Infection caused by *Aspergillus fumigatus* remains a major therapeutic challenge in immunocompromised individuals. Innate immunity represents the first line of defense against pathogens. In the last 20 years, several proteins belonging to this arm of the immune system have been characterized as being endowed with antifungal activity. Among these, the prototype long pentraxin PTX3 has been identified as a non-redundant protective factor against infections caused by *A. fumigatus*. A number of relevant animal models of invasive aspergillosis have indicated that PTX3 exerts its protective activity in several conditions of immunosuppression. In this article, we review the current understanding of PTX3 mechanisms of action that might be of help in further exploration of the pharmacological activity of this protein against *A. fumigatus*.

**Keywords**  Infection, innate immunity, pentraxin 3

**Introduction**

Invasive pulmonary aspergillosis (IPA) is emerging as a leading cause of morbidity and mortality in immunocompromised individuals and is particularly frequent among patients who undergo organ or bone marrow transplantation [1–3]. Major shortcomings in the clinical management of this type of infection include difficulties in establishing a definitive diagnosis, partial efficacy of current treatments, antifungal drug resistance, and side-effects to antifungal drug [4].

Recognition of *Aspergillus fumigatus* by the innate immune system occurs either by soluble or cellular receptors, known as pattern recognition receptors (PRRs), which detect specific pathogen-associated molecular patterns (PAMPs) on the surface of *A. fumigatus* conidia and hyphae [5,6]. In the last decade, in spite of our increased understanding of the complex network of molecular interactions between microbes and PRRs, the Mannose Binding Lectin (MBL) is the only protein of this superfamily that has entered clinical trial as substitutive therapy to counteract high susceptibility to infections in subjects with polymorphisms of MBL gene associated to a functional deficiency of the protein [7–9].

PTX3 is a multimeric glycoprotein expressed by a variety of cell types upon primary inflammatory stimuli such as those mediated by IL-1β, TNFα and agonists of Toll-like receptor family (TLRs) [10–15]. Among soluble receptors of the innate immunity, PTX3 holds new promise as a potential treatment for IPA. This protein has shown to be a non-redundant factor in host resistance to aspergillosis and it has been used successfully in a number of clinically relevant animal models of IPA [16–19]. The aim of this review is to shed light on our current understanding of PTX3 protective activity against *A. fumigatus*, which might direct non-clinical studies in the near future.

**Innate immunity receptors**

The pathogenicity of a microorganism depends on the number and the nature of the interactions it can establish with the host. *Aspergillus* species, including *A. fumigatus*, *A. niger* and *A. flavus*, are ubiquitous saprophytes able to colonize several ecological niches, particularly soil and organic debris [20]. As in other fungi, *A. fumigatus* has a cell wall which is predominantly composed of carbohydrate
polymers interspersed with glycoproteins [21]. Three major components compose the cell wall of *A. fumigatus*: β-glucan (glucose polymer), chitin (N-acetylglucosamine polymer) and mannan (mannose polymer). Several morphological changes in the fungal cells characterize the progression of *A. fumigatus* infection. Four maturation morphotypes are clearly recognizable, these are resting, swollen, and germinating conidia (or germ tubes), and the hyphae. Each morphotype is accompanied by a modification of the general structure of the cell wall with a different organization of the carbohydrate components [22].

Epidemiological studies have shown that humans can inhale an average of 400–1,000 *Aspergillus* conidia per day [23,24]. In mammals, a number of natural immunity cells located on the respiratory mucosa, such as dendritic cells (DCs), macrophages (MOΦ), and neutrophils, are involved in conferring protection against *A. fumigatus* infection [25,26]. The ability of these cells to interact with this fungus is mediated by membrane-associated or soluble PRRs [5,6] (Table 1). The main function of the interaction between PRRs and the fungus is to mediate clearance of conidia from the airway by promoting engulfment by phagocytes and the activation of an adaptive immune response [27–31].

It has been shown recently that the surface of dormant conidia (the inhaled ones) is layered with a high hydrophobic protein, named RodA, which is able to prevent host’s immune system activation [32]. The occurrence of RodA protein on the conidial surface might have two major implications. It might explain why daily inhaled conidia do not trigger a chronic inflammatory response to this fungus and it might represent a way for *A. fumigatus* to escape the host defence until conditions are suitable for its germination. However, what remains to be determined is whether the lack of immune response is dependent on failure of dormant conidia recognition by any PRRs or whether a specific PRR is actually able to mediate conidia clearance thus dampening the inflammatory response.

