Mycopathologia (2012) 173:375–386
DOI 10.1007/s11046-011-9513-8

Capsular Material of *Cryptococcus neoformans*: Virulence and Much More

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Received: 14 July 2011 / Accepted: 28 November 2011 / Published online: 8 February 2012

Abstract The capsule is generally considered one of the more powerful virulence factors of microorganisms, driving research in the field of microbial pathogenesis and in the development of vaccines. *Cryptococcus neoformans* is unique among the most common human fungal pathogens in that it possesses a complex polysaccharide capsule. This review focuses on the *Cryptococcus neoformans* capsule from the viewpoint of fungal pathogenesis, and the effective immune response target of the capsule's main component, glucuronoxylomannan.

Keywords Capsular polysaccharides · *C. neoformans* · Monocytes/macrophages · Fc receptors · Signal transduction · Apoptosis

Introduction

Cryptococcus neoformans (*C. neoformans*) is an environmental opportunistic pathogenic fungus, responsible for serious infection in immunocompromised subjects, including patients with AIDS, transplantation recipients or other patients receiving immunosuppressive medication, and patients with hematological malignancies [1–3]. However, infection can also occur in subjects with a less severe level of immunosuppression, such as that caused by splenectomy [4], cirrhosis [5], necrotizing fasciitis [6] and even pregnancy [7, 8]. Infections including cryptococcal meningitis [9], cerebellar cryptococcoma [10], pneumonia and colonic cryptococcosis [11] can even occasionally occur in otherwise healthy individuals. The initial *C. neoformans* infection is acquired by inhalation of spores or desiccated fungal cells present in the environment. From the lungs, fungi may disseminate to other organs through blood circulation, after which they reach the central nervous system causing devastating meningoencephalitis. Virtually any site can be involved, in particular the liver [12], skin [13, 14], urinary tract [15], eyes [16] and joints [17].

The prominent virulence factor of *C. neoformans* is its polysaccharidic capsule, which is antiphagocytic, serves as an antioxidant and interferes with immunity. The capsule structure is highly variable; it undergoes changes in size and rearranges itself during budding and growth [18, 19]. On the basis of the reactivity of the capsule with different rabbit polyclonal sera, five different serotypes (A, B, C, D and AD) have been classified; *C. neoformans* var. *grubii* (serotype A), *C. neoformans* var. *gattii* (serotypes B and C) and *C. neoformans* var. *neoformans* (serotypes D and AD). Recently, serotypes B and C have been classified as

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belonging to a distinct species, *Cryptococcus gattii,* because they present significant genetic and biological differences when compared with serotypes A and D [20]. The *C. neoformans* polysaccharide capsule is a very dynamic structure. Change in capsule size is a typical feature of the various *C. neoformans* strains during interaction with the host and is regarded as an early morphologic response during infection. Capsule enlargement occurs a few hours after infection in murine models. It has also been observed during *C. neoformans* intracellular parasitism. In addition, during the course of infection, the immunogenic properties of the capsule can change. This phenomenon is considered an adaptation in order to permit survival of the fungus in the host [20]. The remarkable capacity of the capsule to undergo enlargement during infection is associated with cryptococcal virulence in the mammalian host [21]. Indeed, depending on the specific environmental conditions, the size of the capsule is highly variable, not only between strains, but also between individual cells. Several environmental conditions have been shown to induce capsular enlargement, including high CO_2 levels, low iron concentration, basic pH values and the presence of mammalian serum. It is not clear whether these factors induce capsule enlargement by different pathways or whether there is a common element that the cell can sense as a factor inducing capsule enlargement.

Recently, Chrisman et al. [22] reported that phospholipids trigger *Cryptococcus neoformans* capsular enlargement during interactions with amoebae and macrophages. In this study, it was evidenced that *C. neoformans* releases enzymes that damage the cell membrane of amoebae and macrophages, thus releasing phospholipids, possibly in combination with proteins. These phospholipids are then cleaved by phospholipase B, and their polar heads are in turn sensed by *C. neoformans* cells, triggering capsule enlargement and the formation of giant cells that can exceed the size of macrophages [23, 24]. Since capsule enlargement reduces the phagocytic efficacy of both amoebae and macrophages [25, 26], Chrisman et al. [22] proposed that this is a general cryptococcal defensive response when potential danger is sensed.

