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REVIEW ARTICLE

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# The Role of Pentraxin 3 in Aspergillosis: Reality and Prospects

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**ABSTRACT**

Pentraxin 3 (PTX3) is a soluble pattern recognition receptor (PRR), which is produced by several kinds of cells, such as neutrophils, dendritic cells, macrophages, and epithelial cells. PTX3 is known to play an important protective effect against *Aspergillus*. Genetic linkage in gene-targeted mice and human PTX3 plays a non-redundant role in the immune protection against specific pathogens, especially *Aspergillus*. Recent studies have shown that the polymorphism of PTX3 is associated with increased susceptibility to invasive aspergillosis (IA). In this review, we provide an overview of these studies that underline the potential of PTX3 in diagnosis and therapy of IA.

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## 1. Introduction

On average, we inhale 400∼1000 *Aspergillus* spores everyday [1,2]. Although most species of *Aspergillus* are nonpathogenic, some species of *Aspergillus* can cause serious opportunistic infections in patients suffering from immunodeficiency diseases and those undergoing organ transplantation. According to recent studies, most of the instances of invasive aspergillosis (IA) occur in patients with impaired immunity, and chronic aspergillosis often occurs in patients with chronic lung disease or those with mild immunodeficiency, under certain circumstances, chronic *Aspergillus* colonization of airways could transform into an invasive disease [3–5]. Further, IA is an important cause of morbidity and mortality in immunodeficient patients. Although morbidity and mortality associated with IA has been increasing, there are few reliable methods to predict the incidence of invasive aspergillosis (IA) accurately. Galactomannan (GM), a fungal biomarker has been tested for diagnosis of IA in clinical trials; however, its actual effect is still controversial. Thus, pathogenesis, prevention, diagnosis, and treatment methods need further investigation [6].

Human immune system consists of innate immunity and acquired immunity. Innate immunity is the first line of defense against attack by pathogenic microorganisms. The immune system recognizes pathogens *via* pattern recognition receptors (PRRs), which recognize highly conserved structures called pathogen associated molecular patterns (PAMPs) present on the surface of the invasive pathogens. PRRs are useful tools in both cellular and humoral innate immune systems and they are composed of cell-associated pattern recognition molecules (PRMs) and soluble PRMs [7].

Pentraxins belong to a superfamily of conserved proteins, which exhibit a characteristic structural motif. The pentraxin domains are critical in the regulation of immunity. First, PTX3 were identified as cytokine-inducible genes or molecules. However, recently studies have shown that PTX3 plays an important role in the process of resistance against specific pathogens. Furthermore, pentraxins are multifunctional proteins at the crossroads of immunity and inflammation, extracellular matrix construction, and female fertility. Recent reports have suggested that the single nucleotide polymorphisms (SNPs) of pentraxins is closely related to the susceptibility for IA [8].

In this review, we summarize our current understanding of the structure and function of long pentraxins. We focus on the role of PTX3 in *Aspergillus* infection. In addition, we discuss the prospects of PTX3 as a biomarker for diagnosing *Aspergillus* infections.

## 2. Pentraxins

### 2.1. The pentraxin superfamily

The pentraxin superfamily is characterized by a highly conserved sequence of 8-amino-acid residues (H-X-C-X-S/T-W-X-S), where x is any amino acid) at their carboxy-terminal region [9–11]. This

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particular sequence is a sign of the pentraxin proteins, which is called "pentraxin signature". All pentraxins are multifunctional multimeric proteins, but are classified into short pentraxin proteins and long pentraxin proteins, based on their primary structure [9].

All the short pentraxins are 25-kDa proteins sharing common structural organization in five or ten identical subunits arranged with a pentameric radial symmetry [2,12,13]. C-reactive protein (CRP) was the first to be identified as one of short pentraxins. CRP has been widely used as classic biomarkers of acute phase of inflammation in humans [14,15]. Thus, we can hypothesize that PTX3 could be applied in treatment and diagnosis of fungal infections, especially *Aspergillus* infections.