A direct binding to the fungus has been shown for some of the PRRs of *A. fumigatus*, while for other proteins their relationship with the fungus was inferred by their ability to promote cellular responses such as cytokine release and phagocytosis (Table 1). Among cell-associated receptors of *A. fumigatus*, DC-SIGN and Dectin-1 have shown direct interaction with the fungus and discrimination among different maturation morphotypes [33,34]. Dectin-1 has been shown to bind to swollen, germinating conidia and to hyphae. In contrast, conidia but not hyphae appear to be the only target of DC-SIGN. Among the soluble receptors of *A. fumigatus*, Surfactant Protein-A (SP-A), Surfactant Protein-D (SP-D) [35,36] and Mannose binding lectin (MBL) [37] (members of the collectin family) as well as the C reactive protein (CRP) [38,39] and PTX3 [17] (belonging to the pentraxin family) have been shown to establish direct interaction with the fungus. Most of the studies have shown interaction of all these proteins with conidia although they did not clarify which maturation stage these proteins interact with. It is relevant that PTX3 was shown to recognize conidia but not hyphae [17]. Clear evidence was provided for direct binding of MBL to *A. fumigatus* conidia, and only indirect evidence showed that complement deposition on hyphae surface was enhanced in the presence of MBL [37].

The membrane-associated proteins TLR2 and TLR4 have been implicated as important components of the initial host immune response to fungal pathogens [40,41]. Nevertheless, the role that these PRRs have in infection caused by *A. fumigatus* seems to be secondary to other

### Table 1 *Aspergillus fumigatus* pattern recognition receptors’ general features.

<table>
<thead>
<tr>
<th>PRR</th>
<th>KO phenotype</th>
<th>Recognized morphotype</th>
<th>Human polymorphisms&lt;sup&gt;c&lt;/sup&gt;</th>
<th>PAMP</th>
<th>Reference</th>
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<td></td>
<td></td>
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<td>rs36203921: 1011 A/G [intron]</td>
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<tr>
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<td>unknown</td>
<td>[35,36,80]</td>
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<td></td>
<td>rs17886395: 1649 C/G [91A/P]</td>
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<tr>
<td>SP-D</td>
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<td>Galactomannan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>[17]</td>
</tr>
<tr>
<td>CRP</td>
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<td>unknown</td>
<td>Galactomannan&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>unknown</td>
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<td>unknown</td>
<td>[40,41]</td>
</tr>
<tr>
<td>TLR4</td>
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<td>unknown</td>
<td>[40,41,45]</td>
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</table>

<sup>S</sup>, high susceptibility to *A. fumigatus* infection; <sup>S</sup><sup>c</sup>, high susceptibility evaluated on mice previously immunosuppressed; <sup>R</sup>, resistance to *A. fumigatus* infection; <sup>c</sup>evaluated only by competition assay; <sup>d</sup>polymorphisms associated to *A. fumigatus*-caused diseases; <sup>d</sup>no direct evidence of binding; ND, not determined.
proteins that directly interact with the fungus. Cooperation between Dectin-1 and TLR2 in fungus recognition provides a clear evidence of this concept [42,43]. Although no direct binding evidence of TLR2 and TLR4 to A. fumigatus was provided [41], these two type I transmembrane receptors are able to discriminate between conidia and hyphae [44]. Both conidia and hyphae of A. fumigatus stimulate cytokine production in macrophages through TLR2, whereas only conidia are able to stimulate these cells by TLR4.

Signalling through TLR2 and TLR4 is essential to promote neutrophil fungicidal activity [41]. However, only TLR4-deficient mice have a phenotype of severe susceptibility to this fungal infection while TLR2-deficient mice are only partially affected by this type of infection [40]. Consistent with a role of TLR4 on fungal resistance is the recent finding that a human polymorphism in the ectodomain of the TLR4 (Asp299Gly) is associated with chronic otitis media [45].

