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Cryptococcus neoformans galactoxylomannan is a potent negative immunomodulator, inspiring new approaches in anti-inflammatory immunotherapy

Cryptococcus neoformans is an opportunistic fungal pathogen responsible for life-threatening infections in immunocompromised individuals and occasionally in those with no known immune impairment. The fungus is endowed with several virulence factors, including capsular polysaccharides that play a key role in virulence. The capsule is composed of 90–95% glucuronoxylomannan (GXM), 5–8% galactoxylomannan (GalXM) and <1% mannoproteins. Capsular polysaccharides are shed into tissue where they produce many deleterious effects. Since GalXM has a smaller molecular mass, the molar concentration of GalXM in polysaccharide that is shed could exceed that of GXM in *C. neoformans* exopolysaccharides. Moreover, GalXM exhibits a number of unusual biologic properties both *in vitro* and *in vivo*. Here, we summarize the principal immunomodulatory effects of GalXM described during the last 20 years, particularly the mechanisms leading to induction of apoptosis in T lymphocytes, B lymphocytes and macrophages. Since the capacity of GalXM to induce widespread immune suppression is believed to contribute to the virulence of *C. neoformans*, this property might be exploited therapeutically to dampen the aberrant activation of immune cells during autoimmune disorders.

KEYWORDS: apoptosis ■ B cell ■ CD45 ■ galactoxylomannan ■ macrophage ■ proliferation ■ T cell

Cryptococcus neoformans is an opportunistic fungal pathogen with worldwide distribution that can cause life-threatening disease, primarily in immunocompromised hosts [1] including patients with advanced HIV infection [2], renal transplant recipients [3] and those undergoing immunosuppressive therapy [4]. *C. neoformans* is often found in soil contaminated with pigeon droppings [5]. The virulence factors of *C. neoformans* include the presence of a polysaccharide capsule and melanin production, as well as protease, phospholipase and urease activity [6–8]. The capsule is considered to be the major virulence factor and aspects related to its structure, synthesis and, particularly, its role as a virulence factor have been extensively described in a recent review [9]. Capsule synthesis depends on many factors, including the concentration of CO₂ and HCO₃⁻ [10], availability of iron [11,12], mammalian serum, diluted nutrients and mannitol [13–15]. In particular, high levels of CO₂ and iron chelators [12] favor capsule production [10]. The capsule contains two major polysaccharides, glucuronoxylomannan (GXM) and galactoxylomannan (GalXM). GXM and GalXM constitute around 90–95% and 5–8% of the total polysaccharide mass, respectively. Recent work has shown that the name GalXM is a misnomer since the polysaccharide is actually a

glucuronoxylomannogalactan [16]. However, we will continue to refer to it as GalXM to maintain the continuity of the scientific literature. In addition, a small proportion of mannoproteins (MPs) has been identified in the capsule (<1%). Traces of sialic acid have also been described, but the role of this acid in the capsule is unknown [17].

These polysaccharides are constitutively released by the cell into the surrounding medium environment and they can be isolated as exopolysaccharides by specific purification protocols [9]. Although historically the shed polysaccharide was thought to originate from the capsule, there is now considerable evidence that this material is different from the polysaccharide used in capsule construction [18], and that its release is a consequence of an active process. Capsular polysaccharides have a complex structure that has not yet been completely characterized. There is evidence that the capsule structure is highly variable, depending not only on the strain but also on the environment [9]. Moreover, changes in capsule structure have been documented during the course of infection [19] and during treatments with antibodies directed against cell wall components [20]. Regarding the variability of *C. neoformans*, it is now apparent that in certain patients the fungal population is heterogeneous, consisting of

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various combinations of strains with different mating types, serotypes, ploidies and genotypes. In one study, the presence of multiple varieties of *C. neoformans* (both serotypes A and D), genetically unrelated isolates of the same variety, and AD hybrid strains was documented in the same patient [9,21]. The possibility of mixed and/or evolving infections during cryptococcosis should therefore be considered when therapeutic strategies against this pathogen are developed.

C. neoformans strains have been classified into five different serotypes, A, B, C, D and AD, according to the reactivity of their capsule with different rabbit polyclonal sera. These classified serotypes include *C. neoformans* var. *grubii* (serotype A), *C. neoformans* var. *gattii* (serotypes B and C) and *C. neoformans* var. *neoformans* (serotypes D and AD). Serotype AD strains exhibited a mixed A and D restriction profile [22]. Recently, serotypes B and C have been proposed as a new species named *Cryptococcus gattii*, because they present significant genetic and biological differences from serotypes A and D [9,23].

