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Effect of *Histoplasma capsulatum* glucans on host innate immunity



Roberto Lara-Lemus^a, Noé Alvarado-Vásquez^a, Edgar Zenteno^b, Patricia Gorocica^{a,*}

^a Departamento de Bioquímica, Instituto Nacional de Enfermedades Respiratorias, México DF, Mexico

^b Departamento de Bioquímica, Facultad de Medicina, Universidad Nacional Autónoma de México, México DF, Mexico

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ABSTRACT

β -1,3-Glucan is important for infective forms (mycelial phase) of *Histoplasma capsulatum* and shares many features allotted to pathogen-associated molecular patterns. These cell wall carbohydrates interact with phagocytes by binding to Toll and lectin-like receptors, present on cell surfaces of macrophages, neutrophils, and dendritic cells. This review focuses on recent findings of the major *H. capsulatum* and host carbohydrate-driven interactions that account for internalization of fungal infective forms into phagocytes, and its subsequent avoidance of intracellular elimination. The yeast phase of *H. capsulatum* possesses different modulating factors of the macrophagic-anti-fungal mechanisms, mainly α -1,3-glucan, which is considered relevant for virulence.

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Efecto de los glucanos de *Histoplasma capsulatum* sobre la inmunidad innata del huésped

RESUMEN

El β -1,3-glucano es importante para las formas infectivas (fase micelial) de *Histoplasma capsulatum* y comparte varias características asignadas a los patrones moleculares asociados con patógenos. Estos hidratos de carbono de la pared celular interactúan con los fagocitos uniéndose a receptores tipo Toll y tipo lectina, que están presentes en las superficies celulares de macrófagos, neutrófilos y células dendríticas. En esta revisión se presta atención a los hallazgos recientes sobre las principales interacciones entre *H. capsulatum* y las células del huésped mediadas por hidratos de carbono, que permiten la internalización de las formas infectivas del hongo por los fagocitos, así como la posterior evitación de su eliminación intracelular. Se discuten los datos experimentales relevantes publicados recientemente. La fase de levadura de *H. capsulatum* incluye distintos factores moduladores de los mecanismos de macrófagos y antifúngicos, sobre todo el α -1,3-glucano, que se considera relevante para la virulencia.

Este artículo forma parte de una serie de estudios presentados en el «V International Workshop: Molecular genetic approaches to the study of human pathogenic fungi» (Oaxaca, México, 2012).

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Pathogens recognition is commonly based on the identification of molecular patterns by distinct receptors and subsequent activation of signaling pathways, which allow the defense reaction to fend off invading microorganisms. Pathogen fungi have several molecular components in the cell wall that play a critical role in their pathogenicity mechanisms. Indeed, cell wall contains adhesins and a broad number of receptors interacting

with environmental factors that, after activation, start a complex network of downstream intracellular signals.¹⁴ The dimorphic fungal pathogen *Histoplasma capsulatum* var. *capsulatum* causes the respiratory and systemic disease, histoplasmosis.²⁷ Like most systemic-disease-causing fungal pathogens, this infection is acquired via the respiratory tract by inhalation of infective propagules, mainly microconidia, hypha fragments, and spores produced during the mycelial phase of this fungus.^{29,59} Target organs are lungs, where alveolar macrophages and dendritic cells (DCs) are responsible for phagocytosis of infective forms, establishing the link with the adaptive immune response.^{13,32} Dimorphic switching from the mycelial phase (M-morphotype) to yeast phase

* Corresponding author.

E-mail addresses: gorocicap@gmail.com, pgorocica@yahoo.com.mx (P. Gorocica).