### 2.2. The structure and gene of PTX3

At the early 1990s, a new member of the pentraxin superfamily, PTX3, was found and classified as a long pentraxin. Long pentraxins have an unrelated amino-terminal region coupled to a carboxy- terminal pentraxin-like domain [7,11,16]. The PTX3 gene is located in chromosome 3q25, and is encoded by three exons. The long $NH_2$-terminal domain is encoded by the first two exons, while the third exon codes for the COOH-terminal pentraxin-like domain. PTX3 is a 381-amino acid-long protein. Interestingly, the primary structure of PTX3 is highly conserved, the COOH-terminal domain of PTX3 shares 57% amino acid with short pentraxins, while its N-term has a long $NH_2$-terminal domain, which is similar to any sequence [7,9,10,17–19]. The PTX3 gene is found on chromosome 3 (q24-28) in mice with up to 92% similarity. There are many binding sites on both human and murine PTX3 gene promoters for multiple transcription factors, including PU.1, AP-1, NF-$\kappa$B, Sp1, and NFIL-6, [7]. All of which are targets of proinflammatory cytokines [mainly tumor necrosis factor-$\alpha$ (TNF-$\alpha$) and interleukin-1 (IL-1)] and Toll-like receptors (TLR) agonists, which indicate that data from mice could be applied to humans [7,20–22].

### 2.3. The PTX3 expression and storage

Initially, *PTX3* was thought to be a cytokine-inducible gene in vascular endothelial cells and fibroblasts. However, it was later found that PTX3 is expressed by different types of cells, including fibroblasts, endothelial cells, monocytes, macrophages, smooth muscle cells, kidney epithelial cells, synovial cells, chondrocytes, adipocytes and alveolar epithelial cells. Most PTX3s are derived from myeloid dendritic cells [7,9,17,23]. Interestingly, PTX3 is absent in T and B lymphocytes, natural killer cells or plasmacytoid dendritic cells. Although PTX3 is found in neutrophils cell, there is no PTX3 mRNA in neutrophils. PTX3 is stored in specific granules of neutrophils and released when stimulated by microorganisms or TLR agonists [24]. Unlike CRP, Since PTX3 can be expressed by different kinds of cells, unlike CRP, it can be regulated by multiple factors: PTX3 in cells of the myelomonocytic lineage are induced by proinflammatory cytokines IL-1$\beta$ and TNF-$\alpha$, as well as TLR agonists, (monocytes, macrophages, and myeloid dendritic cells) [17], while PTX3 in vascular endothelial cells and smooth muscle cells could be induced by inflammatory signals and modified lipoproteins [23,25].

### 2.4. The PTX3 in innate immunity

Our innate immunity system plays a protective role *via* germline-encoded receptors called pattern recognition molecules (PRMs), which could specifically identify pathogen-associated molecular patterns (PAMPs) expressed by microorganisms [26]. PRMs can be divided into two groups: cell-associated PRM (TLR, NOD- and RIG-like receptors, and scavenger receptors) and soluble PRM (members of the collectin, ficolin, and pentraxin families) [24,27–29]. PTX3, as a part of soluble PRM, participates in the process of recognition of pathogenic microorganisms (bacteria, fungus, virus) and activation of innate immune system. It has been found that PTX3 binds to conidia of *A. fumigatus*, selected gram-positive such as *Staphylococcus aureus*, and gram-negative bacteria, such as *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, *Paracoccidioides brasiliensis* and several viral strains [9].

The role of classic pentraxins in the immune system is to bind the complement *via* calcium-dependent manner, while PTX3 activates the classical complement system through its interaction with plastic-immobilized C1q, confirmed by deposition of C3, C4. On the contrary, fluid-phase PTX3 combined with C1q binds to the relevant sites to activate the complement system through competition [9,30]. These phenomena revealed that PTX3 exerts a dual opposite effects on the process of complement activation [11].

In addition to being involved with classic complement, interaction between PTX3 and factor H can regulate alternative complement pathways as well, causing deposition of factor H and factor iC3b on apoptotic cells. At the same time, combination of PTX3 and factor H might prevent exaggerated complement activation [11,31–33].

PTX3 binding to mannose binding lectin (MBL) recruits C1q and triggers deposition of C3 and C4

on the surface of the target cell, inducing phagocytosis of the microorganisms. Moreover, recent experimental data revealed that PTX3 also interacts with another fluid-phase PRM called L-Ficolin (Ficolin 2). The interaction between PTX3 and Ficolin 2 induces deposition of Ficolin-2-dependent complement and increase host resistance to pathogens [34].

Altogether, these findings showed that PTX3 play a dual and important role *via* three complement pathways (i.e., C1q, Ficolin-2, MBL, factor H) in the regulation of complement system.

As mentioned above, there are many sources of PTX3 and it is stored in neutrophils as specific granules of neutrophils, in the form of mature glycosylated monomers, and assemble into a polymer in the extracellular environment. Neutrophils release PTX3 in response to microbial or inflammatory signals. Some of the released PTX3 can be localized in extracellular traps of neutrophils (NETs), which are formed by extruded DNA [24]. In addition to activation to complement dependent mechanism, research indicates that PTX3 also enhances identification and phagocytosis of conidia by neutrophils *via* Fc$\gamma$ receptor II (Fc$\gamma$RII), which have been proposed as pentraxin receptors [32,35].