The *C. neoformans* capsule has three major components: two different polysaccharides, glucuronoxylomannan (GXM), around 90–95% of the mass, galactoxylomannan (GalXM), around 5–8% of the mass, and mannoproteins (MP), which are considered a minor capsular component around <1% of the mass. The capsular polysaccharides are constitutively released by the cell into the surrounding medium and environment, and they can be isolated as exopolysaccharides by specific purification protocols. It is not known whether the release of capsular material into the medium is an active phenomenon regulated by the cell, or whether it is just an unspecific shedding. It has been reported that patients with cryptococcosis showed high GXM concentrations reaching micrograms per milliliter in their serum and/or cerebrospinal fluid. In infected tissues of organs such as the spleen and liver [27, 28], local concentrations of GXM are similar to those observed in the serum [29]. GalXM is also shed during infection and is found in the body fluids of infected hosts [30].

GXM has a molecular weight that can range from 1,700 to 7,000 kDa, depending on the fungal strain. The basic structural unit of GXM is a tri-mannose repeat with a glucuronic acid residue in the first mannose. This structure is further modified in individual strains by the addition of xylose substitutions on the mannose backbone which can be *O*-acetylated at the carbon 6 of the mannosyl units [18, 31, 32]. The molar ratios of xylose, mannose and glucuronic acid residues vary depending on the serotype, with ratios 1:3:1, 2:3:1, 3:3:1 and 4:3:1 for serotypes D, A, B and C, respectively [31]. In contrast to bacterial polysaccharides, which have a single oligosaccharide repeating unit, GXM has at least six different repeating units found in various proportions in the various serotypes [33]. A seventh GXM repeating unit, called hexasaccharide 1 by Bacon et al. [34], was recently described by Nimrichter et al. [35], who characterized a substituted triad in GXM, which had previously only been described in a hypocapsular mutant [34]. In some *C. neoformans* strains, GXM is composed of a single repeating unit, whereas in other strains, the polysaccharide contains multiple units. To understand the localization of these capsular components, Jesus and co-workers [36] used specific antibodies (Abs) to each of the three components and observed their binding by immunofluorescence. The results obtained defined the distribution of GXM, GalXM and MP on the capsule for the first time. These results provide strong support for the view that capsule-associated GalXM and MP are probably materials in the process of transport to the extracellular space, while only GXM is an integral component of the capsule. The complexity of the

capsular polysaccharide structure and its immunoregulatory properties have recently been elucidated by Cordero et al. [37]. They demonstrated that cryptococcal capsular polysaccharides are branched and that the branch is an important parameter in determining their biological activity.

The Capsule Protects Fungal Cells

Many microorganisms possess capsules surrounding their cell body. Microbial capsules are usually composed of polysaccharides, although some organisms, like *Bacillus anthracis*, have capsules composed of polymerized D-glutamic acids. The capsule may be found in both Gram-negative bacteria, such as *Haemophilus influenzae*, *Escherichia coli*, *Neisseria meningitidis* and *Salmonella typhi,* and Gram-positive bacteria, such as Staphylococci and Streptococci. It is an important virulence factor with antiphagocytic and antibactericidal properties, and it enhances microbial survival during invasion of the host.

Although capsules are commonly found in bacteria, there are few encapsulated fungal species. The best known fungal capsule is that of *Cryptococcus neoformans*. The primary function of this structure is related to survival in the environment, since it provides substantial protection against desiccation. Moreover, it is essential for the formation of the cryptoccocal biofilm, which is an assemblage of microbial cells enclosed in a matrix of primarily polysaccharidic material. The *C. neoformans* capsule has some functional similarities to the capsules of bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* in that: (1) it is composed of polysaccharides; (2) it is antiphagocytic, and antibodies to capsular polysaccharides are protective; (3) its polysaccharides display a repeating epitope structure, have a high molecular weight and resist degradation in vivo. These properties are characteristic of thymus-independent type 2 antigens [38]. The capsule plays a crucial role in the pathogenesis of cryptococcosis, since acapsular mutants do not produce disease in murine models [39]. A definitive experiment establishing the capsule as a virulence factor was accomplished when acapsular mutants were created and shown to be significantly less virulent than wild-type or capsule-reconstituted strains [40]. In general, the virulence of the capsule is thought to prevent phagocytosis of macrophages and amoeboid environmental predators [22].