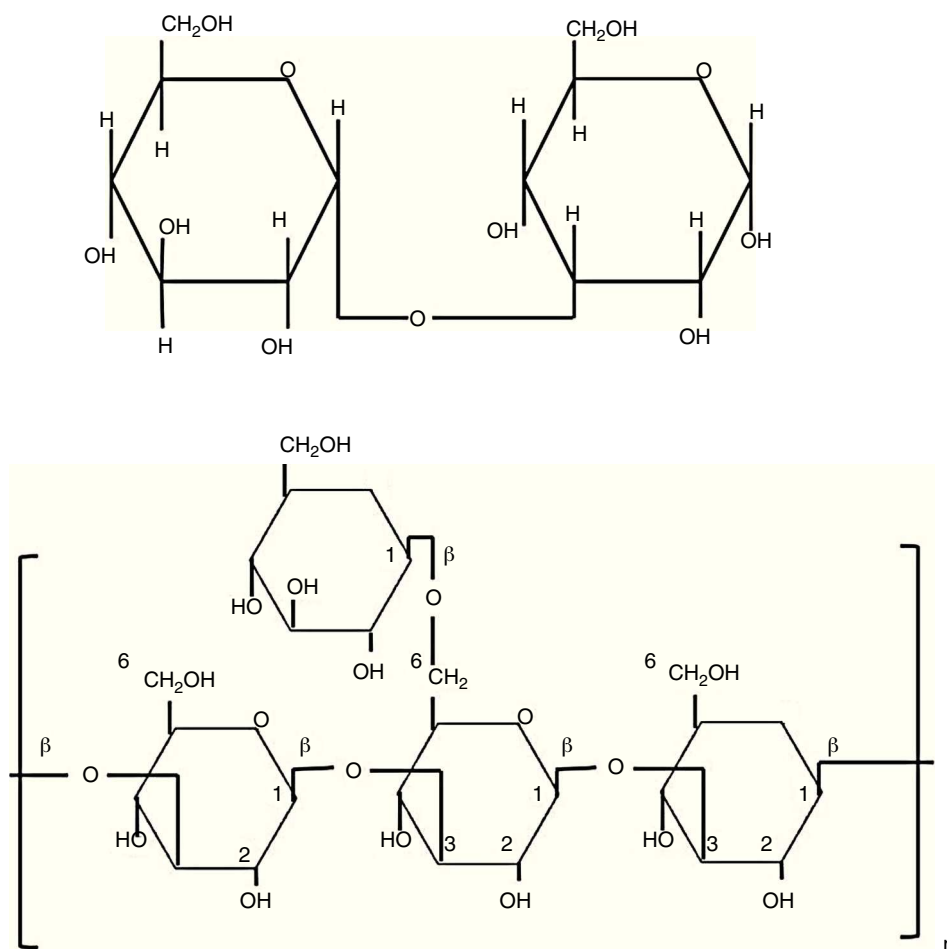


Fig. 1. A schematic view of D-glucose and glycosidic bonds conformation. Upper panel, α -1,4-glycosidic bond; lower panel, β -1,3-glycosidic bond, and branching point showing a β -1,6-glycosidic bond. β -Glucan has repetitive units of this structure.

(Y-morphotype), occurs within alveolar macrophages.²⁵ Infective M-morphotype is considered a non-virulent phase, whereas Y-morphotype is the parasitic-virulent phase of *H. capsulatum*. Extensive changes in gene expression between these two phases are directly responsible for the behavior of each morphotype.⁶³ Cell wall undergoes drastic changes in carbohydrate polymers (polysaccharides) composition by switching from one to the other morphotype.^{24,39}

Polysaccharides constitute about 80% of *H. capsulatum* cell wall components, and they play an important role in biology and pathogenicity of the fungus.^{28,38} Polysaccharides of the cell wall of *H. capsulatum* can be classified as glucans, they are D-glucose polymers linked by α - or β -glycosidic bonds. Both α - and β -glucans are present in cell walls of M- and Y-morphotypes. Chitin is a lineal glycan composed of β -1,4 N-acetyl-D-glucosamine and mannans are lineal polymers of mannose usually linked to proteins (mannoproteins), and both can be either homo- or co-polymers.^{10,17,18,20,35} It has been suggested that glucans and mannans interfere with the innate immune response. Glucans and mannans are recognized by lectin-like receptors of phagocytic cells, and they induce beneficial signals that can promote fungus survival and favor infection; although the specific mechanisms involved in this process are not yet completely defined.⁴⁸

Chemical and ultra-structural studies of cell walls of the Y-morphotype have revealed higher amounts of α -glucan than β -glucan, chitin, and co-polymer galactomannan. In contrast, the M-morphotype contains higher amounts of β -glucan and galactomannan, and has less α -glucan content.^{29,35}

Biological properties of glucans

Carbohydrates perform diverse and important biological functions, such as energy storage molecules or as structural components of the cell wall. Polysaccharides can reach a high degree of polymerization. Glucans are D-glucose polymers linked by glycosidic bonds involving the anomeric hydroxyl group (OH), rendering α - or β -configurations (Fig. 1).¹⁰ Differences between β -glucan bonds and the chemical structure related to their solubility and biological activities are very important. Fungal β -glucans are composed by glucose units connected by β -1,3 or β -1,6 linkages (Fig. 1). Spatial arrangement of β -1,4-glucan is present in structural polysaccharides of some fungal cell walls.^{2,5} These straight chains are transversally linked by hydrogen bonds and turn into parallel structures. On the other hand, α -1,4-glucan brings on helical assemblies, and both α - and β -1,6 bonds, generate flexible and relaxed structures.^{5,10}