GalXM structure & localization in the capsule

Galactoxylomannan constitutes approximately 8% of the capsular mass [24,25] and has an α -(1–6)-galactan backbone containing four potential short oligosaccharide branch structures. Historically, the GalXM backbone consists of galactopyranose and a small amount of galactofuranose [25]. The branches are 3-*O*-linked to the backbone and consist of an α -(1–3)-Man, α -(1–4)-Man, β -galactosidase trisaccharide with variable amounts of β -(1–2)- or β -(1–3)-xylose side groups [24–26]. Recent studies suggest that the structure is actually a glucuronoxylomannogalactan [16]. However, there appears to be tremendous variability in the molecule depending on the strain origin and growth conditions, and additional research into the structure will undoubtedly be necessary to understand the complexity of this molecule [27]. Compositional analysis of GalXM revealed that the molar percentages for GalXM were as follows: xylose 22%, mannose 29% and galactose 50% [25,28]. It has been reported that the GalXM from serotypes A, C and D all contained galactose, mannose and xylose, but with variable molar ratios, suggesting that there may be more than one GalXM entity. GalXMs are thought to be a group of complex, closely related polysaccharides [25,29].

Convincing evidence supports the theory that GalXM is significantly smaller than GXM (1.7×10^6 kDa), with an average mass of 1×10^5 kDa [26].

It is well known that all studies regarding GalXM have been performed using material obtained from nonencapsulated strains that failed to secrete GXM. This is due to the difficulty of separating GalXM from GXM in exopolysaccharide preparations and of yielding GalXM pure enough for structural studies.

The experiments to purify and characterize GalXM revealed that supernatant fractions derived from homogenization of cell walls of the acapsular strain cap67 contained both GalXM and MPs [9]. Indeed, neither GalXM nor MPs are believed to contribute to the formation of the cell wall matrix, since they are not covalently bound to glucans within the cell wall [29]. GalXM is mostly cell wall-associated [25,30] and can be separated from MPs using concanavalin A affinity chromatography, which retains MPs, while GalXM is found in the eluate [25,29]. Recently, it has been reported that only low concentrations of GalXM were detected in the capsule and associated with vesicles found in the capsule. This suggests that of the major polysaccharides, only GXM is an integral component of the capsule, while GalXM plays a role as an exopolysaccharide and does not have a role in the architecture of the capsule [31]. Accordingly, it is important to highlight that GalXM is a powerful immunomodulatory molecule, and investigations regarding GalXM should focus on its own intrinsic capacity to induce widespread dysregulation of the immune system.

GalXM regulation of T-cell response

Galactoxylomannan plays a crucial role in inhibiting T-cell response by suppressing T-cell activation and by inducing apoptosis [32–34].

Apoptosis is induced by a range of stimuli that activate two major cell death signaling pathways: extrinsic and intrinsic. The extrinsic pathway of apoptosis is triggered via the receptor-mediated apoptotic pathway when Fas is engaged by FasL, and this leads to the activation of caspase-8, which in turn activates the effector caspases-3, -6, and -7 to induce DNA fragmentation. The intrinsic pathway is induced by cellular stress with consequent activation of mitochondria, which subsequently releases the proapoptotic molecule cytochrome c that leads to activation of caspase-9 and its relative downstream effector caspases. Moreover, active caspase-8 can cleave the Bcl-2 family member Bid [35], with consequent

generation of a small fragment called truncated Bid (tBid); tBid inhibits the function of the anti-apoptotic protein Bcl-2, thereby leading to the activation of the intrinsic death pathway [36–39].

In studies performed using the Jurkat cell line and human CD3⁺ T cells, we obtained evidence that the interaction of GalXM with T cells induced Fas and FasL expression, with consequent activation of caspase-8. The analysis of the mechanism involved in the GalXM-mediated apoptotic effect revealed that both the extrinsic and intrinsic apoptotic pathways are activated leading to DNA fragmentation. In particular, after Fas/FasL interaction, caspase-8 activation initiates the death signal pathway directly by activating downstream caspases such as caspases-3, -6 and -7, and indirectly by affecting Bid, with subsequent activation of caspase-9 that promotes effector caspases-3, -6 and -7. This results in cross-talk between the extrinsic and intrinsic pathways, with consequent activation of caspase-9 (FIGURE 1) [32,33].