Cryptococcus neoformans is regarded as a facultative intracellular pathogen, and it has been demonstrated that the capsule is critical in cryptococcal pathogenesis [41–44]. Indeed, it has been shown that acapsular mutants cannot replicate inside phagocytic cells [43], indicating that the capsule plays a key role in intracellular parasitism. Once internalized, *C. neoformans* is able to overcome the attack by way of intracellular replication and cytoplasmic accumulation of GXM-containing vesicles [44], which become permeable during the course of infection, causing an accumulation of intracellular polysaccharides [45] with consequent multiple alterations of macrophage functionality. For example, once phagocytosed, encapsulated cells do not induce nitric oxide synthase (NOS), a phenomenon that does occur when acapsular mutants are ingested [46]. Recently, it has been demonstrated that the capsule confers protection against reactive oxygen species, important antifungal molecules produced during phagocytosis. Capsule enlargement also increases the survival of fungal cells in the presence of these radicals and of antifungal molecules such as defensins and amphotericin B [25]. These results indicate mechanisms by which *C. neoformans* can evade killing inside the phagolysosome and are in agreement with published data on *Klebsiella pneumoniae* [47] which demonstrate that the bacterial capsule impedes the expression of beta-defensins by epithelial cells and facilitates pathogen survival in the hostile environment of the lung [47, 48]. The accumulation of encapsulated cells within macrophages ultimately leads to bursting of the host macrophage or extrusion of the cryptococcal phagosome [49]. Recent data demonstrated that trapped *C. neoformans* in the infected macrophage can exit the host and immediately enter another uninfected macrophage without being exposed to the extracellular environment [50]. Once it escapes the host defense system in the lung, *Cryptococcus* disseminates into other organs, such as the brain. The capsule also plays an important role in extrapulmonary dissemination; in fact acapsular mutants show impaired dissemination to the brain [51]. Although this effect could be due to lack of virulence of specific strains and rapid clearance by the immune system, it has been demonstrated that *C. neoformans* is able to modulate its capsule structure and size during infection, allowing for adaptation to

different environments, thus facilitating the invasion of different tissues, especially the brain [52]. During the course of infection and dissemination, *C. neoformans* must cross epithelial and endothelial barriers. It has been demonstrated that *C. neoformans* can bind to epithelial cells [53], and Barbosa et al. [54, 55] showed that the capsule contributes to the binding of *C. neoformans* to human alveolar epithelial cells [55] by interaction with CD14 [54]. This interaction resulted in a decreased viability of epithelial cells. *C. neoformans* can also bind to endothelial cells, but the role of the capsule in this phenomenon is not clear. Fungal binding to endothelial cells occurs both with encapsulated and acapsular strains, although binding, and transcytosis, was more efficient with encapsulated strains [56]. In agreement with these results are the findings of Chang et al. [57], who identified a *C. neoformans* gene, *CPS1,* which causes alterations in ultrastructures between the cell wall and the capsule and regulates the association of *C. neoformans* and brain microvascular endothelial cells. Invasion of the brain by *Cryptococcus* initiates with mechanical trapping of the fungus in the postcapillary vessels followed by early endothelial capillary damage and fungal proliferation, and then seeding of the meningeal spaces. This process is believed to occur through the blood–brain barrier in the cortical capillary. Three ways of transmigration across the blood–brain barrier have been proposed: (1) transcellular passing through endothelial cells [58]; (2) a paracellular route between the endothelial cells; (3) a 'Trojan horse' phenomenon whereby monocytes act as the horse carrying the *C. neoformans* through the vessels [59].

The Capsule and Its Principal Component, GXM, Induce Immunomodulation

During *C. neoformans* infection, the expression of a large number of immune mediators are modulated by encapsulation of *C. neoformans* and by the GXM released [60, 61], producing a suppression of the immune response that contributes to cryptococcosis pathogenesis. The outcome of the interaction between *C. neoformans* and monocytes differs depending on whether the yeast cell has a capsule or not. Acapsular strains elicited higher levels of certain pro-inflammatory cytokines secreted by monocytes, such as TNF-α, IL-1β, IL-12 and IFN-γ [62, 63], than encapsulated *C. neoformans* did. In contrast, encapsulated fungal cells induced the production of a large quantity of anti-inflammatory cytokines, such as IL-10, by human monocytes [63, 64]. Many effects of the capsular polysaccharide are mediated by GXM, as demonstrated by the fact that addition of GXM to an acapsular strain produces strong immunosuppressive effects [61].