All of the above-mentioned receptors of A. fumigatus are variably expressed by cells that compose the surface of the respiratory mucosa, which is the primary site of contact between A. fumigatus and the human host [46]. Whether a hierarchical order exists in the spatial and temporal way each receptor interacts with the fungus or whether some level of cooperation takes place between these receptors, still remains to be fully elucidated.

**PTX3 mechanism of action**

The phenotype of PTX3 gene-targeted mice has shown that the protein plays two major functions: it is protective against some types of harmful microorganisms, and it is required during ovulation for the oocytes to become fertilized [17,47–49]. The mechanism proposed for a PTX3 protective effect against some types of pathogens is that the protein may act as an opsonin. Herein, we present the current understanding on the role of PTX3 as an opsonin with reference to the activity of the protein in protecting against the infection caused by A. fumigatus.

**Recognition of A. fumigatus by PTX3**

PTX3 binds to conidia but not to hyphae of A. fumigatus [17]. PTX3 also recognizes other Aspergillus species such as A. niger and A. flavus [Bozza et al. unpublished data]. It is unknown whether PTX3 recognizes all the conidial morphotypes (dormant, swollen and germinating) or only one or two of them. Galactomannan was indicated as a potential PAMP recognized by PTX3 since an excess of galactomannan inhibited the protein binding to conidia [17]. However, galactomannan is also expressed on the fungal cell wall of hyphae, thus suggesting that the sugar might be masked to PTX3 on hyphae cell wall or that some other molecular component of conidia surface might be required for an effective PTX3 binding.

PTX3 is traditionally depicted as composed of an N-terminal unrelated domain and a C-terminal domain, also referred to as pentraxin domain because of the sequence similarity with that of short pentraxins CRP and SAP [50]. The protein is composed of eight subunits linked by disulfide bounds and organized into two oppositely oriented tetramers [12]. PTX3 binding to conidia is mediated by N-terminal domain of the protein [51]. However, this domain is unable by itself to mediate recognition and phagocytosis by neutrophils and macrophages, a function that likely requires the C-terminal domain.

**PTX3-mediated phagocytosis**

PTX3 binds to different innate immunity cells including DCs, MΦ and PMNs. The short pentraxins CRP and SAP are both known to bind Fγ receptors with variable affinity [52]. In addition, PTX3 was shown to bind the FγRIIa and the FγRIII. The binding interface between FγRIIa and SAP was identified by the crystal structure of human SAP in complex with the extracellular domain of the FγRIIa [52]. The lower sequence similarity between PTX3 and both the short pentraxins, and the recently acquired notion that PTX3 lacks pentameric symmetry (i.e., is organized in two oppositely oriented tetramers), makes difficult to predict the mode of interaction between PTX3 and the FγRIIa.

Consistently in PTX3 interaction with FγRIIa it was found that PTX3 pro-phagocytic activity was inhibited by an anti-CD32/FcγRIIa blocking antibody but not by anti-CD16/FcγRIIIa on PMN cells. Moreover, an in vivo model of IPA in mice deficient for FcγRs showed that PTX3 was totally ineffective in protecting against the fungus, thus suggesting a crucial role of these receptors in PTX3-mediated anti-fungal activity [51].

PTX3 and Dectin-1 are both recognized as key receptors for the immune response to fungal infection [18,34]. A general model of cooperation between these receptors has been proposed, based on experimental evidence related to zymosan internalization by MΦ [53]. In such a model, the multimeric PTX3 was proposed to simultaneously coordinate several microorganisms. In this way, PTX3 works as an amplifier of Dectin-1 mediating particles internalization. Indeed, instead of internalizing a single microorganism at a time, the interaction of Dectin-1 with microorganism clustered by PTX3 would enhance phagocytosis effectiveness.