Recently, we also observed that GalXM regulation of T cells occurred via interaction with specific glyco-receptors such as CD7, CD43 and

CD45, expressed on the T-cell surface, which are normally involved in galectin-induced apoptosis [33]. The specific role of CD45 in GalXM-induced activated T-cell damage was investigated using BW5147 T-cell lymphoma CD45 wild-type and knockout. In wild-type cells expressing CD45, but not in knockout cells, GalXM treatment produced inhibitory effects including decrease of T-cell activation and induction of T-cell death [34]. CD45 is a type 1 transmembrane molecule found on the surface of all nucleated hematopoietic cells and their precursors, except for mature erythrocytes and platelets [40,41], and is expressed in various isoforms. Expression of different CD45 isoforms changes during T-cell activation, and 'naive' T cells switch from expressing high-molecular-weight (CD45RB) to low-molecular-weight CD45 (CD45RO) isoforms upon stimulation. CD45 has intrinsic tyrosine phosphatase activity, has been implicated in cell proliferation, signaling and differentiation and is associated with the B-cell receptor during signaling [42]. CD45 is a positive regulator of T-cell receptor (TCR) signaling and is essential for signal transduction

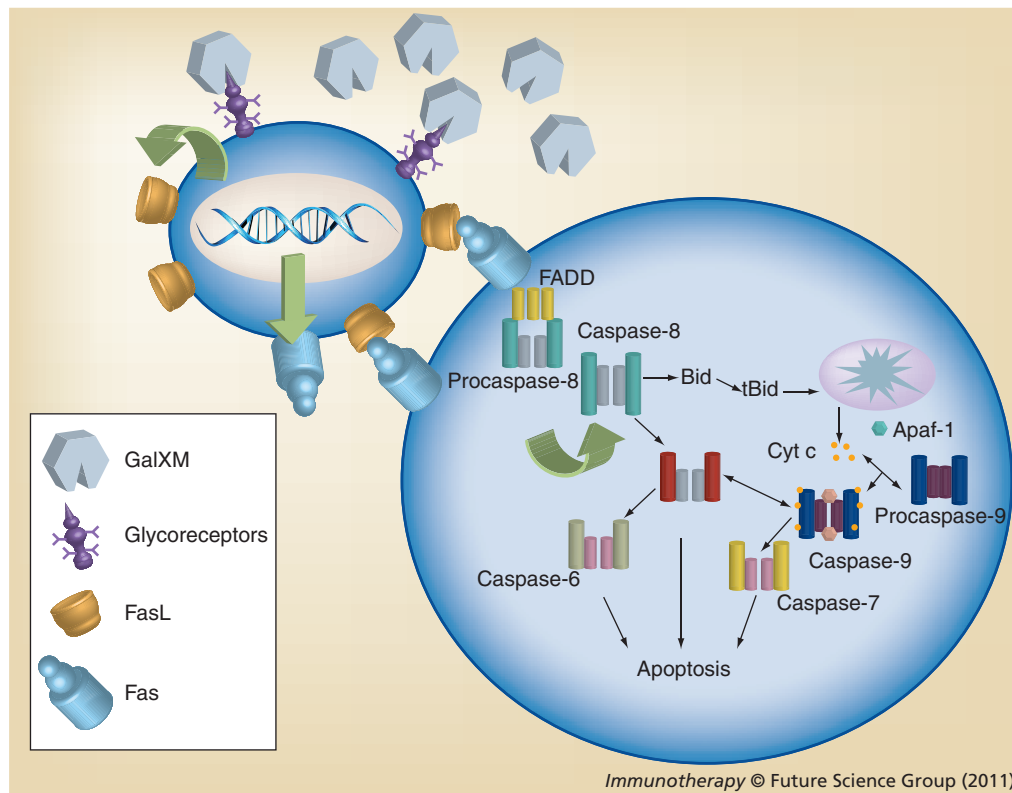


Figure 1. Galactoxylomannan-mediated T-cell death. GalXM is recognized by CD45 and elicits Fas/FasL upregulation. This effect leads to increases in Fas/FasL interaction, which induces apoptosis via activation of caspase-8. Caspase-8 triggers apoptosis directly via activation of effector caspases and indirectly via Bid cleavage and subsequent activation of caspase-9, which in turn activates the effector caspases and finally apoptosis. GalXM: Galactoxylomannan.; tBid: Truncated Bid.