PTX3 plays an non-redundant role in the regulation of inflammation, [36,37] cancer [20,38], female fertility [39,40] and tissue repair [41], and in the resistance against pathogens (selected fungal, bacterial and viral) [28,42,43]. More recently, several studies have reported that PTX3 is involved in the recognition, phagocytosis, and killing of conidia of fungi, especially in case of aspergillosis, which indicates that PTX3 may be a useful tool for the prediction, detection, and treatment of aspergillosis infection [8,24,44].

## 3. Association of PTX3 and *Aspergillus*

### 3.1. Aspergillus *and aspergillosis*

*Aspergillus*, is a fungi that is present all over the world, especially in water, soil, dust, foods, and decaying vegetation. While most of the *Aspergillus* species are nonpathogenic, some of them are pathogenic and even lethal [45], especially for patients with immunodeficiency diseases, and invasive pulmonary aspergillosis (IPA) has become a major complication for patients who receive organs or bone transplants. Additionally, the patients who are critically ill in the ICU are also susceptible to Aspergillosis [3,4,44,46]. Mortality in patients with invasive Aspergillosis varies from 1% to 36% [46,47].

### 3.2. The PTX3 and the aspergillosis

In aspergillosis, the bronchial epithelial cells are the first layer of protection against invasion of *Aspergillus fumigatus*. These epithelial cells recognize $\beta$-glucans on the surface of the fungi [47–49]. During the binding event, bronchial epithelial cells block fungal colonization by generating reactive oxygen species, antimicrobial peptides, and cytokines. However, some of the *Aspergillus* still escape into the lungs. Phagocytes (especially neutrophils) and dendritic cells (DCs) stationed in the lungs together with the recruited inflammatory cells can spot PAMPs of *Aspergillus* on its cell wall. PRRs recognizing fungal PAMPs include toll-like receptors (TLR-2, 3, 4, 9) and dectin-1 combined with cell membrane, which can activate intracellular conduction pathways, in addition, other soluble PAMPs such as PTX3 and MBL, as mentioned before, can activate the complement pathway and promote phagocyte activation. Collectins, ficolins, pentraxins, and complement components perform opsonization in this process of promoting the interaction between phagocytes and fungi.

In addition to opsonization, PTX3 in neutrophils can be released and these later participate in the formation of neutrophil extracellular traps (NETs), thus preventing the invading organism from spreading further. Subsequently, the dendritic cells transport the conidia and hyphae of the fungus to the lymph nodes, thus activating the adaptive immunity of the body, which produce T cells and B cells and at the same time leading to the generation of appropriate T helper cells, together with effective resistance against *Aspergillus fumigatus* [4,46,48–50].

Thus, PTX3 is crucial in immunity and resistance against *Aspergillus* infection [4]. PTX3 binds to conidia *via* the N-terminal domain while the recognition and phagocytosis by neutrophils and macrophages occur *via* the C- terminal domain [32]. Both PTX3 and Dectin-1 are critical for PRR and are needed for the identification of *Aspergillus* [51,52], the interaction between PTX3 and Dectin-1 can effectively promote phagocytosis of *Aspergillus*, and PTX3 might also exist as an amplifier of Dectin-1, mediating particles internalization, according to an experimental model related to zymosan internalization by MΦ [51].

PTX3 can interact with many serum proteins including C1q, Factor H, Ficolin2, and MBL. One of the main functions of PTX3 is the activation of classical complement pathways in combination with C1q; however, there is strong evidence that C3 rather than C1q is a critical component against *Aspergillus* infection [53]. The immune evasion mechanism of *Aspergillus* may be related to the combination of factor H and C4b. To avoid immune

evasion, PTX3 may enhance its binding to *Aspergillus* and promote its phagocytosis through interaction with Factor H, thus accelerating deposition of C4b [54]. Ficollin-2 is another PRR with lectin complement activity. Combination of Ficollin-2 and PTX3 can strengthen the chains of PTX3 and conidia, which can also facilitate the deposition of C4b. Furthermore, to a certain extent, the interaction of PTX3 and factor H can control the inflammatory reaction so as to prevent over-response and autoimmunity [4].

Another component of the lectin complement pathway, MBL also binds to PTX3. The structural features and functions of MBL are similar to those of ficolins. The complex MBL/PTX3 can activate the lectin complement pathway to promote phagocytosis of *Aspergillus*.

