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Review

The yin-yang of long pentraxin PTX3 in inflammation and immunity

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ABSTRACT

Pentraxins are a family of multimeric proteins characterized by the presence of a pentraxin signature in their C-terminus region. Based on the primary structure, pentraxins are divided into short and long pentraxin: C-reactive protein (CRP) is the prototype of the short pentraxin subfamily while pentraxin 3 (PTX3) is the prototypic long pentraxin. Despite these two molecules exert similar fundamental actions in the regulation of innate immune and inflammatory responses, several differences exist between CRP and PTX3, including gene organization, protein oligomerization and expression pattern. The pathophysiological roles of PTX3 have been investigated using genetically modified mice since PTX3 gene organization and regulation are well conserved between mouse and human. Such *in vivo* studies figured out that PTX3 mainly have host-protective effects, even if it could also exert negative effects under certain pathophysiologic conditions. Here we will review the general properties of CRP and PTX3, emphasizing the differences between the two molecules and the regulatory functions exerted by PTX3 in innate immunity and inflammation.

1. Introduction

Pentraxins are a superfamily of phylogenetically conserved and multi-functional proteins [1–3], which exert basic and evolutionarily conserved innate immune functions such as complement activation and opsonization [4]. Based on the primary structure, pentraxins are divided into two subfamilies: short and long pentraxin [1]. C-reactive protein (CRP) [5] and pentraxin 3 (PTX3) [6] are the well-known, prototypic short and long pentraxin, respectively. These two pentraxins share fundamental functions as fluid-phase pattern recognition molecules (PRMs); however, their structure and expression pattern are diverse. Unlike CRP, the sequence and regulation of PTX3 are conserved from mouse to human, this pushing forward the genetic approach to understand the roles of PTX3 *in vivo*. Therefore genetically modified mice have been essential to reveal the multifunctional properties of PTX3 at the crossroad between innate immunity, inflammation, matrix deposition and female fertility [1,4]. Here, we will compare the main characteristics of CRP and PTX3 as prototypes of the short and long pentraxin family respectively, and we will then focus on the complex "yin-yang" roles of PTX3 in innate immunity and inflammation.

2. The pentraxin family

2.1. General features of pentraxins

Pentraxins are evolutionarily conserved, multimeric proteins which share a conserved ~200 amino acid pentraxin domain containing the so-called "pentraxin signature" (His-x-Cys-x-Ser/Thr-Trp-x-Ser, where x is any amino acid residue) [7] in its C-terminus (Fig. 1A). CRP and Serum Amyloid P component (SAP) [8] are the prototypes of the short pentraxin subfamily [9], while PTX3 is the first identified long pentraxin [6] characterized by the presence of a long unrelated N-terminal domain associated to the C-terminal pentraxin domain. After PTX3, other members of the long pentraxin subfamily were identified, including guinea pig apexin, neuronal pentraxin 1 (NPTX1) [10,11], neuronal pentraxin 2 (NPTX2, also called Narp) [12,13] and the transmembrane protein neuronal pentraxin receptor (NPTXR, reviewed in [1,4]). In an attempt to find new pentraxin domain-containing proteins we recently identified PTX4 [14], a molecule conserved from mammals to lower vertebrates which clusters alone in phylogenetic analysis. However, PTX4 has a unique pattern of mRNA expression, which is

