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PTX3, a humoral pattern recognition molecule at the interface between microbe and matrix recognition

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Abstract

Innate immunity consists of a cellular and a humoral arm. PTX3 is a fluid pattern recognition molecule (PRM) with antibody-like properties. Gene targeted mice and genetic associations in humans suggest that PTX3 plays a non-redundant role in resistance against selected pathogens (e.g. *Aspergillus fumigatus*, *Pseudomonas aeruginosa*, uropathogenic *Escherichia coli*) and in the regulation of inflammation. PTX3 acts as an extrinsic oncosuppressor by taming complement elicited tumor-promoting inflammation. Recent results indicate that, by interacting with provisional matrix components, PTX3 contributes to the orchestration of tissue repair. An acidic pH sets PTX3 in a tissue repair mode, while retaining anti-microbial recognition. Based on these data and scattered information on humoral PRM and matrix components, we surmise that matrix and microbial recognition are related functions in evolution.

Keywords

Pentraxin; innate immunity; inflammation; pattern recognition molecules; clinical biomarker

Introduction

Pentraxins are a superfamily of evolutionarily conserved proteins with multi-functional properties in innate immunity (i.e. regulation of complement activation and opsonisation of pathogens). They are characterized by a cyclic multimeric structure and a pentraxin domain (~200 amino acid) in their carboxy-terminal region containing a pentraxin signature (HxCxS/TWxS, where x is any amino acid) [1,2].

Based on the primary structure of the protomer, pentraxins were divided into short and long pentraxins. C-reactive protein (CRP) and serum amyloid P (SAP) are prototypic short pentraxins produced by hepatocytes and constitute the main acute phase proteins in human

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Conflict of interest

AM, CG, BB are inventors of patents related to PTX3 and receive royalties on PTX3-related reagents.

and mouse, respectively, while PTX3 is the first long pentraxin identified in the early 1990's.

PTX3, the main focus of this review, was identified as an IL-1 or TNF-inducible gene. Data collected over the years demonstrate that PTX3 acts as a fluid phase pattern recognition molecule (PRM) and regulator of inflammation [3–8]. In particular PTX3 exerts non-redundant functions in resistance against selected pathogens, a finding at the basis of ongoing translational efforts. Here we review recent progress made in defining the structure, immunobiology and *in vivo* role of PTX3, which we used as a paradigm for humoral innate immunity. Based on recent and scattered results [8], we propose that matrix and microbe recognition are evolutionary linked processes.

The long pentraxin PTX3

PTX3 is a 381 aa long secreted molecule characterized by a C-terminal pentraxin like domain and a unique N-terminal domain unrelated to any known protein. Both human and murine PTX3 genes are localized on the chromosome 3 and organized in three exons. The leader peptide and the N-terminal domain of PTX3 are coded by the first two exons, respectively, and the C-terminal pentraxin domain is coded by the third exon. The promoter of both human and murine *PTX3* gene displays potential binding sites for many transcription factors including Pu1, AP-1, HIF-1 α , C/EBP β , NF- κ B, Sp-1 and NF-IL-6. The IL-1RI/MyD88 pathway is involved in the induced of PTX3 in different sterile models of tissue injury [7–9], whereas the TLR4/MyD88 pathway controls PTX3 production in infectious conditions, for instance in urinary tract infections mediated by uropathogenic *Escherichia coli* [6].

The primary sequence of PTX3 is highly conserved, suggesting an evolutionary pressure to maintain a functional role [1]. PTX3 has a unique quaternary structure with eight subunits associated to form an octamer by covalent interactions between cysteine residues present on both the N-terminal and C-terminal domain [10]. A single N-glycosylation site at Asn220 is occupied by complex type oligosaccharides [11]. PTX3 interacts with different ligands including microbial moieties, complement components and extracellular matrix components. The glycosidic moiety is involved in the interaction between PTX3 and selected ligands, such as P-selectin and influenza virus [12,13]. The N-terminal domain is responsible for the interaction with different PTX3 ligands, including microbial components, FGF2, Factor H, but the full-length molecule is required for optimal binding of most ligands. Recently, it has been shown that PTX3 interacts with fibrinogen and plasminogen in acidic conditions, through the N-terminal domain [8].