Overall, PTX3 binds to conidia and activates the relevant complement cascade. Thus, PTX3, alone or when bound to the associated PRRs, interact with Fc$\gamma$RIIa to mediate the activation of CR3, which ultimately leads to phagocytosis of conidia [4]. As for hyphae, neutrophils accumulate around them and release the reactive oxygen intermediates (ROIs) and antimicrobial peptides, such as lactoferrin, lysozyme and defensins to destroy them.

### 3.3. Genetic variability of the host and susceptibility to invasive Aspergillus

There are several clinically common pathological conditions susceptible to *Aspergillus* infections, such as reduced white blood cell counts, damage to drug substances, impaired immune function, such as hematological cancer, bone marrow or solid organ transplantation, and congenital immunodeficiency. Even though immunodeficient patients are more susceptible to *Aspergillus*, according to observations, not all patients are at enhanced risk of *Aspergillus* infections. Among the patients who were attacked by *Aspergillus*, only a subset show *Aspergillus* colonization, and only a few patients show acute infection [3]. Therefore, researchers and doctors focused on the critical risk factors associated with the genetic variability.

As explained earlier, PTX3 is a key component in the immune response against *Aspergillus*. Several studies have reported an association between IA development and single nucleotide polymorphisms (SNPs) especially homozygous haplotype h2/h2 (rs2305619-rs3816527:G-A/G-A) [8,55–58]. In order to explore the impact of single nucleotide polymorphisms (SNPs) on the development of IA in PTX3, the researchers collected and screened 268 patients undergoing hematopoietic stem-cell transplantation (HSCT) and their donors. At the same time, they analyzed their lung specimens as research samples for a multicenter study. The close relationship between donor haplotype h2/h2 and the higher incidence of IA was discovered, both in the discover study and the confirmation study [8].

By analyzing the 22 SNPs of the PTX3 gene, only three SNPs (+281 A/G, +734 A/C (D48A) and +1449 A/G) were identified as being closely related to the incidence of IA. Linkage disequilibrium analysis shows that there are three different chain-unbalanced blocks: T-A (block 1), A-A (block 2), and A-C (block 3), which are all related to an increased risk of IA; however, there is no significant difference in terms of cumulative infection rate in patients with block 1 and block 2. In block 3, data analysis shows that donor with a homozygous haplotype G-A/G-A(h2/h2) in PTX3 was associated with a remarkably increased risk of infection and a higher incidence of infection than patients with transplants from A-C/A-C (h1/h1) donors and A-C/G-A (h1/h2) donors. These researchers also found that the +281 A/G and +1449 A/G SNPs are in strong linkage disequilibrium and can be used interchangeably within haplotype block 3. To understand the consequences of the SNPs in PTX3 haplotype block 3, investigations into the protein function of SNP were carried out. The results suggested that the +734 A/C (D48A) mutation occurs in the conserved region of the PTX3 gene. Alignment of PTX3 sequences showed the mutation occurred at the conserved site and it affected the mRNA folding. However, the mutation had no effect on the protein [8]. The researchers added exogenous PTX3 to the purified neutrophils cells, which restored the immune mechanisms of these cells to the fungus. Interestingly, both kinds of PTX3 (48 D and 48 A) can restore the immune mechanisms [8,59,60]. Therefore, we can surmise that the function of PTX3 to defend *Aspergillus* infection is dependent on quantity rather than quality.

As mentioned above, there is an association between PTX3 SNP and the high risk of IA infection among patients receiving hematopoietic stem cell transplantation. In a cohort study of 2,609 HCT subjects containing donors and receptors, significant association between SNP and PTX3 has been established again. Two years of observations demonstrated that only two SNPs in two genes: rs1840680 in PTX3 and rs7309123 in CLECL7a are associated with the susceptibility to IA [55], which is inconsistent with the previous conclusion.

Recently, the Swiss Transplant Cohort Study focused on the potential connection of invasive mold infection (IMI) and PTX3. In this cohort study, most of IMI was caused by *Aspergillus* species or other fungi. Data analysis indicated that a

