



Fungal polysaccharides: biological activity beyond the usual structural properties

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Studies on structure and function of polysaccharides in biological systems classically involve sequence and compositional analyses, anomeric configuration, type of glycosidic linkage, and presence of substituents. Recent studies, however, indicates that other structural parameters, so far little explored, can directly influence the biological activity of microbial polysaccharides. Among these parameters, we highlight the molecular dimensions of *Cryptococcus neoformans* polysaccharides, which appear to be inversely correlated with their immunobiological activity. These recent observations raise new concepts about the structure and function of polysaccharides, which stimulates the design of new experimental approaches and suggests previously unknown applications.

Keywords: polysaccharides, fungal pathogens, immunity, structure and function of polysaccharides, *Cryptococcus neoformans*

Polysaccharides are cellular structural components found in the three domains of life. In microorganisms, several studies have shown that polysaccharides play crucial roles in the architecture of the cell envelope (Roberts, 1996; Nimrichter et al., 2005). In both prokaryotic and eukaryotic microbial pathogens, polysaccharides are major cell wall components (Roberts, 1996; Nimrichter et al., 2005). This surface distribution is in agreement with the fact that polysaccharide molecules directly influence host–pathogen interactions (Moxon and Kroll, 1990; Smith, 1990; Levitz, 2004; Zaragoza et al., 2009).

Polysaccharides consist of polymeric structures composed of at least ten monosaccharides sequentially connected by glycosidic bonds (Bertozi and Rabuka, 2009; Mulloy et al., 2009; Stanley and Cummings, 2009). These structures may be linear or branched, a characteristic that is observed when a monosaccharide constituent of a polysaccharide is involved in more than two glycosidic bonds. Polysaccharides can be classified as homopolymers, a term used to indicate a polymer composed of identical monosaccharides, or heteropolymers, a term used for classification of polysaccharides composed of two or more types of monosaccharides. Classic approaches for the determination of polysaccharide structure include chromatographic methods in association with spectrometric and spectroscopic techniques. These approaches allow determination of sequence and composition, anomeric configuration, type of glycosidic linkage, and presence of substituents (Mulloy et al., 2009).

Capsular polysaccharides were amongst the earliest microbial virulence determinants described in the literature, as demonstrated in the classic Griffith's experiment [review in (Smith, 1990)]. This pioneering study established a direct relationship between the presence of polysaccharide capsules in bacterial

pathogens and protection against host defenses. Subsequently, over several decades, the association between microbial virulence and capsular polysaccharides has been consolidated (Moxon and Kroll, 1990; Monari et al., 2006; Vecchiarelli, 2007; Zaragoza et al., 2009), although it is clear that in some cases, these structures work in favor of the host (Mazmanian and Kasper, 2006; Pletz et al., 2008; Kumar et al., 2009). Consequently, microbial polysaccharides may work in favor of the pathogen or induce immune responses that promote infection control, depending on their chemistry and/or structural aspects.

Classically, polysaccharide antigens have been considered poor inducers of cellular immunity. In fact, polysaccharide molecules are considered T-cell independent antigens that are more efficient activators of antibody production than of cell-mediated immune responses (Weintraub, 2003). In the last decade, however, a number of studies have demonstrated the role of polysaccharides in the activation of innate immunological mechanisms [reviewed in (Raetz and Whitfield, 2002; Kumar et al., 2009)]. In addition, the conjugation of polysaccharides to protein structures can generate hybrid molecules of increased immunogenicity. In fact, vaccines containing polysaccharides against several prokaryotic pathogens have proven successful and are commercially available (Pichichero, 2005; Pletz et al., 2008).

Polysaccharides are essential for pathogenic mechanisms and for the immune response during fungal infections (Roeder et al., 2004). Unlike mammalian cells, fungi have a cell wall, a complex compartment mainly composed of polysaccharides (Nimrichter et al., 2005). Glucans, chitin, and mannans (polymers consisting of repeating units of, respectively, glucose, *N*-acetylglucosamine, and mannose) are particularly abundant in the fungal cell wall. Depending on their structural particularities, cell wall

polysaccharides function as regulators of virulence or activators of innate immunity (Roeder et al., 2004; Zaragoza et al., 2009). Well characterized immunoactive polysaccharides produced by fungi include α - and β -glucans (Brown et al., 2003; Hohl et al., 2005; Bittencourt et al., 2006; Rappleye et al., 2007; Wheeler et al., 2008; van de Veerdonk et al., 2009; Chai et al., 2011) and complex mannans (Leitao et al., 2003; Cambi et al., 2008; van de Veerdonk et al., 2009). *Candida albicans*, *Aspergillus fumigatus*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, and *C. gattii* are examples of fungal pathogens in which the immune functions of polysaccharides are known in great detail (Monari et al., 2006; Rappleye et al., 2007; Cambi et al., 2008; Chai et al., 2011).

Cryptococcus neoformans and *C. gattii* are the etiologic agents of cryptococcosis, a disease that presumably begins in the lung. In immunocompromised individuals, *C. neoformans* can disseminate to the central nervous system and other organs (Bicanic and Harrison, 2004). *C. gattii*, on the other hand, can cause disseminated disease in immunocompetent individuals (Byrnes et al., 2011). It is estimated that about one million new cases of cryptococcosis occur annually, with mortality rates that can reach 60% (Park et al., 2009). In Brazil, cryptococcosis is the fungal disease with highest mortality rates among HIV-positive individuals (Prado et al., 2009). *C. neoformans* and *C. gattii* have polysaccharide capsules surrounding the cell body. Bacterial capsules are common in bacterial pathogens, but relatively rare and still poorly defined among eukaryotic organisms.