after antigen stimulation [43,44]. In particular it is a membrane-associated tyrosine phosphatase that dephosphorylates Src-family kinases, which in T cells are predominantly the family members Lck and Fyn. Lck is a primary initiator of signal transduction upon TCR engagement, and the absence of Lck leads to a severe block in T-cell differentiation and profound impairment of T-cell activation [45]. Lck subsequently phosphorylates the immunoreceptor tyrosine-based activation motifs present in the ζ and CD3 ϵ , δ , and γ subunits of the TCR. Double-phosphorylated immunoreceptor tyrosine-based activation motifs promote the recruitment and subsequent activation of Zap70 protein tyrosine kinase. This results in T-cell activation with new gene transcription, cytoskeletal reorganization, cytokine production and proliferation [46,47].

Our studies have shown that GalXM-induced apoptosis [33,34] was mainly mediated via recognition of GalXM by CD7 and CD43 in human T cells [32,33], while in the Jurkat and T-cell lymphoma (BW5147) cell lines it was primarily mediated by its interaction with CD45 [33,34].

The molecular events ensuing after GalXM/CD45 association include the inhibition of CD45 phosphatase activity, through the downregulation of Lck activity, with consequent inhibition of Zap70 and T-cell proliferation, and induction of T-cell apoptosis.

Indeed, a relationship between Lck phosphorylation and apoptosis was evidenced by the fact that the induction of dephosphorylation of Lck resulted in inhibition of GalXM-induced apoptosis. This provided indirect evidence that Lck activity, and the subsequent signaling cascade, can influence T-cell apoptosis. In agreement with this hypothesis, recent results revealed a direct link between Lck and apoptosis, because Lck protects cells from glucocorticoid-induced apoptosis and its inhibition enhances sensitivity to dexamethasone [48]. However, the main mechanism of GalXM-induced apoptosis is related to upregulation of Fas. The precise mechanism that leads to Fas upregulation on T cells is unknown. However, it is plausible to envisage that the GalXM-mediated Lck inhibition could account for a mechanism that involves mitochondrial apoptosis signaling cascade [49]. The fact that GalXM-induced death receptor apoptosis cell signaling pathway is amplified by activation of the mitochondrial pathway supports this hypothesis [33].

Galactoxylomannan has also been shown to be involved in inhibition of T-cell proliferation [32,34] and was also able to suppress

peripheral blood mononuclear cell proliferation. This effect was associated with the increase of IFN- γ and IL-10 production [32]. We recently observed that GalXM-induced inhibitory effects were evident in activated T cells pretreated with monoclonal antibody to CD3 or with phytohemagglutinin (PHA). This activation involves, respectively, direct TCR stimulation [50] or CD45 activation via PHA stimulation. Accordingly, the effect of PHA activation on the phosphatase activity of CD45 has been shown [51]. The mechanism is mediated by GalXM/CD45 interaction that leads to inhibition of phosphatase activity with consequent inhibition of TCR-induced activation.

The inhibition of proliferation could be considered a consequence of GalXM-mediated T-cell apoptosis. Although we observed both effects, apoptosis of T cells and inhibition of T-cell proliferation, the exact contribution of their reciprocal regulation remains to be determined.

A model of the proposed mechanisms of inhibitory effects induced by GalXM through CD45 is proposed (FIGURE 2) [34].

Given that differential expression of CD45 splice variants has frequently been used to distinguish between 'naive' CD45RB and 'memory activated' CD45RO T cells [46], the finding that GalXM is able to induce biological effects, particularly in preactivated T cells, suggests that GalXM could preferentially bind to the hypoglycosylated, low-molecular-weight CD45 isoform (CD45RO). We interpret these findings as suggesting that the susceptibility of T cells to the inhibitory effect exerted by GalXM depends on their state of activation. This is supported by the observation that GalXM does not affect the biological function of unactivated T cells from healthy donors. However, we cannot exclude the idea that GalXM may affect naive T cells from patients who present T-cell-mediated inflammatory pathologies. This remarkable inhibitory activity suggests that GalXM could be exploited to dampen T-cell response during aberrant activation. Moreover, the interaction of GalXM with CD45 is a process that produces dramatic changes on the surface of T cells. There is a marked propensity of GalXM to cluster and segregate CD45 on T cells, and this occurs quite early after GalXM/T-cell association; it is possible that this segregation is regulated by attachment to the cytoskeleton through the linker protein fodrin [52]. However, we do not know the real consequences of this observed CD45 segregation and whether this phenomenon produces specific