Compelling evidence indicates that *C. neoformans* encapsulation is associated with reduced antigen presentation by macrophages [65] and that GXM inhibits antigen presentation in monocytes/macrophages [66]. This inhibition is dependent on an increase in IL-10 levels, resulting in a significant reduction in MHC class II molecules. The capsular polysaccharide also interferes with the normal function of dendritic cells, which are professional antigen-presenting cells needed for initiation of T cell mediated responses. Primary dendritic cells phagocytose *C. neoformans* via mannose receptors and Fcgamma receptor II [67]. Acapsular *C. neoformans* mutants are rapidly ingested by dendritic cells, with consequent up-regulation of maturation markers, such as MHCI and II, CD40 and CD83 [68]. This maturation is not observed when dendritic cells are exposed to encapsulated cells or purified GXM [68]. In addition, the capsule was a poor stimulator of the expression of co-stimulatory molecules such as B7-1 (CD80) and B7-2 (CD86) on the surface of antigen-presenting cells (APC) [61] and was able to induce the expression of CTLA-4 on T cells [69]. These effects lead to a reduction of T cell proliferation [66] and to a dominant Th2 response [70].

The *C. neoformans* capsule, as well as purified GXM, also modulates the functionality of peripheral neutrophils by inducing the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-8 [71]. However, this effect is not the result of a direct interaction of GXM with neutrophils, but rather of GXM-induced complement activation [72, 73].

It has been brought to light that the capsule of *C. neoformans,* and particularly GXM, limits the infiltration of inflammatory cells observed during cryptococcal infections [74–76]. GXM has been shown to interfere with the migration of phagocytes to sites of inflammation by regulating both chemokinesis [77, 78] and leukocyte adhesion to the endothelium. In agreement with this, it has also been shown to modulate the expression of adhesion molecules

L-selectin and CD18 on the surface of leucocytes [79–81]. However, the role of CD18 seems to be marginal in this process. A subsequent paper showed that GXM interferes with firm neutrophil adhesion to the endothelium in a static adhesion model, presumably by interference with E-selectin binding pathways and not by CD18 binding or L-selectin shedding [82].

Recently, microbial polysaccharides from bacteria or fungi have been found to exert profound effects on the regulation of immune responses during the progression of infectious diseases. Studies have begun to define structural aspects of these molecules that govern their function and their interaction with cells of the host immune system. Some of these have received attention, such as curdlan, which shows anti-tumor and anti-viral activity [83]. Hence, many microbial compounds are now classified as immunomodulators or biological response modifiers [84].

In recent years, it has been demonstrated that GXM is able to modulate the innate and adaptive immune response through multi-faceted mechanisms of immunosuppression. In our experimental system, we observed that it can affect the immune response in different ways. The innate response is affected directly because the exopolysaccharide is recognized by neutrophils [80], monocytes, macrophages [85–87] and dendritic cells [68]. Indirectly, the adaptive response is affected as well, because even though GXM is apparently unable to bind to T lymphocytes, the suppression of the latter is mediated by antigen-presenting cells [60].

GXM Regulates the Innate Response

GXM directly affects multiple functions of innate immunity cells by influencing the biological activity of monocytes/macrophages, neutrophils and dendritic cells (Table 1). Monocytes/macrophages are the cells predominantly responsible for the capture and internalization of GXM by multiple cellular receptors such as TLR4, TLR2, CD14, CD18 and FcγRIIB, which is the main receptor involved in macrophage uptake [87, 88].

Accumulating within the macrophages, GXM produces primarily: (1) disregulation of pro-inflammatory and anti-inflammatory cytokine secretion [62, 64, 89]; (2) reduction of the APC function [87]; and (3) induction of FasL surface expression [90, 91]. Regarding the effect on cytokine production, we demonstrated that in both in vitro and in vivo experimental models, this polysaccharide produces a reduction of pro-inflammatory cytokines and an enhancement of anti-inflammatory cytokine production. In particular, in vitro GXM produces a down-regulation of TNF-α and IL-1β [62], triggered in response to various stimuli such as LPS, and an induction of IL-10 [87, 89], a potent anti-inflammatory cytokine. In addition, it inhibits APC secretion of IL-12, a critical cytokine that drives the protective response against a wide variety of microorganisms [89, 92]. Recently, in an in vivo animal model for rheumatoid arthritis (collagen type II-induced arthritis, CIA), we showed that GXM produces a drastic decrease of TNF-α, IL-1β, IL-6 and IL-17, a cytokine marker of Th17 cells which has a prominent role in the pathogenesis of human rheumatoid arthritis [93]. Concurrently, a beneficial effect on the arthritic symptoms was evidenced. This benefit was also accompanied by an increase in IL-10 production which in turn likely contributed to dampening the production of pro-inflammatory cytokines, particularly TNF [94].