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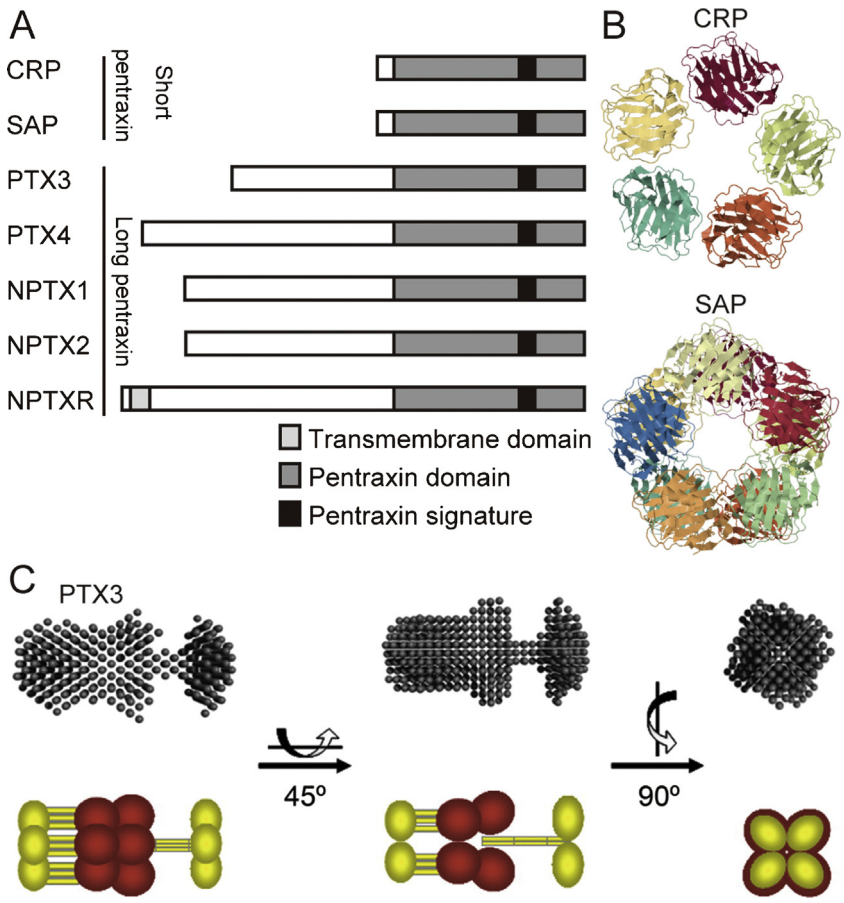

Fig. 1. The molecular structures of pentraxin family. (A) Primary structures of human short and long pentraxins. (B) Crystal structures of short pentraxins. Upper panel indicates the pentameric structure of human CRP (Protein Data Bank code 1GNH). The lower panel indicates the structure of human SAP bound to Bis-1,2-{[(Z)-2carboxy-2-methyl-1,3-dioxane]-5-yloxycarbonyl}-piperazine (Protein Data Bank code 2A3X). In SAP two pentamers are interacting face to face to form a decameric structure. (C) Small angle X-ray scattering (SAXS) analysis of PTX3 and its schematic representation. PTX3 N-terminal domain is shown in yellow and C-terminal domain is shown in red, respectively. Panel C is adapted form Inforzato et al. [25].

distinct from that of other long pentraxins, and it does not behave as acute phase protein [14].

2.2. Genome, structure and expression pattern of human CRP and PTX3 as prototype of short and long pentraxin

A brief comparison of the main characteristics of CRP and PTX3 is reported in Table 1. Human CRP gene, located in chromosome 1q23.2, consists of two exons: the first one encodes for the signal peptide (aa 1–18) and for aa 19–20 of the mature protein, the second exon encodes for the remaining amino acids (21–224) of the polypeptide chain [15,16]. CRP protein assembles into radial symmetric pentamer with planar symmetry (Fig. 1B) [17]. Two cysteine residues (aa 36 and 97 of the mature protein), which are conserved between pentraxins, forms intra-molecule disulfide bonds [18], while non-covalent interactions stabilize the pentamer. Some transcription factor binding sequences (HNF1α, C/EBPβ/δ, STAT3, p50 and c-Rel) are located in the promoter region of human CRP gene [19,20]. CRP is produced in the liver in response to cytokine stimulation, mostly contributed by interleukin (IL)-6 and, to less degree, by IL-1β. CRP is known as major acute phase protein in human: under inflammatory condition, its circulating level increases as much as 1000-fold from the basal value (3 mg/L) [21,22]. Thus circulating CRP levels reflect the systemic inflammatory responses. SAP has 51% amino acid identity with CRP and a similar pentameric structure (Fig. 1B). The two proteins share many structural and biological characteristics including the capacity to interact in a calcium-dependent fashion with different ligands.