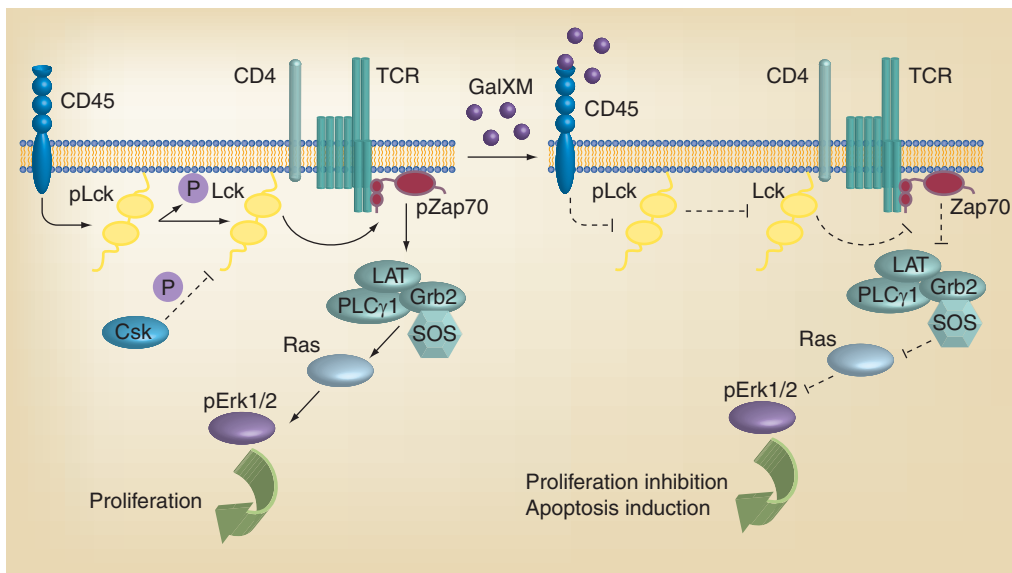


Figure 2. Effect of galactoxylomannan on BW5147 cells. GalXM induces immunosuppressive effects on T cells through Lck inactivation. These effects occur after GalXM association with CD45, which inhibits its dephosphatase activity. GalXM: Galactoxylomannan; TCR: T-cell receptor. Reproduced with permission from [34].

biological effects. It should also be taken into account that CD45 may be sequentially cleaved by serine/metalloproteinase and γ -secretase upon activation with fungal cell wall components leading to release of a fragment of the CD45 cytoplasmic tail (ct-CD45). Soluble ct-CD45 selectively binds to preactivated T cells and inhibits T-cell proliferation [53]. Thus, because GalXM is a fungal antigen [7], soluble ct-CD45 could be released in its presence, and this might represent an additional mechanism contributing to the inhibition of T-cell activation.

These results suggest that GalXM has a functional role in virulence by targeting human T cells and impairing specific T-cell responses, and that its mechanism may potentially be different from that of GXM [54].

GalXM regulation of macrophage activity

A recent paper showed that purified GalXM and GXM induced intense macrophage apoptosis mediated by Fas/FasL interaction, and that GalXM was more potent than GXM in inducing Fas. However, low doses of GalXM were sufficient to induce FasL expression and to block proliferation in RAW264.7 cells [55]. This study also provided evidence that intraperitoneal injection of GalXM or GXM in mice induced apoptosis of peritoneal macrophages and that FasL expression was necessary for the induction of macrophage apoptosis *in vivo*. The critical role of FasL expression was underlined by data showing that the

polysaccharide failed to induce apoptosis in macrophages from FasL-deficient mutant *gld* mice. These results demonstrated that FasL is required for apoptosis induction in macrophages both in *in vitro* and *in vivo* experimental systems.

Comparing the immunomodulatory effects of GXM and GalXM, the results provide strong evidence that GalXM is much more potent than GXM in inducing suppressive effects [55]. This is consistent with the current literature suggesting that GalXM is crucial for virulence. This theory is supported by the evidence that *C. neoformans* strains that do not produce GalXM, but are able to produce GXM as well as a large capsule, are unable to colonize the brain, while GXM-negative strains that produce GalXM can do so [56].