PTX3 is expressed by various myeloid cell types (dendritic cells, monocytes, macrophages, neutrophils), epithelial cells, vascular and lymphatic endothelial cells, and mesenchymal cells (e.g. fibroblasts and adipocytes), upon exposure to inflammatory signals (e.g. TNF α , IL-1 β), TLR agonists, and microbial moieties (e.g. LPS, OmpA) [2]. PTX3 expressed by mammary epithelial cells and by uroepithelial cells contributes to innate resistance to infections in neonates and urinary tract infections, respectively [6,14], whereas PTX3 produced by mesenchymal cells contributes to tissue repair processes [8]. As opposed to *de*

novo synthesized PTX3, neutrophils store this PRM in their granules and rapidly release the protein, in part associated with neutrophil extracellular traps (NETs), in response to microorganisms or TLR agonists, thus contributing to resistance to infections [5].

Role of PTX3 in innate resistance to infections

Since its identification, PTX3 has emerged as a fluid phase PRM exerting a protective role in resistance against selected fungal, bacterial and viral pathogens, including *Aspergillus fumigatus*, *Paracoccidioides brasiliensis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, influenza virus, by acting as an opsonin for bacteria and fungi, facilitating recognition and phagocytosis in an Fc γ receptor- and complement-dependent manner, and by neutralizing virus infectivity [2].

More recently, the protective role of PTX3 has been extended to urinary tract infections, where PTX3 emerged as an essential component of innate resistance against uropathogenic *Escherichia coli*, acting by facilitating neutrophil-dependent microbial clearance [6]. PTX3 was also found to interact with acapsular *Neisseria meningitidis*, through outer membrane vesicles and selected meningococcal antigens and to reduce the bacterial load in infected infant rats, acting as an amplifier of responses to this bacterium [15].

In contrast with the described protective role of PTX3 in viral infections, it has recently been shown that PTX3 interacts through the N-terminal domain to arthritogenic alphaviruses (chikungunya virus and Ross River virus), facilitating viral entry and replication during the acute phase of infection, and causing enhanced viral infectivity and prolonged disease [16,17].

Several studies have reported single nucleotide polymorphisms (SNPs) in the PTX3 gene. Most SNPs are located in non-coding regions, and one exonic SNP causes an amino acid variation of the protein. When associated in particular haplotypes, three PTX3 SNPs influence susceptibility to infections. In particular, PTX3 variants are associated with susceptibility to pulmonary tuberculosis [18], *Pseudomonas aeruginosa* infections in cystic fibrosis Caucasian patients [19], *Aspergillus fumigatus* infections in patients undergoing hematopoietic stem cell transplantation [20], fungal infections in solid organ transplanted patients [21], and urinary tract infections [6]. Specific PTX3 haplotypes have been associated to higher protein expression [20,22], but the molecular mechanisms responsible of this association are still poorly understood. These data underline the functional evolutionary conservation of PTX3 in innate responses to microbes.

Regulation of inflammation and resistance to microbes by PTX3: activation and regulation of complement

Several evidences indicate that PTX3 plays a role in inflammation: i) production by myeloid and stromal cells in inflammatory conditions [23]; ii) amplification of the pro-inflammatory effects of recognized microbial moieties [4,24]; iii) higher tissue damage in *ptx3*-deficient mice [6,9] and lower susceptibility to endotoxic shock in PTX3 over-expressing animals [25]. In particular genetic models have been essential to define that PTX3 can exert a

regulatory role on inflammation through modulation of complement activation and regulation of inflammatory cell recruitment.

PTX3 modulates all the three complement pathways, (e.g. the classical, the alternative and the lectin pathways) through the interaction with different complement components, including negative regulators [26–33]. PTX3 interaction with surface immobilized C1q activates the classical complement cascade promoting C3 and C4 deposition, while interaction in the fluid phase inhibits the complement cascade via competitive blocking of relevant interaction sites. PTX3 interacts with members of the lectin pathway, i.e. ficolin-1, ficolin-2 and mannose binding lectin (MBL), and enhances ficolin-2- and MBL-dependent complement deposition on the surface of *Aspergillus fumigatus* and *Candida albicans*, respectively [29–31,34]. Formation of the MBL/PTX3 complex recruits C1q, promotes C4 and C3 deposition on *Candida albicans* and enhances the phagocytosis of the pathogen. Similarly, immobilized PTX3 is able to trigger ficolin-1-dependent activation of the lectin complement pathway [34].