In *C. neoformans* and *C. gattii*, the capsule is mainly composed of the polysaccharides glucuronoxylomannan (GXM) and galactoxylomannan (GalXM; Zaragoza et al., 2009; Rodrigues et al., 2011). An alteration in the GalXM nomenclature to glucuronoxylomannogalactan (GXMGal) has been recently proposed based on structural aspects and monosaccharide composition (Heiss et al., 2009). The principal capsular polysaccharide component in both species is GXM, which consists of a polymer composed of an α 1,3 linked mannosyl backbone with β 1,2 and β 1,4 xylosyl and glucuronyl substitutions (for details, see Zaragoza et al., 2009). Structural variation resulting from differences in composition, substitution, and conformation results in different serological properties. These GXM properties divide *C. neoformans* strains into four main serotypes: A and D, produced by *C. neoformans*, and B and C, produced by *C. gattii* [review in (Zaragoza et al., 2009; Rodrigues et al., 2011)]. Hybrid serotypes have been also characterized in different regions (Xu et al., 2002). GXM is believed to be synthesized intracellularly, possibly in close association to lipid structures (Rodrigues et al., 2007; Oliveira et al., 2009). For construction of the capsule, yeast cells secrete polysaccharides into the extracellular environment by mechanisms that involve the release of vesicles for subsequent polysaccharide incorporation into the cell surface, for distal capsular enlargement (Zaragoza et al., 2006; Rodrigues et al., 2007).

It is assumed that synthesis of GXM and its release to the extracellular space are crucial for the immunopathogenesis of cryptococcosis. In general, GXM is deleterious to the immune system (Monari et al., 2006), although several reports indicate that this polysaccharide is a potent activator of the complement system and of the innate immunity [review in (Zaragoza et al., 2009)]. Fractions of extracellular GXM released into the

medium were recently shown to differ in structure and function from capsular polysaccharide extracts (Frases et al., 2008). These observations suggested that *C. neoformans* and *C. gattii* cells produce highly diverse populations of GXM that show structural peculiarities with possible implications on their biological roles. In fact, various studies have established that the production of polysaccharides by *C. neoformans* includes GXM molecules with highly variable dimensions, which interact through several mechanisms to form the capsular network (Nimrichter et al., 2007; Frases et al., 2009). These studies raised an important question: do polysaccharide samples of identical composition but variable size and degree of polymerization present distinct biological functions?

The hypothesis raised above is supported by observations that have recently become available in the literature. Chitin, a linear polysaccharide found in fungi, crustaceans, insects, and parasites, is a water insoluble polymer composed of units of β 1,4-linked *N*-acetylglucosamine. As described by Da Silva et al. (2008, 2009), fractions of chitin with high molecular dimensions are immunologically inert. Polysaccharide samples with reduced dimensions, however, were associated with the effective stimulation of innate immunity and production of pro- and anti-inflammatory cytokines. These observations have established a clear precedent in the literature indicating that polysaccharide samples of identical composition but with varying dimensions may have different functions.

The observation described above and the fact that capsular structures of *Cryptococcus* species are composed of GXM molecules of various sizes (Mcfadden et al., 2006; Frases et al., 2009) support the hypothesis that variation in these structures could translate into different biological effects. In fact, Fonseca et al. (2010) recently established a parallel between the functions of GXM fractions and their dimensions. Through the use of an experimental model that included tests of the activation of cellular responses resulting in nitric oxide production by phagocytes and activation of Toll-like receptors in epithelial cells, it was observed that GXM samples isolated from *C. gattii* (serotype B) with monosaccharide compositions that were similar to other polysaccharide fractions produced by *C. neoformans* (serotypes A and D) and even by other strains of *C. gattii* (serotype C) generated very distinct cellular responses. Measurements of polysaccharide diameter by dynamic light scattering (for details about the technique, see Frases et al., this issue) revealed that the increased capacity of *C. gattii* GXM to induce cellular responses was correlated with a reduced molecular diameter (Fonseca et al., 2010). These results led to the conclusion that serotype B GXM samples with reduced dimensions have greater immunobiological potential, as demonstrated for chitin (Da Silva et al., 2008, 2009; Lee et al., 2008). It remains unknown, however, whether this concept would be pertinent to other GXM-producing species, including members of the *Trichosporon* genus (Fonseca et al., 2009).

The findings discussed above imply new concepts about the structure and function of fungal polysaccharides. Besides structural aspects traditionally studied, such as sequence analysis, compositional determination, anomeric configuration, type of glycosidic linkage type, and presence of substituents, it becomes

clear that other structural parameters, including molecular diameter and degree of polymerization, must be considered for functional studies. In fact, the conclusion that polysaccharide functions are influenced by these additional parameters was further supported by Cordero et al. (2011). Using static and dynamic light scattering, viscosity analysis, and high-resolution microscopy of *C. neoformans* polysaccharides, this study demonstrated that spatial conformation (branching) influences phagocytosis, nitric oxide production by macrophage-like cells, and susceptibility to reactive oxygen species, serology, and clearance during infection. These previously unexplored parameters can generate new insights, for example, on immunogenicity assays of polysaccharides, as well as their use in therapy or prevention of diseases. Studies in this area are still embryonic and, clearly, much remains to be discovered. For

conceptual validation, future studies must include evaluation of the relationship between immunoactivity and molecular dimensions of polysaccharides synthesized by other organisms, as well as of fungal glycans other than GXM and chitin.

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