**Table 1.** PTX3 SNP polymorphism and IPA.

| Patients type | Number | PTX3 polymorphism | HR/OR (95% CI) | *p* Value | Reference |
|---|---|---|---|---|---|
| HSCT | 268 | +281A/G SNP | 2.92(1.69–5.05) | <0.001 | [8] |
| | | +734A/C SNP | 2.62(1.52–4.54) | <0.001 | |
| | | Haplotype h2/h2 | 3.08(1.47–6.44) | 0.003 | |
| HSCT | 112 | +281A/G SNP | 0.61(0.20–1.92) | 0.4 | [60] |
| | | +734A/C SNP | 0.70(0.25–1.94) | 0.49 | |
| | | Haplotype h2/h2 | 0.65(0.21–2.06) | 0.47 | |
| HSCT | 2609 | +281A/G SNP | 1.33(1.09–1.64) | 0.005 | [55] |
| | | +281A/G SNP | 1.54(1.02–2.34) | 0.039 | |
| | | +734A/C SNP | 1.82(1.11–5.34) | 0.017 | |
| Lung Transplant | 102 | Haplotype h2/h2 | 6.69(1.57–28.5) | 0.01 | [58] |
| SOT | 1101 | +281A/G SNP | 2.29(1.04–5.03) | 0.04 | [56] |
| | | +734A/C SNP | 3.18(1.45–6.98) | 0.004 | |
| | | Haplotype h2/h2 | 2.43(1.11–5.34) | 0.03 | |
| COPD | 173 | +1449A/G | 5.94(2.31–15.31) | 0.0004 | [57] |
| | | +281A/G SNP | 1.44(0.44–4.73) | 0.52 | |
| | | +734A/C SNP | 1.86(0.19–18.65) | 0.49 | |

Haplotype h2/h2 refers to the +281 A/G - +734 A/C: G-A/G-A.

significant association existed between IMI and PTX3 polymorphisms, including the rs3816527 AA genotype, rs2305619 GG genotype, and h2/h2 haplotype. Even after eliminating interference factors, such as age and sex, the researchers found a stronger role for the rs3816527 AA genotype [56].

Other studies on chronic obstructive pulmonary disease (COPD) patients detected the three single nucleotide polymorphisms as rs2305619, rs3816527 and rs1840680. After excluding the possibility of interference such as gender and age, the research team concluded that all the three SNPs were consistent with Hardy-Weinberg equilibrium, while only the patients with AA homozygote of SNP rs1840680 showed a higher susceptibility for pulmonary aspergillosis. No statistical difference was observed for other SNPs [57].

Based on the above study, results of patients suffering underlying disease, to some degree, we can speculate that PTX3 plays an irreplaceable role in the progression of IA infection and development (Table 1).

## 4. Conclusion and the future of PTX3

Mannose-binding lectin (MBL) is the only protein in the PRR superfamily which enters clinical trials and it has become useful as monitoring markers of fungus infection. Recently, a randomized controlled trial has proven that the effect of MBL as a marker for medication guidance [61,62]. Meanwhile, in another study, plasma PTX3 levels significantly increased upon fungal infection, whereas CRP did not, which suggest a useful role for PTX3 in the diagnosis of IA [63]. However, for the purpose of confirming the function of PTX3, investigators analyzed the cells in the lung and purified cells *in vitro*. Interestingly, data analysis showed that PTX3 is expressed more in bronchoalveolar lavage fluid other than plasma of patients with IA, which imply

**Table 2.** Information about the PTX3 SNP.

| SNP ID | Allele | Genotype |
|---|---|---|
| rs2305619 | +281A/G | AG |
| | | AA |
| | | GG |
| rs3816527 | +734A/C | AC |
| | | CC |
| | | AA |
| rs1840680 | +1449A/G | AA |
| | | AG |
| | | GG |

that the level of PTX3 might become a new marker for IA (Table 2) [62].

The current treatment regime for *Aspergillus* infections focuses on the use of empirical antifungal drugs. Current major drug therapy for invasive pulmonary Aspergillosis includes liposomal amphotericin B, itraconazole, posaconazole (PCZ) and voriconazole [64–66]. Supplying exogenous PTX3 may restore PTX3-deficient cells and provide immunity against *Aspergillus*. During the last decade, a series of pharmacological studies in many 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 [4,67,68]. The results of research and observation in a rat model of invasive pulmonary aspergillosis proved that co-administration of PTX3 and VRC can effectively improve respiratory function and reduce pulmonary fungal burden [68]. We cannot ignore the strong association between PTX3 gene polymorphism and susceptibility to *Aspergillus*. Although the role of PTX3 in clinical practice need to be evaluated. All these studies indicate favorable prospects of PTX3 as treatment and marker of *Aspergillus* infections. More accurate tests are needed to verify the role of PTX3 in *Aspergillus* infection. There is a huge difference between the survey results. The inconsistencies in the results may be due to variations in samples with different clinical conditions and immunity states; however, this still needs to be ascertained.

## Author contributions

Yuening Kang drafted and revised the manuscript.

Yuetian Yu conceived and designed the work that led to the submission and revised the manuscript.

Liangjing Lu helped perform the analysis with constructive discussions and approved the final version.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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