Published in final edited form as:
Trends Mol Med. 2016 June ; 22(6): 497–510. doi:10.1016/j.molmed.2016.04.007.

The Dual Complexity of PTX3 in Health and Disease: A Balancing Act?

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Abstract

The humoral arm of innate immunity is complex and includes various molecules that serve as markers of inflammation with complementary characteristics, such as the short pentraxins C reactive protein (CRP), Serum Amyloid P (SAP) and the long pentraxin, PTX3. There is a growing amount of evidence — including mouse and human genetics — that suggests that PTX3 is essential in conferring host resistance against selected pathogens and moreover, that it plays a dual antagonistic role in the regulation of inflammation. Dissection of such a yin and yang role of pentraxins in immunity and inflammation is timely and significant as it may pave the way to achieve better clinical exploitation against various diseases.

The Humoral Arm of Innate Immunity: Pentraxins

The innate immune response is the first line of defense against invading microbes and tissue damage and is composed of both a cellular and a humoral arm. Sensing of microbes and tissue injury through pattern recognition molecules (PRM. See Glossary) triggers a complex response in the organism that includes the production of inflammatory cytokines, the activation of the acute phase response, and leukocyte recruitment and polarization [1, 2]. This response has the general significance of defense and orchestration of tissue repair; however, it is potentially part of the pathogenetic mechanisms associated with the original cause of a particular disease, for instance in sepsis or in chronic inflammatory diseases, such as arthritis.

The cellular arm consists in cell-associated PRM located in different cellular compartments (plasma membrane, endosomes, cytoplasm) belonging to different molecular classes, such as the toll like receptors (TLR), the Nucleotide-binding oligomerization domain (NOD) and RIG like receptors, and the scavenger receptors. The humoral arm of innate immunity includes biochemically heterogeneous molecules such as the classic short pentraxins, C reactive protein (CRP) and serum amyloid P component (SAP), the long pentraxin PTX3, complement recognition molecules such as C1q and ficolins, and the collectins. The activation of such molecules represents an important component of the host response against invading microbes or tissue injury [3]. These fluid-phase PRMs harbor antibody-like

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properties, recognizing microbial moieties, exhibiting opsonic activity activating and regulating the complement cascade [4], as well as interacting with extracellular matrix (ECM) components [5]. The expression of humoral PRMs is induced following infection or injury in various cell types and with different kinetics, thus providing the continuous presence of these molecules both in the circulation and in tissues [3]. The liver supports the expression and production of short pentraxins systemically. Other cell types, in particular macrophages, dendritic cells (DCs) and endothelial cells (ECs), produce PTX3 in a gene expression–dependent fashion [4]. Finally, neutrophils act as a reservoir of ready-made PTX3, rapidly released within minutes to sites where tissue damage or microbial stimulation are occurring, thus representing a primary source of soluble PRM [6].

The rapid production of pentraxins at the systemic level or within tissues has been shown to correlate with the severity of various clinical conditions, such as cardiovascular diseases [7–9]. This in turn appears to sustain their high levels of expression, and consequently has often raised the question of their precise role in a given disease; are they simple markers, innocent bystanders, or actual players in disease pathogenesis [7–9]?. In particular, CRP is a widely used biomarker of inflammation in humans, however, lack of a strict evolutionary conservation between mouse and man has precluded the use of straightforward genetic approaches to explore its functions *in vivo* [10, 11]. By contrast, gene-targeted mice have allowed to define the role of PTX3 in innate immunity and inflammation as a predecessor to antibody functions and an active player in tissue remodeling [5, 12–14].

Even if most animal studies on long pentraxin PTX3 are supported by human genetic findings to suggest that PTX3 is in conferring host resistance to infection [15, 16], a prevalent concept has surfaced: depending on the disease context, cellular source or the levels of protein released, PTX3 may actually contribute to disease pathogenesis [12, 17–19]. Consequently, this review focuses on the multifaceted and yin-yang role of PTX3, in humoral innate immunity, microbial defense, as well as in the regulation of inflammation, and tissue remodeling and repair. This concept is presented at an exciting moment, when key players of innate immunity, the pentraxins, have emerged as being capable of exerting potential contradictory roles in health and disease. As such, there is no better time to begin making a larger effort to elucidate the exact roles of PTX3 in disease pathogenesis, and to better dissect its precise mechanisms of action in a context-specific manner.