Glycosidic β -1,3 and β -1,6 bonds yield insoluble molecules, thus, they exhibit higher biological activity than soluble β -1,4-glucan.⁶⁰ Biological and immunological characteristics of β -glucans are sustained on molecular and structural features, such as polymer length, branching degree, and kind of glycosidic bond. As long as β -glucans have more β -1,3 chains, branched with D-glucose attached to position β -1,6, they reach the most active form. Interestingly, length of side chains, more than length of main chain, determines the β -glucans activity on the immune system,⁶⁰ and some pathogen fungi, such as *Pneumocystis carinii*, *Saccharomyces cerevisiae*, and *Candida albicans*, have both type of glycosidic bonds,

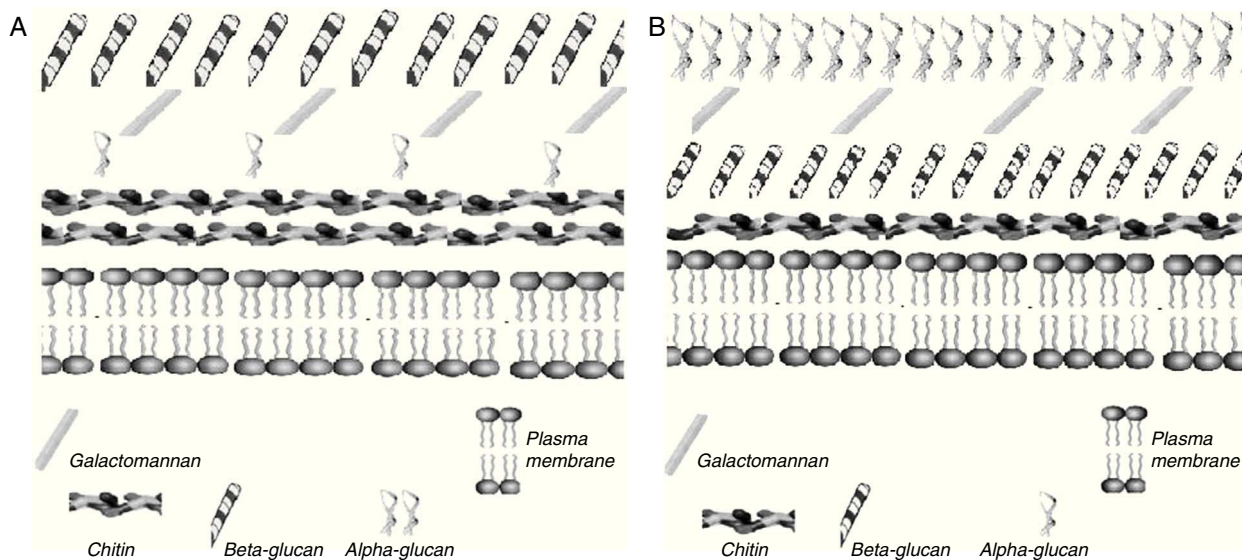


Fig. 2. A schematic view of *H. capsulatum* cell wall. (A) M-morphotype; (B) Y-morphotype, chemotype II. Note important disproportion in α -, β -glucans, and chitin contents, as well as their differential distribution within the cell wall. The figure was constructed based on data from Guimaraes et al.,²⁸ in accordance with major *H. capsulatum* cell wall components.

β -1,3 and β -1,6.^{30,41,61} Commercially available β -glucans from different biological sources have been used as adjuvant to stimulate innate and adaptive immune responses and in the control of some diseases.⁵⁵

Insoluble β -glucans derived from yeasts activate DCs and macrophages through the Dectin-1 receptor, promoting TH1, CD4⁺ T-lymphocytes response. This type of response is characterized by activation of cytotoxic effectors against intracellular infections or neoplastic cells; thus, these molecules have been used widely in anti-tumoral therapy. In spite that soluble β -glucans can bind to macrophages and DCs, they interact with receptors other than the Dectin-1, in such way, they do not activate the immune response and, hence, they lack any therapeutic effect.⁵²