Soluble GXM, like the GXM present in the *C. neoformans* capsule, influences the function of APC and of T cells responding to them [60]. The monocyte—macrophage cell targets of GXM show a prompt and long lasting up-regulation of the death receptor FasL, which in turn induces apoptosis of activated T cells and Jurkat T cells via the FasL/Fas pathway [90, 95]. Recently, it has also been demonstrated that GXM can induce apoptosis of macrophages through a mechanism involving an increase in both Fas and FasL in the phagocytic cells [91], or by inducing cytokine-inducible NOS expression and NO in a caspase independent pathway [96].

Many, if not all, GXM-mediated suppressive effects appear to be directly consequent to the interaction of the polysaccharide with inhibitory immune receptors such as FcγRIIB. This molecule presents a tyrosine-based inhibitory motif (ITIM) in its cytoplasmatic region that associates with and activates the Src homology 2 domain-containing inositol phosphatase (SHIP). This induces the cleavage of phosphatidylinositol triphosphate (PIP3) to phosphatidylinositol biphosphate (PIP2), with consequent inhibition of calcium mobilization and mitogen-activated protein kinase activation. [97, 98]. GXM-FcγRIIB interaction is responsible for:

Table 1 GXM: effect on innate immunity

GXM effects	References
IL-10 increase	Vecchiarelli et al. [64]
	Chiapello et al. [106]
	Mariano Andrade et al. [107]
	Tissi et al. [108]
	Monari et al. [93]
TGF-β increase	Liu et al. [105]
TNF-α, IL-1 and IL-12 decrease	Vecchiarelli et al. [62]
	Retini et al. [109]
	Monari et al. [93]
MHC class II decrease	Monari et al. [87]
CD40 and CD86 increase	Monari et al. [87]
FasL increase	Monari et al. [90]
	Villena et al. [91]
Apoptosis induction	Villena et al. [91]
	Chiapello et al. [96]
MIP-1α and MIP-2 suppression	Tissi et al. [108]
Interference with dendritic cell maturation	Vecchiarelli et al. [68]
Promotion of tolerogenic dendritic cells	Liu et al. [105]

(1) the reduction of NFkB transcriptional activation and consequent negative regulation of some pro-inflammatory cytokines, such as TNF-α and IL-1β [88]; (2) the induction of potent anti-inflammatory cytokines such as IL-10 [88]; (3) the up-regulation of FasL on the macrophage surface with consequent induction of T cell apoptosis via the FasL/Fas pathway [99].

It has been demonstrated that multiple receptors that bind to GXM, such as TLR-4, CD14 and CD18, are involved in FasL up-regulation [90]. We recently showed that the mechanism controlling FasL up-regulation is principally ascribable to GXM/FcγRIIB interaction, and it is mediated by activation of JNK, p38 and c-Jun [99]. GXM induces JNK and p-38 MAPK activation simultaneously, but through different transduction pathways. Indeed, the up-regulation of p-JNK was completely blocked by inhibiting the interaction of GXM with FcγRIIB, whereas the up-regulation of p38 was inhibited, but not completely blocked. So we cannot exclude the possibility that other receptors exploited by GXM might participate in the activation of p38. It is possible that GXM might induce FasL up-regulation by JNK activation following GXM interaction with FcγRIIB, and by p38 activation following GXM interaction not only with FcγRIIB, but also with TLR-4, CD14 and CD18.

The final outcome is up-regulation of FasL and consequent T cell apoptosis, which is significantly inhibited in the presence of antibody to FcγRIIB, as well as in the presence of JNK or p38 MAPK inhibitors. A schematic representation of this pathway has been reported in Fig. 1.

GXM Regulates the Adaptive Response

Purified GXM exerts a series of immunosuppressive effects on the T cell response (Table 2), the most important being the reduction of T cell proliferation, as a consequence of its interaction with APC. In our experimental system, GXM appears unable to bind to T cells, in contrast with data reported in another study [100]. This apparent discrepancy could be related to the different doses of GXM used, as 200 μg/ml was used in our system, while 500 μg/ml was used in the other study. We demonstrated that negative regulation of the T cell function derives from GXM interaction with monocytes/macrophages that take up and process GXM. This leads, through cell-to-cell contact or via release of soluble factors, to inhibition of Th1, Th17 and DTH response and to induction of T cell apoptosis.