Human PTX3 gene, located in chromosome 3q25, consists of three exons with the first and second exons encoding the signal peptide (aa 1–17) and the N-terminal domain (aa 18–178) and the third exon encoding the C-terminal pentraxin domain (aa 179–381) [6]. An N-linked glycosylation site is located on Asn220 and is

Table 1
General features of CRP and PTX3.

	CRP (short pentraxin family)	PTX3 (long pentraxin family)
Gene location	1q23.2	3q25
Exons	Two	Three
Glycosylation	No	N-glycosylation site at Asn220
Multimeric formation	Pentamer with non-covalent interactions	Octamer with intra-molecule disulfide bonds
Binding sequences in promoter region	HNF1α, C/EBPβ/δ, STAT3, p50, c-Rel	Pu-1, AP1, NF-κB, SP1, NF-IL6
Major stimulus	IL-6	TLR agonists, IL-1, TNF
Producers	Liver (Hepatocytes)	Monocytes, macrophage, PMN, EC, DC, fibroblasts, epithelial cells

Abbreviations: CRP, C-reactive protein; PTX3, pentraxin 3; PMN, polymorph nuclear neutrophil; EC, endothelial cell; DC, dendritic cell.

occupied by fucosylated and sialylated biantennary, triantennary and tetraantennary structures [23]. Eight identical protomers are assembled to form an elongated octamer with a molecular weight of 344 kDa stabilized by inter-molecular disulfide bonds [24]. The N-terminal domain participates in the formation of radial asymmetric tetramers, and the C-terminal domain participates in the dimerization of two tetramers by a "stacking" manner [24,25] (Fig. 1C).

Some transcription factor binding sequences (Pu-1, AP1, NF-κB, SP1 and NF-IL6) are located in the promoter region of human PTX3 [26,27]. In contrast to the IL-6-mediated CRP production, PTX3 is produced in response to several primary inflammatory signals such as TLR agonists, IL-1β and tumor necrosis factor α (TNFα) [1,28]. In addition, various types of cells express PTX3 upon appropriate stimulation. PTX3-expressing cells include myeloid dendritic cells [29], monocytes/macrophages [30,31], vascular endothelial cells [6,32], smooth muscle cells [33], fibroblasts [31,32], adipocytes [34], glial cells [35], cumulus oophorus cells [36], mesangial cells [37] and synovial cells [38]. An unexpected constitutive expression of PTX3 has been observed in lymphatic endothelial cells [39]. In addition, polymorphonuclear neutrophils (PMN) contain a storage of mature protein accumulated in specific granules during their maturation process in the bone marrow [40]. Stored PTX3 is promptly released to the extracellular space upon bacterial stimulation (*i.e. E. coli*, *S. aureus* or zymosan), as well as following phorbol 12-myristate 13-acetate (PMA), ionomycin or TNFα treatment. Released PTX3 is localized to neutrophil extracellular traps (NETs) and exerts non-redundant role in pathogen resistance [40]. NETs are a mesh-like component consisting of DNA decorated with histones and anti-microbial proteins, which can trap microbes and form an antimicrobial proteins-rich microenvironment [41–43]. The variety of PTX3-producing cells ensures that PTX3 is produced at local sites where the primary inflammation occurs.

Similarly to CRP, PTX3 is an acute phase biomarker. The basal circulating levels of PTX3 are low (<2 ng/mL) [44–46] and increase rapidly (peaks at 6–8 h) in acute myocardial infarction (AMI) to values 3–5 times higher than the normal range [46,47] A more dramatic increases in PTX3 plasma levels (200–800 ng/mL up to 1500 ng/mL) has been observed during endotoxic shock, sepsis, and other inflammatory and infectious conditions, including meningococcal diseases, dengue infection, tuberculosis and leptospirosis [45,48–50] In a small group of critically ill patients with systemic respiratory distress syndrome, sepsis or septic shock, PTX3 levels correlate with severity of disease and infection [51–54].