PTX3: Gene and Protein

Pentraxins are conserved multimeric proteins, characterized by the presence of a conserved 8-amino acid long-sequence, the “pentraxin domain”, in their carboxy-terminal [4]. Based on the primary structure of the protomer, pentraxins have been divided into short pentraxins, including CRP and SAP, and long pentraxins, such as the prototype long pentraxin PTX3 [4]. CRP and SAP are approximately 25-kDa proteins organized in five identical subunits, and arranged in a pentameric radial symmetry [3, 4]. CRP and SAP are the main acute phase proteins produced by human and murine liver, respectively [3]. They act as players of the innate immune response by regulating the complement system, recognizing pathogens, and interacting with Fcγ receptors (FcγR), thus favoring cytokine secretion and phagocytosis of microorganisms by immune cells [20].

PTX3 was the first long pentraxin identified [4], followed by other long pentraxins, including guinea pig apexin, neuronal pentraxin (NP) 1, NP2, neuronal pentraxin receptor (NPR), and PTX4 [21]. The gene coding for *PTX3* is localized to chromosome 3 for humans and mice, and comprises three exons coding for the leader signal peptide, the N-terminal domain and the C-terminal pentraxin domain, respectively [4]. The expression of *PTX3* is mainly induced by inflammatory stimuli such as inflammatory cytokines (TNFα and IL-1β) and damage associate molecular patterns (DAMPs) or microbial moieties. In particular, IL-1 is a major inducer of local PTX3 production in sterile tissue damage, such as in mouse models of acute myocardial infarction and in 3-Methylcholanthrene-induced carcinogenesis [12, 22]. In skin wound healing, TLR sensing and IL-1 amplification are involved in the expression and production of PTX3 [5]. In urinary tract infections (UTI) mediated by uropathogenic *Escherichia coli* (UPEC), PTX3 production by human and murine uroepithelial cells has been shown to be under the control of the TLR4/MyD88 signaling pathway [14]. Accordingly, the human and murine *PTX3* gene promoter have potential binding sites for many inflammatory transcription factors, including PU.1, AP-1, NF-κB, Sp-1 and NF-IL-6 [23, 24]. The PI3K/Akt axis and JNK have also been shown to activate *PTX3* transcription [14]. In addition, epigenetic mechanisms have been implicated in the regulation of human *PTX3* expression, since methylation of a *PTX3* enhancer and a *PTX3* promoter have been deemed responsible of *PTX3* gene silencing in human colorectal and oesophageal cancer cell lines [12].

The protein is a multimer with a complex quaternary structure consisting of two tetramers linked together by interchain bridges to form an octamer of 340 kDa. The protomer consists of 381 amino acids including a 17 amino acid-long signal peptide, a N-terminal domain unrelated to any known protein and a C-terminal pentraxin domain homologous to the short pentraxins CRP and SAP [25]. A single N-glycosylation site localized in the C-terminal domain at Asn220 is occupied by core-fucosylated and sialylated complex-type oligosaccharides [26], which have been shown to modulate the interaction of human PTX3 with complement components, such as human C1q [26], factor H [27] and ficolin-1 [28], and to be required for influenza virus recognition [29] and binding to the human and murine adhesion molecule P-selectin *in vitro* and *in vivo* [30].

Various cell types, including DCs, monocytes, macrophages, epithelial cells, ECs, fibroblasts and adipocytes produce PTX3 upon stimulation with inflammatory cytokines (e.g. TNF-α, IL-1β), TLR agonists and microbial moieties (e.g. lipopolysaccharide (LPS), *Klebsiella pneumoniae* Outer membrane protein A (KpOmpA) and other pathogens such as UPEC and fungal *Aspergillus fumigatus*) [14] (Figure 1). Neutrophils store PTX3 in specific granules and rapidly release it upon encounter with microorganisms or upon cell stimulation due to infection, such as aspergillosis, or sterile tissue damage, such as human acute myocardial infarction [6, 31]. *PTX3* mRNA is transcribed only by myeloid precursors (promyelocytes and myelocytes/metamyelocytes), and not by resting mature cells in mice and humans [6].