In addition, surface-bound PTX3 enhances Factor H (FH) recruitment and iC3b deposition, modulating the activation of the alternative complement pathway and preventing an excessive inflammatory response to tissue injury, while increasing the deposition of opsonic molecules [28]. Similarly, PTX3 recruits C4 binding protein (C4BP) on apoptotic cells reducing the deposition of the lytic C5b-9 terminal complex [32]. Also in this case PTX3 is capable of targeting functionally active C4BP to sites of tissue injury, thus limiting complement-mediated inflammation. Mutation and polymorphisms of FH leading to dysregulation of the alternative complement pathway are associated with various diseases, including atypical hemolytic uremic syndrome (aHUS). Interestingly, mutations in FH observed in patients with aHUS are associated with a reduced interaction between FH and PTX3 [35]. Given the capability of PTX3 to recruit FH and to control excessive local complement activation, the defective interaction between the two molecules in aHUS patients could amplify local complement-mediated inflammation essential in the pathogenesis of the disease. The modulation of complement activity by PTX3 is involved in the regulation of tissue damage observed in a murine model of acute myocardial infarction [9], as well as in cancer models (see below).

Besides complement activation, PTX3 can regulate the inflammatory response acting on cell recruitment. PTX3 binds the adhesion molecule P-selectin, an interaction occurring via its N-linked glycosidic moiety [12], and inhibits leukocyte rolling on endothelium. In agreement, PTX3 administration *in vivo* reduces leukocytes recruitment in models of pleurisy, acute lung injury and ischemia/reperfusion-induced kidney damage [12,36].

Role of PTX3 in cancer

Inflammation is an essential component of the tumor microenvironment that sustains tumor development and growth [37]. The role of PTX3 as paradigm of humoral innate immunity in cancer-related inflammation has been recently investigated [7]. Results showed that PTX3-deficiency in mice caused increased susceptibility to mesenchymal and epithelial carcinogenesis in the models of 3-Methylcholanthrene (3-MCA)-induced carcinogenesis,

and 7,12-dimethylbenz [a] anthracene/terephthalic acid (DMBA/TPA)-induced skin carcinogenesis. In these models, PTX3 was produced by infiltrating macrophages and endothelial cells in response to IL-1. PTX3-deficiency was associated with exacerbated cancer-related inflammation as revealed by enhanced macrophage tumor infiltration, pro-inflammatory cytokine production, angiogenesis, and complement C3 deposition and C5a levels. In addition, increased DNA damage was observed in PTX3-deficient tumors, as demonstrated by increased *Top53* mutations, oxidative DNA damage and expression of DNA damage (DDR) markers, in line with the evidence that cancer-related inflammation (CRI) is potentially a cause of gene instability [38]. In the 3-MCA-induced cancer model, PTX3 regulated C3-deposition on sarcoma cells by interacting with and recruiting the negative regulator FH. Indeed, genetic inactivation of C3 reverted the increased susceptibility to 3-MCA-induced carcinogenesis and macrophage recruitment. In addition, CCL2-inhibition was sufficient to revert the increased susceptibility of PTX3-deficient mice to 3-MCA and the M2-like phenotype of tumor-associated macrophages. These results indicate that in 3-MCA-induced sarcoma, unleashed Complement activation and increased C5a production associated to PTX3-deficiency are likely responsible of exacerbated production of chemokines, which in turn cause increased recruitment of tumor promoting macrophages and favor M2-like polarization [37]. These data are in line with studies showing that C5a plays a pro-tumoral role by recruiting myeloid-derived suppressor cells, amplifying their T cell suppression activity and CCL-2 production [39], and represents a potent inducer of IL-1 β and IL-17 response in neutrophils thus promoting colon carcinogenesis [40].