The unique local production pathways and ready-to-release system suggest that PTX3 may become a sensitive biomarker which reflects the primary and local signal of innate immune response and inflammation. Data collected so far indicate that PTX3 could be a new candidate prognostic marker in cardiovascular diseases and might be associated with risk of mortality in severe sepsis and septic shock [47,53,55–60].

3. The positive and negative roles of PTX3 in inflammation and innate immunity

3.1. Effects and roles of PTX3 in infectious conditions

PTX3 has an ability to bind to certain microbes, including fungi (conidia of *Aspergillus fumigatus*, *Paracoccidoides brasiliensis* and zymosan) [61,62]; selected Gram-positive and Gram-negative bacteria (*e.g. Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Neisseria meningitides*) [63,64] and unpublished observation; and viruses (influenza virus type A, human and murine cytomegalovirus, murine hepatitis virus) [65–67]. *In vivo*, PTX3 plays non-redundant roles in the defense against infections caused by recognized microbes. *Ptx3*−/− mice are more susceptible to infections with *Aspergillus fumigatus*, *Pseudomonas aeruginosa* [61], murine cytomegalovirus [65] and influenza virus [66]. We reported that PTX3 has therapeutic effects acting as an opsonin, thus facilitating recognition and phagocytosis of microbes in an Fcγ receptor- and complement-dependent manner [64,68] (Table 2). PTX3 also exerts protective effect to infection-induced organ injury. In a murine model of severe acute respiratory syndrome (SARS) caused by murine hepatitis virus 1 (MHV-1) infection, *ptx3*−/− mice exhibit a more severe lung injury compared to wild type mice at early time points (days 1–4 after infection) [67]. PTX3 deficiency is associated with a higher early infiltration of neutrophils and macrophages into the lung. Indeed recombinant PTX3 administration significantly enhanced viral clearance, reduced lung injury, neutrophils influx in lungs and levels of inflammatory cytokines, thus indicating a protective role of PTX3 in this model of lung injury [67] (Table 2). Analyses of PTX3-overexpressing mice further support the protective role against infection. PTX3-overexpressing mice result to be protected from severe inflammatory reactions such as LPS-induced endotoxemia and cecal-ligation and puncture (CLP) [69], which are common experimental sepsis models [70]. However in a model of infection with *Klebsiella pneumonia*, PTX3-overexpressing mice show different susceptibility depending on the doses of the pathogen. In fact these mice showed

Table 2
Mechanisms of PTX3 in inflammation and innate immunity.

Effects exerted by PTX3	Suggested and/or reported mechanisms by PTX3	References
Protection against infections	- Facilitates phagocytosis of pathogens through complement, complement receptor and Fcγ receptor - Enhances viral clearance, suppresses neutrophil infiltration and inflammatory mediators in MHV-1 induced lung injury - Exerts reversible effects depending on bacteria burden (*K. Pneumoniae*), suppressing neutrophil infiltration and increasing TNFα level in higher inoculation, while facilitating neutrophil infiltration and un-affecting TNFα level in lower inoculation	[64,68][67][71]
Protection against acute myocardial infarction	- Reduces no-reflow area, IL-6 level, neutrophil infiltration and C3 deposition	[72]
Protection after ischemic stroke	- Reduces blood–brain barrier (BBB) damage, and participates in the resolution of edema and glial scar formation	[74]
Protection against lung injury	- Reduces neutrophil infiltration, cell death and fibrin deposition in LPS-induced ALI	[75,81]
Protection against LPS damage	- Controls IL-10 production, and enhances nitric oxide production from macrophages in a model of endotoxemia	[69]
Protection against acute kidney injury	- Prevents leukocyte recruitment and abrogates acute renal failure	[77]
Detrimental effects	- Facilitates neutrophil infiltration and proinflammatory cytokine levels (TNFα, IL-1β, CCL2; CXCL1) in a model of intestinal ischemia and reperfusion Increases IL-1β, CCL2 and CXCL1 mRNA level in ventilation-induced lung injury	[78,79] [80]