GalXM regulation of B-cell response

Very early studies using unfractionated capsular material of *C. neoformans* revealed that polysaccharide fractions had a marked propensity to induce immunological paralysis [57,58].

In a subsequent study, it was reported that the capsular polysaccharide induced a primary immunological response in mice as indicated by the increase in antibody level, but a subsequent booster with the polysaccharide induced a state of immunological unresponsiveness with diminution of antibody response [59].

In recent studies, the possibility of obtaining an antibody response to GalXM was investigated at different times after immunization with this compound. A modest amount of serum

antibodies reactive to GalXM regardless of immunization dose was observed. This humoral response was then monitored after a subsequent booster with GalXM. The results showed that antibody titers were reduced to levels that were no longer detectable [60].

In an attempt to increment antibody response, the immunization was performed with GalXM in a complete Freund's adjuvant emulsion, but this approach led to a low and transient antibody response. Another attempt to increment antibody response was made by generating a GalXM–protein conjugate using the protective antigen from *Bacillus anthracis*. Although modest titers of GalXM-binding antibodies were observed after initial immunization, the boosting of immunization was associated with a decrease in GalXM-specific titers. This was related to the ability of GalXM to suppress antibody-producing cells. Presumably, the abrogation of B-cell activity mirrored apoptosis induction by GalXM as reported for other cells, including T cells. In fact, the complete depletion of B cells producing antibodies to GalXM was avoided by administering a cocktail of general pan-caspase inhibitors [30]. Although Fas upregulation seems to be responsible for GalXM-induced apoptosis, high doses of the polysaccharide only modestly – not significantly – increased the expression of the Fas receptor. These results argue against a possible direct proapoptotic toxicity of GalXM on B cells and suggest that other cell types may be involved in the upregulation of the Fas receptor in B cells. Moreover, GalXM injection produced alterations in the splenic follicle morphology, and in the numbers and proportions of total B and T lymphocytes and macrophages in the spleen. Indeed, for both CD4⁺ and CD8⁺ T lymphocytes there was a decrease in the percentage of cells after the first injection of GalXM, but conversely an increase in the percentage of macrophages was observed.

Immunization with GalXM resulted in a dose-dependent global reduction of inflammatory cytokine expression. The cytokine array revealed that, in the spleen, the expression of the inflammatory cytokines decreased with prolonged exposure to GalXM. In particular, this decrease included IL-1 β and IL-12 production.

Recently, a further study by Chow *et al.* reports the generation of two GalXM conjugates with bovine serum albumin (BSA) and protective antigen of *B. anthracis* respectively, using 1-cyano-4-dimethylaminopyridinium tetrafluoroborate as the cyanating reagent [60]. The inactivity of early GalXM conjugates were clearly due to excess polysaccharide and/or abundant free,

unconjugated polysaccharide in the vaccine formulation. Free GalXM continued to mediate B-cell depletion and immunological paralysis. To optimize the vaccine efficiency, free GalXM was separated from the conjugated product, and this step elicited antibody responses against GalXM. The success of this conjugate vaccine in eliciting persistent antibody responses was attributed to the removal of free GalXM from the vaccine preparation, thus avoiding its deleterious effects on the host response [60]. The serum response to GalXM included both IgG and IgM, with IgG being the predominant isotype. When mice were challenged with *C. neoformans*, despite the presence of serum antibodies to this polysaccharide, the survival rate was similar regardless of the immunization state. Antibodies to GalXM elicited by the conjugate vaccine were not opsonic, and these vaccines, despite their high immunogenicity, did not appear to modify the course of experimental cryptococcal infection [60]. Overall, GalXM was able to elicit strong antibody responses when conjugated to a carrier protein, but these antibodies did not contribute to protection. In conclusion, the generation of a robust antibody response by using GalXM–protein conjugate was obtained, but this response was not effective in inducing protection against *C. neoformans* infection. This opens up new questions about the role of GalXM in the capsular material and the location of GalXM, which, being in the cell wall, is thus unlikely to be reached by specific antibodies. However, given the immunosuppressive effects exerted by GalXM, it should be interesting to evaluate whether the anti-GalXM antibody, even if not opsonic, can indeed block the interaction of GalXM with glyco-receptors that bring about many alterations in the biological function of immune cells.