Insoluble forms of glucans, mainly in α -1,4 or α -1,6 bonds, activate pro-inflammatory cytokines and hydrogen peroxide production in macrophages.⁹ α -Glucans are crucial for yeast cell wall function, and they play an important role in the virulence of several pathogenic fungi, like *Aspergillus fumigatus*, *H. capsulatum*, *Cryptococcus neoformans*, and *Blastomyces dermatitidis*.^{2,4,12} It is clear now that α -glucan of *B. dermatitidis* is vital for the yeast-phagocyte interaction.³³ In this sense, *Paracoccidioides brasiliensis* shows a change from β - to α -glucan when cells convert from mycelial into yeast phase.^{4,57}

Several important aspects are related with α -1,3-glucan in the cell wall of *H. capsulatum*, this glucan is associated with virulence,^{21–23,34} because it contributes to intracellular latency of the fungus, probably by protecting yeasts inside phagolysosomes,²¹ and regulating proliferation of *Histoplasma* within macrophages³⁸; furthermore, it reduces tumor necrosis factor alpha (TNF- α) production by infected cells.⁵³ Unlike the α -1,3-glucan of *H. capsulatum*, the insoluble α -glucans activate macrophages to produce pro-inflammatory cytokines such as interleukin-8 (IL-8) and TNF- α , which participate in the pathogenesis of disease.⁴⁸ Polysaccharides in the cell wall of *H. capsulatum* have different arrangements depending on the morphotype. According to soluble polysaccharides and chitin content, the Y-morphotype of *H. capsulatum* is classified as chemotype I and II.^{18,19} Chemotype I cell walls are characterized by lower content of soluble material and higher chitin content than chemotype II. On the other hand, the Y-morphotype has an external coat of α -1,3-glucan, masking an internal envelope rich in immunostimulatory β -glucan and chitin (Fig. 2).^{20,24} In

general, for *H. capsulatum* chemotype II, the M-morphotype contains β -1,3-glucan, higher proportions of mannose, and lower chitin content when compared to yeast phase.^{18,19} The molecular organization of cell walls of *H. capsulatum* is shown in Fig. 2. Finally, an interesting feature of *H. capsulatum* is that it can regulate synthesis of α -1,3-glucan, depending on the environmental conditions.³⁸

The role of glucans of *H. capsulatum* associated with pathogenesis of histoplasmosis

Success of pathogenic fungi depends on the capacity of the host innate immune response to recognize fungal cell wall components, like glucans. The host innate immune system responds through the pattern recognition receptors. Structurally, β -glucans are greatly conserved among fungi, and share many of the characteristics assigned to pathogen-associated molecular patterns (PAMPs). It is known that some PAMPs located on the cell wall of fungi interact with macrophages and DCs, by binding to Toll-like receptors (TLR), for example TLR2 and TLR4.^{44,45,54} Even though, these receptors do not participate in phagocytosis, they can trigger different cellular signals. PAMPs are also recognized by diverse carbohydrate receptors known as lectin-like receptors, located on the cell surfaces of macrophages, neutrophils, and DCs. After activation, they stimulate the inflammatory immune response. The most important lectin-like receptors recognizing β -glucan of *H. capsulatum* are: complement receptor 3 (CR3 or CD11b/CD18) and the lectin-like receptor associated to dendritic cells type1 (Dectin-1).^{6,7,16,26,33,52} CR3 has two recognition domains, one is for C3bi binding and the other binds carbohydrates like β -glucans. When microorganisms are opsonized with C3bi, C3bi binds to the CD11b domain, while β -glucan binds to the C-terminal of the CD18 domain; afterwards, fungal cells are phagocytized. Macrophages kill these microorganisms through usual microbicidal mechanisms.⁶²

The function of Dectin-1 is still controversial in host defense against pathogenic fungi. This receptor can mediate interactions with different fungi, such as *Candida*, *Aspergillus*, *Pneumocystis*, and *Coccidioides*.²⁸ Different ligands have been reported for Dectin-1, one of them is the fungal β -glucan. When this polysaccharide activates immune system cells, reactive oxygen species (ROIs) are

produced, and transcriptional factor NF- κ B is translocated to the nucleus and increases expression of pro-inflammatory cytokines.⁴¹

Dectin-1 has extracellular domains for carbohydrates recognition, mainly β -glucans, and a transducer domain facing the cytoplasm, which shares an activation motif with the tyrosine immune receptors.⁵⁶