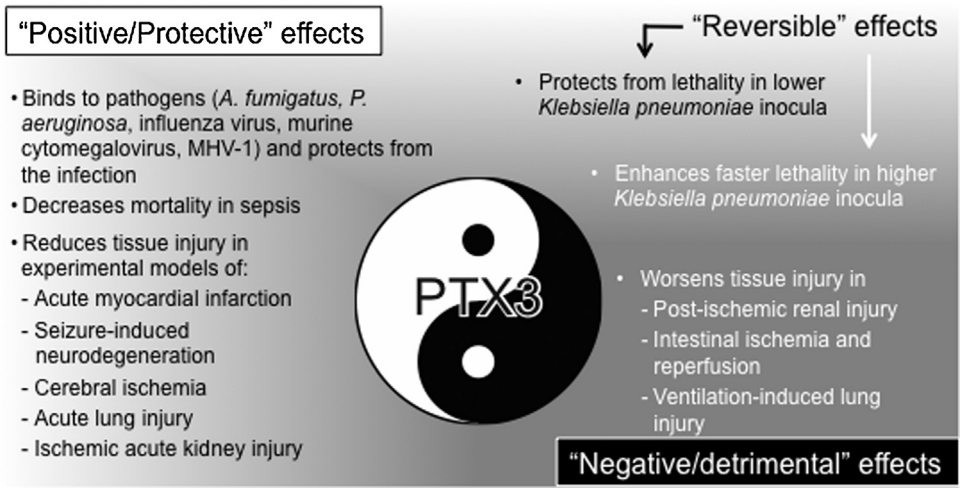

Fig. 2. The "yin-yang" effects of PTX3 in infectious or sterile inflammatory conditions. The protective effects of PTX3 are shown in black text and the detrimental effects of PTX3 are shown in white text. The upper half of the panel assigns infectious conditions and the lower half assigns sterile inflammatory conditions.

faster lethality when receiving higher inocula, and protection when treated with lower amount of bacteria [71]. This reversible response of PTX3-overexpressing mice was accompanied by reduced neutrophil influx and increased TNFα level in higher inocula, and enhanced neutrophil influx and no-change of TNFα level in lower inocula [71] (Table 2).

3.2. Effects and roles of PTX3 in sterile inflammatory conditions

The protective effect of PTX3 was also reported in sterile inflammation such as acute myocardial infarction (AMI) [72], seizure-induced neurodegeneration [73], cerebral ischemia [74] and acute lung injury (ALI) [75]. In a murine AMI model caused by coronary artery ligation and reperfusion, an increased myocardial damage associated with a greater no-reflow area, an increased neutrophil infiltration, a decreased number of capillaries, and an increased number of apoptotic cardiomyocytes were observed in *ptx3*−/− mice [72]. Additionally we observed an increased deposition of the complement component C3 delimiting the injured area, suggesting that modulation of complement activation could contribute to the cardioprotective role of PTX3 (Table 2). In a model of limbic seizure, PTX3 binds to dying cells protecting them from irreversible damage and conferring resistance to neurodegeneration [73]. On the contrary, at early time point (48 h) of ischemic brain injury, no differences were observed in infarct volume, brain edema and blood–brain barrier (BBB) damage between *ptx3*−/− and wild type mice [74]. However after 6 days of ischemic brain injury, BBB damage was higher and edema resolution did not occur in *ptx3*−/− mice. Additionally the scar formation was impaired in mice lacking PTX3, with less extracellular matrix production and reduction of microglial proliferation (Table 2). The higher susceptibility of *ptx3*−/− mice to LPS-induced ALI [75] indicates the defensive role of PTX3. In this model, the lung injury was accompanied by elevated neutrophil infiltration, cell death and fibrin deposition in the lung. PTX3 deficiency also enhanced LPS-induced tissue factor expression/activation in the lung and increased TNFα and CCL2 levels in the plasma [75] (Table 2). The higher resistance to endotoxemia by LPS was also observed in PTX3 overexpressing animals [69], which is associated to higher levels of IL-10 and nitric oxide (NO) production by peritoneal macrophages (Table 2).