Studies in human esophageal squamous cell carcinoma had shown that the *PTX3* promoter is hypermethylated in this cancer and PTX3 expression is inhibited [41]. Along the same line, epigenetic analysis showed that *PTX3* promoter and regulatory regions were highly methylated in selected human mesenchymal and epithelial tumors [7]. This epigenetic modification was responsible of silencing of PTX3 protein expression since treatment of cancer cells with a methylation inhibitor (5-Aza-2'-deoxycytidine) rescued PTX3 protein expression. Thus, PTX3 acts as an extrinsic oncosuppressor gene in mouse and man by acting at the level of Complement-mediated, macrophage-sustained, tumor promoting inflammation.

PTX3 binds through the N-terminal domain selected fibroblast growth factors (FGFs), including FGF2, and FGF8b, and inhibits FGF-dependent angiogenic responses [42]. PTX3-overexpression in cancer cells is associated with reduced angiogenesis and tumorigenic potential in FGF-dependent murine tumors, including prostate cancer [43], and transgenic mice overexpressing PTX3 in endothelial cells are protected in different FGF-dependent cancer models [44]. The actual significance of this pathway in primary carcinogenesis remains to be established.

In contrast to the evidences outlined above, there are two reports suggesting that PTX3 may play a pro-tumorigenic role, but through poorly defined mechanisms [45,46].

Role of PTX3 in Tissue Repair

The cellular arm of innate immunity contributes to tissue repair by sensing damage-associated molecular patterns, such as matrix components, nuclear proteins and nucleic acids, and initiating tissue repair processes. Recently, PTX3 has been shown to play a non-redundant role in tissue repair in different models of tissue damage (skin wound healing, chemically-induced sterile liver and lung injury, arterial thrombosis) [8] (Fig. 1). In these conditions PTX3-deficiency was associated with increased clot formation, fibrin deposition and persistence, followed by increased collagen deposition. *In vitro* and *in vivo* studies demonstrated that by interacting through the N-terminal domain with fibrin and plasminogen at acidic conditions, which occur in damaged tissues, PTX3 promoted remodeling of the fibrin-rich inflammatory matrix ensuring a normal tissue repair, thus providing a novel link between innate immunity, haemostasis and tissue repair. The interaction of PTX3 with the provisional matrix component fibrinogen/fibrin and plasminogen was pH dependent, in that optimal binding was observed at acidic pH *in vitro* and *in vivo*. Thus, the acidic pH observed at sites of tissue damage and inflammation sets the PTX3 molecule in a tissue repair mode, without interfering with microbial recognition.

Concluding remarks

PTX3 is evolutionarily well conserved in terms of expression, regulation and function. Gene targeted mice have allowed defining the functional roles of this molecule in innate immunity and inflammation and genetic and epigenetic data are consistent with the hypothesis that PTX3 exerts similar functions in humans. As a component of the humoral arm of innate immunity, PTX3 acts as functional predecessor of antibodies, by contributing to complement activation, opsonization of pathogens and glycosylation-dependent regulation of inflammation. Recently PTX3 has emerged as an extrinsic oncosuppressor acting as key regulator of complement-driven, macrophage-mediated tumor promotion.

It has long been known but poorly appreciated that extracellular matrix components (e.g. fibronectin, mindin, osteopontin, vitronectin) (Fig. 2) have opsonic activity [47,48]. On the other hand, modules of extracellular matrix proteins are essential constituents of humoral PRM, such as the fibrinogen domain in ficolins [2]. Moreover, humoral PRM interact with matrix components [49–52] as shown for PTX3 and fibrinogen/fibrin. The ancestral function of fibrinogen-like molecules was resistance rather than hemostasis. On this basis we propose that matrix and microbial recognition are related functions of PRM in an evolutionary perspective.

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Highlights

- PTX3 acts as an extrinsic oncosuppressor gene
- PTX3 tunes complement-mediated, macrophage-sustained, tumor promoting inflammation
- An acidic pH sets the PTX3 molecule in a tissue repair mode
- Matrix and microbial recognition are related functions in evolution.

Figure 1.

An acidic pH sets the PTX3 molecule in a tissue repair mode.

Figure 2.
Matrix and microbe recognition as related functions.