membrane receptor seens to participate in mechanisms that activate macrophages and those that regulate phagocytosis (Maldonado et al. 1998).

In some cases, opsonins are required to capture fungi by phagocytic lectin-like receptors. Serum opsonins that have lectin-like receptor activity, such as CR3 and the family of collectin molecules, play an important role in the immune response against microorganisms (Lu et al. 2002). Collectins play a dual role in the innate response: as a possible mechanism for dissemination (McMahon et al. 1995) and as serum opsonin (McCormack et al. 2003). The collectins commonly associated with *H. capsulatum* are lung surfactant proteins A and D (SP-A and SP-D) and Man-binding lectin. SP-A and SP-D provide a mechanism to control *H. capsulatum* proliferation during the preinflammatory phase of the host-pathogen interaction. Both collectins inhibit fungal growth by increasing the microorganism's permeability and circumventing its aggressiveness. *H. capsulatum* is protected from collectin-mediated killing by rapidly entering pulmonary macrophages (McCormack et al. 2003).

Surface carbohydrates on numerous pathogens are important for the early activation of the innate immune response and the subsequent control and destruction of these pathogens. *H. capsulatum* utilizes its cell wall carbohydrates or the host cell surface carbohydrates to bind and colonize the host, as well as to activate the innate response. Moreover, they seem to provide *H. capsulatum* with the capacity to survive in macrophages. The cell wall is the major fungal structure involved in interactions with the host. It is a highly dynamic entity and changes in its composition or structure may trigger critical consequences for the host-parasite relationship.

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