Apoptosis is a fundamental biological mechanism adopted by nearly all types of tissues and cells. It is essential to embryogenesis, tissue renewal, receptor repertoire selection and immune regulation. Altered apoptosis is associated with many diseases. There are three major pathways of apoptosis-associated caspase activation: the death receptor pathway, the mitochondrial/apoptosome pathway and the cytotoxic T lymphocyte/natural killer-derived granzyme B-dependent pathway [101, 102].

GXM-mediated apoptosis was first described in rat lymphocytes [103]. This phenomenon was first observed in an in vitro experimental system and in experimental cryptococcosis, but a similar finding was observed when rats were treated with purified GXM [104]. In addition, this phenomenon was accompanied by a decrease of IL-2 and IFN-γ production and by an increase of IL-10 production.

We demonstrated that GXM induction of T cell apoptosis starts early and is long lasting. In general, the interaction between Fas and FasL results in the

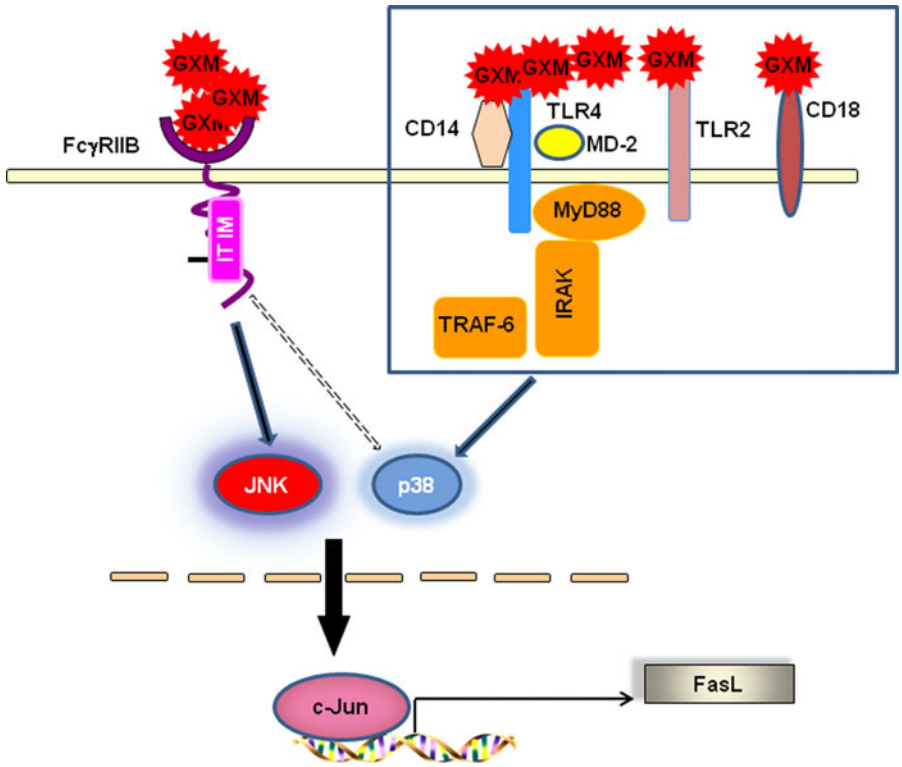

Fig. 1 Signal pathway of GXM-induced FasL up-regulation

Table 2 GXM: effect on adaptive immunity

GXM effects	References
DTH regulation	Blackstock and Casadevall [110]
	Chiapello et al. [104]
Lymphoproliferation inhibition	Chiapello et al. [106]
	Chiapello et al. [104]
	Monari et al. [60]
Th1 response decrease	Retini et al. [109]
Apoptosis increase	Chiapello et al. [104]
	Monari et al. [90], Monari et al. [95]
IL-2 suppression	Chiapello et al. [104]
IL-17A suppression	Monari et al. [93]
Lymphocyte apoptosis increase	Chiapello et al. [103]
	Monari et al. [90]
	Monari et al. [95]
Treg generation	Liu et al. [105]
IL-4 increase	Mariano Andrade et al. [107]
IFN-γ decrease	Mariano Andrade et al. [107]
	Chiapello et al. [104]