In general, macrophages stimulated by fungal β -glucans, secrete pro-inflammatory cytokines, such IL-1 and IL-6, TNF- α , macrophage inflammatory protein-2 (MIP-2), ROIs, and eicosanoids.^{31,55} In addition, β -glucans directly participate in the inflammatory process by recruiting leucocytes.⁴⁴ Other important properties of β -glucans include: stimulation of hematopoietic stem cells, activation of alternative complement pathway, and also the activation of B and T lymphocyte, macrophages, DCs, and NK cells. In this sense, the involvement of β -glucans in stimulation of anti-tumor responses has been reported recently, which is an interesting topic for further investigation.^{46,51} The Y-morphotype of *H. capsulatum* is well adapted to the intracellular environment, and it has different ways to avoid macrophagic anti-fungal mechanisms; one of the most important is the α -glucan of the cell wall.⁵³ As we mentioned before, there are important differences between M- and Y-morphotypes of *H. capsulatum* regarding its capacity to induce or not an inflammatory response, and these differences can be explained, in part, by the type and amounts of glucans in the fungal cell wall.^{8,58} α -1,3-Glucan, is the less abundant form of α -glucans in microorganisms. In *H. capsulatum*, virulence is multifactorial; however, there are some virulent strains of *H. capsulatum* chemotype I that lack α -1,3-glucan in their cell walls.²⁰ Yeast chemotype II has the α -1,3-glucan located in the most external face of the cell wall, and this molecule is associated with pathogenicity mechanisms not well-determined yet.^{20,54} Nevertheless, in the Y-morphotype of *H. capsulatum*, evidence has been found regarding the role of α -1,3-glucan in virulence by avoiding β -1,3-glucan recognition by a β -glucan receptor (Dectin-1).^{52,53} In fact, this mechanism could explain blockade of β -glucan interaction with Dectin-1 and, consequently, abrogation of the host innate immune response.

So far, a specific receptor for α -1,3-glucan has not been identified. However, interestingly, Bittencourt et al.³ demonstrated that α -glucan from *Pseudallescheria boydii* induces TNF secretion by cells of the innate immune system in a mechanism involving TLR2, MyD88, and CD14. Morphotypes of *H. capsulatum* have an impact on the particular type of immune response developed by the host. Histoplasmosis depends on the balance between responses mediated by T-helper lymphocytes Th1 characterized by high IFN- γ production, which reinforces a cellular immune response associated to control the infection process, and Th2 linked to IL-4 production together with elevated antibodies production, and this correlates with the severity of the infection.^{1,25,43,47}

In murine models, IL-17 favored elimination of *H. capsulatum*. In contrast, IL-23 could extend mice survival in absence of IL-12.^{13–15} Th17 response has been associated to protective mechanisms against several microorganisms, including fungi.^{11,36} Receptors implicated in this response include lectin-like receptors, such as Dectin-1 and Dectin-2, DC-SIGN, CLEC-1, and CD161.^{12,56} Th17 cells show ability to produce IL-17 and a number of pro-inflammatory cytokines, such as TGF β , IL-1 β , IL-6, IL-21, IL-22, and IL-23. It is possible that IL-17, which also displays pro-inflammatory attributes,^{40,49} regulate the equilibrium of Th1 along with Th2 responses,^{37,42,50} favoring elimination of the intracellular infection by *H. capsulatum*.

Concluding remarks

Major polysaccharides of the fungal cell wall are chitin, β -glucans, and α -glucans. Chitin and β -glucans seem to participate

in keeping structural integrity of fungi⁵; however, the precise role of α -glucan is still controversial.

The most virulent yeast phase of *H. capsulatum* contains high amounts of α -glucans corresponding to 35–46% of total carbohydrates of the cell wall, whereas in the M-morphotype and in some Y-morphotype cells, the amount of this polysaccharide is minimal. Nevertheless, controversial results have been reported in *P. brasiliensis* strains, because virulence increases with α -glucan content.⁵⁸ Pathogenicity of *H. capsulatum* does not depend solely on any alteration of the immunologic status of the host, as *Candida* and other opportunistic fungi do. Instead, *H. capsulatum* exerts virulence factors endorsing survival, by avoiding the immune-based antifungal mechanisms. In part, this successful performance is due to properties related to the polysaccharide α -1,3-glucan. This molecule can modulate the host immune response developed against *H. capsulatum*, and is associated also to the ability of yeasts to survive inside immune cells. Structural changes of the cell wall of *H. capsulatum* in the course of infection are a critical aspect during host-cells invasion process and the whole host–parasite relationship. More precise characterization of the role of fungal glucans in the clinical course of histoplasmosis is a central subject of future research.

Conflict of interests

The authors declare that they have no conflict of interests.

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