In contrast to the results mentioned above, *in vivo* studies revealed that PTX3 could also have detrimental effects in certain pathologic conditions. A reversible effect was reported in ischemic acute kidney injury (AKI). Chen and coworkers reported that *ptx3*−/− mice have a reduced early expression of endothelial adhesion molecules and chemokines, and an ameliorated acute kidney injury [76]. On the contrary other reports showed that the post-ischemic renal injury was aggravated in *ptx3*−/− mice [77], and PTX3 administration was able to prevent renal leukocyte recruitment and post-ischemic kidney injury (Table 2). In an intestinal ischemia and reperfusion model, only negative effects of PTX3 were observed both in PTX3-overexpressing mice [78] and *ptx3*−/− mice [79]. The impaired survival rate of PTX3-overexpressing animals after ischemia and reperfusion of the superior mesenteric artery correlated with enhanced neutrophil influx and higher levels of proinflammatory cytokines (TNFα, IL-1β, CCL2, CXCL1) [78]. In agreement, when the same model was applied to *ptx3*−/− mice, a decreased neutrophil influx and reduction of lethality was observed accompanied to decreased cytokine production [79] (Table 2). The negative effect of PTX3 also occurred in ventilation-induced lung injury [80]. In this model PTX3 overexpression led the increased mRNA levels of IL-1β, CCL2, CXCL1 and accelerated the development of lung injury (Table 2).

Neutrophils recruitment into tissues is a common hallmark observed during the inflammatory/infectious response. Neutrophil infiltration can act as a double-edged sword during the inflammatory response, participating in tissue repair and defense but also further promoting tissue damage, as observed in ischemia-reperfusion injury, shock, systemic septicemia and ALI. Searching for a possible mechanism explaining the regulatory role of PTX3 on inflammation, we explored the interaction of this protein with adhesion molecules involved in the initial steps of leukocyte extravasation. Indeed we observed a specific binding of PTX3 to P-selectin but not to L- and E-selectin [81]. We also demonstrated that, through the interaction with P-selectin, PTX3 either derived from activated leukocytes or administered exogenously could attenuate neutrophils recruitment at sites of inflammation in a model of pleurisy or acute lung injury [81] (Table 2). This negative feedback mechanism may globally participate in the protective role of PTX3 in inflammation as well as ALI [81].

Over all, these positive or negative, sometimes reversible, effects of PTX3 (Fig. 2) reflect that the major PTX3 functions may differ in each pathophysiological condition. The elucidation of each specific role of PTX3 is essential for the clinical use of the protein.

4. Concluding remarks

CRP is a prototypic short pentraxin and a typical acute phase biomarker since it is produced as a result of systemic inflammatory responses. Conversely, PTX3 is distinguished by being an early and

local acute phase biomarker, differing from CRP for gene organization, protein oligomerization and expression pattern. In addition a main difference between CRP and PTX3 is represented by the different gene regulation from mouse to human. *In vivo* experiments on genetically modified animals are helpful to understand the roles of PTX3 in innate immunity and inflammation. Accumulated evidences from *in vivo* studies indicate that, although the predominant roles of PTX3 were host-protective, detrimental effects were observed in certain experimental settings. This "yin-yang" behavior in host-defense (Fig. 2) likely derives from the multi-functional properties of PTX3. Further investigations are necessary for the clinical use of the protein as diagnostics and therapeutics.

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