Conclusion

Galactoxylomannan has generally been considered a minor component of *C. neoformans* capsular material and there are only a few reports on its immunoregulatory activity.

With this article, we have summarized the principal immunomodulatory effects of GalXM described during the last 20 years. Particularly, the most important effect of GalXM is the induction of apoptosis of T and B lymphocytes and macrophages; moreover, GalXM is able to exert its effects at low doses [32,33,55].

The main effect of GalXM on innate and adaptive immunity is related to its inhibitory activity and in particular to its ability to trigger apoptosis. Many questions need to be clarified, including the possible role of CD45 or other

cellular receptors in GalXM-induced inhibition of B-cell activity and, given the capacity of GalXM to upregulate Fas/FasL expression on immune cells, it should be of particular interest to define upstream and downstream signal transduction implied in this phenomenon. Another issue that should be unraveled is the set of molecular events leading to immunological paralysis, and whether the induction of immunosuppression and apoptosis are interdependent.

Future perspective

The *C. neoformans* capsule is widely acknowledged to be its key virulence factor, and studies performed on capsule components GXM, GalXM and MPs have provided important data delineating their immunoregulatory role. During the last 20 years, studies on the immunomodulatory effects of GalXM have clearly indicated that this polysaccharide is a potent negative regulator of T- and B-cell activity and macrophage function. The remarkable effects of GalXM on T cells have particular relevance for pathogenesis and raise new questions concerning the mechanism responsible for GalXM-induced T-cell apoptosis. It is noteworthy that certain capsular polysaccharides, which are considered T-cell-independent antigens, may be able to bind and directly affect T-cell function. For the first time, our studies show direct regulation of the biological function of T cells by a capsular polysaccharide. The specificity of GalXM effects is clearly demonstrated by the fact that very low doses of this polysaccharide are able to cause T-cell damage selectively through interaction with glycoreceptors such as CD45. Possible clinical use of this polysaccharide has been considered for the treatment of diseases mediated or aggravated by glycoreceptor activation, as well as in the treatment of autoimmune diseases in which aberrant CD45 expression has

been described (i.e., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and autoimmune hepatitis). However, the complexity of the native molecule suggests that this microbial product may be impractical for therapeutic use in itself. On the other hand, identification of the polysaccharide motifs that interact with the cellular receptor could result in the synthesis of oligosaccharides; this may greatly simplify the regulatory and pharmaceutical aspects involved in the translation of these findings into new immune therapies for autoimmune diseases. As with bioactive molecules, polysaccharide motifs may present some advantages over the native molecule owing to their small size, better tissue penetration, higher specificity and affinity for targets, and low systemic toxicity.

Remarkable advances are likely to occur in the field of new anti-inflammatory drug production during the next 10 years. Perhaps GalXM-based therapy will emerge with new anti-inflammatory drugs. The promising preliminary results obtained from the study of GalXM-induced immunosuppressive effects on T cells recovered from arthritis rheumatoid patients revealed the crucial role of this polysaccharide in the suppression of the aberrant inflammatory response.

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Executive summary

- Galactoxylomannan (GalXM) plays a crucial role in inhibiting T-cell response by suppressing T-cell activation and by inducing apoptosis.
- GalXM causes significant impairment of peripheral blood mononuclear cell proliferation and increases IFN- γ and IL-10 production.
- GalXM induces apoptosis in Jurkat and T cells, upregulates Fas/FasL expression, and activates the extrinsic and intrinsic apoptotic pathways. These effects seem to be mediated by the interaction between GalXM and the glycoreceptors CD7, CD43 and CD45.
- CD45 is the primary molecular target for GalXM-induced T-cell modulatory effects.
- GalXM-mediated T-cell immunoregulation requires the interaction of CD45 with protein tyrosine kinases such as Lck and Zap70.
- GalXM induces macrophage apoptosis and inhibition of RAW264.7 cell proliferation.
- GalXM immunization elicits a state of immunological paralysis in mice characterized by the disappearance of antibody-producing cells in the spleen. Presumably, the abrogation of B-cell activity was related to apoptosis induction by GalXM as reported for other cells, including T cells.
- The results demonstrate that GalXM could represent a negative regulator of activated T lymphocytes. In light of this, possible clinical use of GalXM could be considered for the treatment of diseases mediated or aggravated by glycoreceptor activation, and the treatment of autoimmune diseases in which aberrant CD45 expression has been described (i.e., rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and autoimmune hepatitis).

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