formation of the death-inducing signaling complex (DISC) with consequent activation of caspase-8. In some types of cells (type I), the execution of apoptosis is triggered by caspase-8 that directly activates other members of the caspase family. In other types of cells (type II), the Fas-DISC starts a feedback loop that spirals into increasing release of pro-apoptotic factors from mitochondria, amplifying the activation of caspase-8. In our experimental system, both pathways are active: in particular, the activation of the extrinsic pathway via the death receptor triggers the activation of the mitochondrial pathway of apoptosis-inducing cell death. Therefore, GXM activates both pathways in one single cell involving cross-talk between the extrinsic and intrinsic pathways [95].

Recently, it has been demonstrated that GXM is able to suppress the T cell response by promoting the generation of antigen-specific T regulatory cells (Tregs), which play a critical role in the maintenance of immune tolerance in the body. GXM-pulsed DC showed activation of FcγRIIB, SHIP-1 and c-Jun, followed by an increased production of TGF-β, a crucial cytokine for Treg generation. Pre-treatment of human dendritic cells with RNAi to knock down the

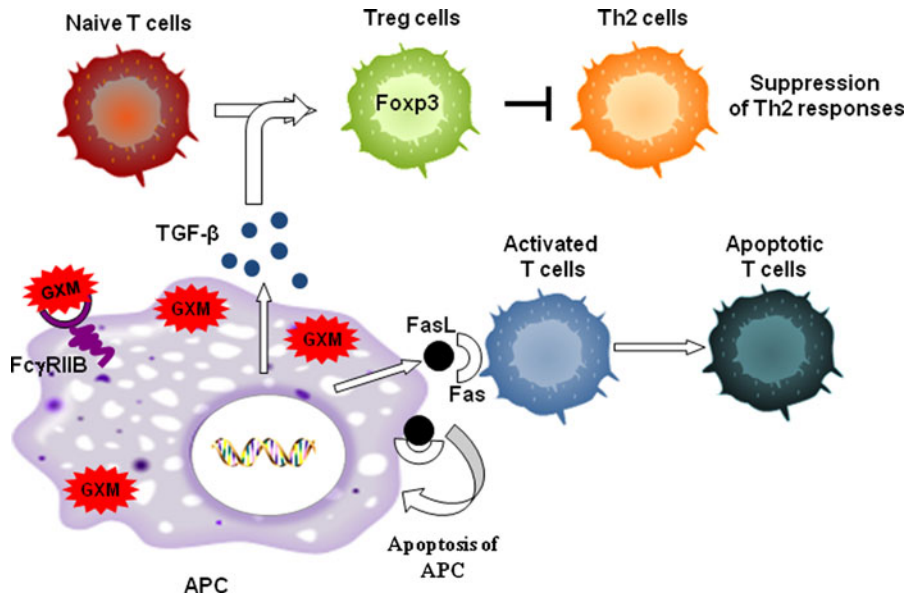

Fig. 2 Mechanisms of GXM inducing suppression of T cell response

genes of FcγRIIB, SHIP-1 or c-Jun abolished the increase in TGF-β promoter activation. [105]. A schematic representation of GXM driving the generation of the T cell response is reported in Fig. 2.

Conclusion

The capsule of *C. neoformans* and its most important component, GXM, are widely acknowledged to be indispensable virulence factors and continue to be the object of much investigative attention in the cryptococcal field. A comprehensive approach to identifying the multifaceted aspects of this key virulence factor could help to elucidate the complex network that explains the variation in capsule enlargement, the role of capsular branched polymers and the damage associated with suppression of the host immune response.

At present, there is a good understanding of the various mechanisms by which GXM contributes to virulence. This polysaccharide appears to be the main factor responsible for suppression of the protective response during cryptococcosis, through inhibition of both the innate and adaptive immune response. The manipulation of natural immune cells, which are the main target of GXM, may be beneficial in compensating for the immunosuppressive properties of GXM.

Acknowledgments This study was funded by the European Commission, FINSysB Marie Curie Initial Training 16 Network: PITN-GA-2008-214004, and the Fondazione Cassa di Risparmio di Perugia: 2010.011.0398. We thank Thomas Kozel, from the School of Medicine of the University of Nevada, USA, for supplying us with GXM. We thank Catherine Macpherson for editorial assistance.

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