The pro-phagocytic activity of PTX3 on innate immunity cells requires the presence of serum [51], thus suggesting that this activity is not only limited to its interaction with CD32/FcγRIIa but more likely relies on multiple interactions.
with serum proteins and other transmembrane receptors. It is well known that PTX3 is able to establish interactions with a number of serum proteins including C1q, Factor H, Ficolin 2 and MBL [54–58]. Although the interaction of PTX3 with C1q is functional to the activation of complement classical pathway [58] it might not be essential to PTX3 opsonic activity against *A. fumigatus*, since the protein maintains its capacity to be protective against this fungus also in C1q-deficient mice [17]. The relevancy of the interaction of PTX3 with Factor H in *A. fumigatus* infection remains to be fully elucidated. It has actually been suggested that the ability of PTX3 to bind apoptotic cells may be instrumental to guide Factor H regulatory activity on complement activation on these cells, hence controlling inflammatory response in injured tissue and eventually preventing autoimmunity [56]. *Aspergillus* immune evasion through interaction with Factor H and C4b binding protein has been recently demonstrated [59]. Given that PTX3 interacts with both *Aspergillus* and Factor H, it is possible that PTX3 might counteract the *A. fumigatus* immune evasion by activating complement classical pathway on conidia surface [58] or by enhancing conidia recognition by phagocytes [17]. In addition, it is interesting to observe that *Pseudomonas aeruginosa* (another micro-organism recognized by PTX3) [60] also binds to Factor H through the surface protein Tuf [61]. The binding of Factor H to *P. aeruginosa* was described as a mechanism this microorganism puts in place to evade complement activation on its surface. The binding domain of Factor H with Tuf maps in the short consensus repeats (SCRs) 15–20. The same SCRs are also recognized by PTX3 [55] thus allowing the speculation that PTX3 may compete with the interaction between Factor H and *P. aeruginosa* and thereby prevent immune evasion.

Ficolin 2 is another PRR of *A. fumigatus* endowed with lectin complement activity [56]. The interaction of PTX3 with Ficolin 2 enhances binding to *A. fumigatus* conidia of the latter and vice versa. Furthermore, Ficolin 2-mediated complement activation, evaluated as C4b deposition on conidia surface, was enhanced by PTX3, hence providing a clear example of how a combination of PRRs strengthens innate immunity response [56].

MBL, another key component of the lectin complement pathway that shares structural and functional similarities with Ficolins, also binds to PTX3 [57]. Although neither *in vitro* nor *in vivo* data are available on the role of this interaction against *A. fumigatus*, clear evidence was provided that the complex MBL/PTX3 enhances complement activation on the fungus *C. albicans*, likely combining the lectin pathway by MBL and the classical pathway by PTX3.

Consistent with the observation that PTX3 is able to activate complement either by itself or in combination with other PRRs on the surface of *A. fumigatus*, it is not surprising that the complement receptor CR3 was recently described as being essential for PTX3 opsonic activity against *A. fumigatus* [51]. Previous studies have provided clear evidence that FcγR-derived signals are essential to CR3 activation [62]. Precisely, FcγR stimulation promotes release of the CR3 receptor from its cytoskeleton constraints (inside-out activation), thus enhancing lateral diffusion and clustering of the receptor into high-avidity complexes in the phagocytic cup that is the prelude to its internalization.

Therefore, the currently available data strongly suggest that upon binding to conidia, PTX3 may activate complement cascade on conidia surface, either alone or in combination with other PRRs, interact with FcγRIIα that in turn mediates activation of the CR3. Complement-opsonized conidia are recognized by CR3 in the phagocytic cup and thereafter internalized (Fig. 1).

**PTX3 and neutrophils**

Conidia that escape phagocytosis give rise to *aspergillus* hyphae. Hyphae could be engulfed by phagocytes through a different internalization pathway [63]. Moreover, in those...

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**Fig. 1** Proposed mechanism of PTX3 opsonic activity. (1) *Aspergillus fumigatus* conidia are recognized by PTX3 and complement (C3b). (2) Interaction of PTX3 with FcγRIIα promotes the recruitment of CR3 in the phagocytic cup, which in turn recognizes C3b on conidia surface. PTX3 is depicted as describe in Reference [15]. In yellow the N-terminal domain, in red the C-terminal domain of PTX3. This Figure is reproduced in colour in the online version of Medical Mycology.
cases where phagocytosis occurs through the epithelial cells of the respiratory mucosa, hyphae could persist in internalized vesicles and eventually be released in the environment [64]. Hyphae are the primary target of neutrophils [65]. These cells aggregate around hyphae and damage them by releasing reactive oxygen intermediates (ROI) and antimicrobial peptides such as lactoferrin, lysozyme and defensins [66].

PTX3 is stored in neutrophils granules containing lactoferrin [67]. After secretion, the protein remains associated with the extracellular trap that surrounds activated neutrophils and acts as a focal point for antimicrobial effector molecules [66,67]. Expression of PTX3 by neutrophils is essential for the host resistance to A. fumigatus. Indeed the adoptive transfer of neutrophils deficient for PTX3 in PTX3 competent mice previously infected with A. fumigatus resulted in an increase of fungal growth in the lung [67].

It has also been shown that high blood level of PTX3 moderates neutrophil recruitment to the infection site [68]. PTX3 exerts this function by antagonising PGL-1 interaction on leukocytes surface with P-selectin on endothelial cells, thus reducing leukocytes rolling and adhesion on vascular endothelial cells. Thus, PTX3 functions in two ways. Firstly, it acts locally on the infected tissue acting as an opsonin and helping to resolve the infection. Secondly, in the blood stream it moderates leukocytes recruitment at the inflammatory site avoiding exacerbation of the inflammatory reaction that could delay the restoration of normal homeostasis.

PTX3 and adaptive immune response

Innate immunity, mediated by PRRs and phagocytes, detects and destroys the fungus within a few hours. However, if A. fumigatus infection opens a breach in this early line of defence, the adaptive immunity will ensue with the generation of T cell and B cell-mediated antifungal response. DCs sample fungus conidia and hyphae, transport them to the draining lymph nodes and activate CD4 + and CD8 + T lymphocytes [63]. Activation of an appropriated T-helper response is instrumental to an effective resistance to A. fumigatus. Polarization of T cell CD4 + towards a Th1 phenotype confers resistance to the fungus while a Th2 polarization is associated with susceptibility and allergic reaction [69]. However, it is the balance between Th1 and Th2 response that has been described as being crucial to IPA outcome [69].

Ingestion of PTX3 opsonized conidia by DCs is essential to orient the adaptive immune response toward a Th1 phenotype, which is the phenotype associated with resistance to aspergillus infection [17]. PTX3-deficient mice have a cytokine profile that is typical of a Th2 polarization of CD4 + lymphocytes (low IL-12 and IFNγ and high IL-10 and IL-4) [17]. Such a condition could be reverted to Th1 phenotype by administering recombinant PTX3 [17].

Pharmacological use of PTX3

Several clinical conditions are susceptible to infection with A. fumigatus. A general reduction in leukocytes count (particularly neutrophils), a dysregulated adaptive immune response or treatments with pharmacological substances that impair innate immunity cell activity are all conditions at high risk of aspergillosis [70–72]. Some of these conditions can be due to an underlying disease such as haematological cancer, bone marrow and solid organ transplantation or to a congenital disease such as the Chronic Granulomatous Disease (CGD) [73].

PTX3 knockout mice were shown to be highly susceptible to A. fumigatus pulmonary infection, thus indicating that the protein exerts a non-redundant role in the immune response to this fungus and suggests that recombinant PTX3 (rPTX3) administration could be a perfect substitute therapy in case of PTX3 deficiency. However, no deficiency or polymorphism of PTX3 have yet been identified in humans that correlate with a high risk of contracting aspergillosis. In contrast, PTX3 polymorphism Asp48Ala has been found to occur with higher frequency in cystic fibrosis patients contracting pulmonary infection by P. aeruginosa [60].

In the last 10 years, a number of pharmacological studies on PTX3, in different animal models of IPA, have indicated that rPTX3 can be effectively used in solving pulmonary infection caused by aspergillus in animals that normally express PTX3 [16,18,19]. The protein acts by reducing fungal burden and enhancing survival, thus suggesting that exogenously administered PTX3 could compensate for the host immune deficiency by strengthening innate immunity.

PTX3 preferentially works on IPA when administered in prophylaxis, a result that likely depends on the ability of PTX3 to recognise conidia but not hyphae. The protein has shown the ability to solve the pulmonary infection caused by Aspergillus in a number of different immune deficiencies (Table 2). PTX3 acts as a protective factor against IPA in mice subjected to allogeneic bone marrow transplantation. In these mice, two major defects enhance susceptibility to fungus infection, namely, a partial reduction in neutrophil counts and an unbalanced T lymphocytes-mediated immune response, mainly polarized toward a Th2 phenotype [69]. PTX3 administration in bone marrow transplanted-mice was shown to enhance phagocytic activity upon A. fumigatus infection, hence compensating for neutropenia and to skew T lymphocytes towards a Th1 phenotype, as established by profiling cytokines in the lung and in the blood of the PTX3-administered mice [17].
PTX3 was also protective against IPA in a mouse model of CGD, a congenital disease also occurring in humans, caused by a defect on one of the genes involved in NADPH oxidase assembly, namely the p47 phox gene [16]. In these mice, lack of NADPH oxidase activity is associated with defective phagosome maturation, a reduction of killing activity by phagocytes and a higher susceptibility to infection by microorganisms, including Aspergillus [74,75]. Such a susceptibility to Aspergillus infection is furthermore associated to an exacerbated immune reaction to this fungal infection with a significant increase in the number of neutrophils within the lung of infected mice [75]. The ability of PTX3 to sustain conidiocidal activity by endothelial cells and neutrophils isolated from p47 phox-/- mice suggests that PTX3 exploits NADPH oxidase independent mechanism to kill the fungus within the phagosome. Moreover, PTX3 shows the ability to restrain inflammation, reducing primary inflammatory cytokines level and balancing the relative percentage of mononuclear cells and neutrophils in the lung [16]. Whether the later ability of PTX3 depends on the role of the protein in moderating leukocytes recruitment remains to be investigated.

The protective activity of PTX3 against IPA was also shown in rats immunosuppressed with cortisone acetate, where PTX3 was shown to reduce lung fungal burden and enhance survival [19]. This activity is also associated with a reduction of the myeloperoxidase level in the lung. This observation supports the hypothesis that PTX3 is able to rapidly resolve the infection by enhancing phagocytosis and simultaneously mitigating inflammation by modulating neutrophils recruitment at the infection site [68].

Antifungal drug resistance represents one of the major shortcomings of the cure of IPA. A surge of interest for therapeutic approaches exploiting combination of antifungal drugs is justified by the idea that antifungals with different mechanisms of action may reduce the chance to select fungal strains otherwise resistant to one of the drugs [76].

The combination of PTX3 with already registered antifungals such as Ambisome and Voriconazole was evaluated in order to exploit antifungal cytotoxicity while boosting immune system with PTX3 [16,18]. The results of combined treatments reported additive efficacy either when PTX3 was combined with Ambisome or with Voriconazole. Notably, when combined with PTX3, the antifungal dose could be reduced while maintaining efficacy. Thus, a combination of antifungal drugs with PTX3 may represent a therapeutic option in those cases where adverse side-effects on severely compromised patients might discourage administration of full-dose antifungal therapy.

The use of PTX3 has also been evaluated for different types of infectious diseases that include viruses and bacteria [77,78]. Particularly relevant to the etiology of the invasive aspergillosis in bone marrow-transplanted patients is the infection caused by CMV. Many clinical cases of invasive aspergillosis have a preclinical history of infection with CMV [77]. PTX3 is able to bind CMV and to inhibit viral infection of cells. Accordingly, PTX3 was shown to protect against CMV infection and reactivation and the subsequent super infection with A. fumigatus [77] (Table 2). This observation points to a key role of PTX3 in infectious diseases and further supports its clinical use in preventing viral infection and super infection in transplantation settings.

### Conclusion and future remarks

The landscape of membrane-associated or soluble proteins that play a role as A. fumigatus receptor is quite crowded, suggesting that a certain level of functional redundancy exists. On the other hand, the importance of multiple PRRs mediated signals as a safety network to counteract harmful microorganisms seems to be a general paradigm of innate immunity. Indeed protein coupling and a combination are a well-characterized molecular strategy to expand ligand discrimination and recognition ability of several PRRs.

PTX3 does not escape this view. Moreover, it remains the only soluble PRR whose genetic deficiency in mice is linked directly to a high susceptibility to A. fumigatus pulmonary infection (Table 1) [16].

PTX3 is highly expressed on the respiratory mucosa by epithelial cells, recognizes conidia but not hyphae, and pharmacologically works better when administered in prophylaxis than in therapy [18,19,79]. The protein has been shown to complement several different conditions of immunodeficiency in counteracting aspergillosis, an observation that suggests that PTX3 may play a high
PTX3 protective activity on A. fumigatus infection

Consultant


PTX3 protective activity on A. fumigatus infection


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