PTX3 in Innate Immunity

The binding of PTX3 to select microorganisms, including bacteria, fungi and viruses, leads to the activation of different antimicrobial effector mechanisms [3] (Figure 1 and 2). In

addition, PTX3 behaves as an immunoregulatory molecule; it can interact with P-selectin, which results in the modulation of neutrophil recruitment, but it can also interact with components of the complement cascade and tune complement activation [30, 32]. During infection, such as in the case of human sepsis, PTX3 blood levels rapidly increase from approximately 2 ng/ml to 200 - 800 ng/ml, correlating with both infection and disease severity, and predicting patient survival [16, 33–36] (Figure 1). Importantly, although PTX3 has long been demonstrated to exert a protective role during microbial infections, it has now emerged as a potential player in contributing to immunopathology under specific circumstances.

For instance, *in vitro* specific binding of PTX3 to fungal components has been observed, for *A. fumigatus* [37], *Paracoccidoides brasilienis* and zymosan [38]. In particular, *in vivo* studies have revealed that global PTX3-deficient mice are more susceptible to *A. fumigatus* infection due to defective recognition of conidia by alveolar macrophages and DCs, and to the induction of an impaired T helper (Th) 1 lymphocyte response [37]. Intravenous or intraperitoneal treatment with recombinant PTX3 alone or in combination with antifungal agents such as amphotericin B or voriconazole, resulted in therapeutic outcomes, such as reduction of fungal burden, in murine and rat models of pulmonary aspergillosis [6, 37, 39, 40], by favoring phagocytosis. PTX3 is stored in neutrophil granules and in response to microbial recognition, it was found in human neutrophil extracellular traps (NETs), suggesting that PTX3 is involved in antimicrobial activity of NETs [6]. In this same study, the recognition and elimination of *A. fumigatus* conidia by PTX3-deficient neutrophils was poorly efficient, but opsonization of conidia by PTX3 reversed this phenotype [6, 39]. Furthermore, neutrophil adoptive transfer protected PTX3-deficient mice from aspergillosis and reduced fungal burden, revealing that neutrophil-associated-PTX3 exerted a major control of *A. fumigatus* infection [6]. PTX3 has also been reported to increase recognition and phagocytosis of microbes in an Fcγ receptor II (FcγRII) and complement-dependent manner, as evidenced from studies with C1q-, C3- and FcγR-deficient mice, which presented impaired phagocytosis of conidia [39]. In particular, the binding of PTX3-opsonized conidia to FcγRII, (which acts as a pentraxin receptor) [20], induced inside-out activation of CD11b, resulting in facilitated phagocytosis of C3b-opsonized conidia by human neutrophils [39]. In addition, other *in vitro* studies have also shown that the interaction and heterocomplex formation of PTX3 with ficolin-2 and of PTX3 with mannose binding lectin (MBL) on fungal surfaces, could increase complement deposition on the same surfaces of *A. fumigatus* and *Candida albicans*, respectively [41, 42].

Zymosan has also been shown to induce the expression of *PTX3* in mouse peritoneal macrophages *in vitro* [38]. PTX3 in turn, by binding to zymosan particles as well as to the yeast form of *P. brasiliens*, was found to induce their aggregation and phagocytosis by macrophages (in high numbers) through a Dectin-1-dependent mechanism, as demonstrated using blocking anti-Dectin-1 antibodies [38].

Moreover, single-nucleotide polymorphisms (SNPs) and haplotypes in the human *PTX3* gene have been associated with a high susceptibility to invasive aspergillosis following allogeneic hematopoietic stem-cell transplantation [43]. Since then, a link between *PTX3* genetic variants and susceptibility to mold infections has been confirmed for more than 1000

patients in the Swiss Organ Transplantation Cohort [44] as well as in a small cohort of lung transplantation patients [45], which indicate that results obtained on PTX3 in mouse models of fungal infections can be translated to humans.

PTX3 can also bind different bacteria, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Neisseria meningitidis* and uropathogenic *Escherichia coli* (UPEC) [13, 14, 37, 39, 46]. In particular, PTX3 has been reported to behave as an opsonin of *P. aeruginosa* and *UPEC*, facilitating their recognition and ingestion by human and mouse phagocytes [14, 39] (Figure 2). Accordingly, in acute and chronic models of *P. aeruginosa* lung infection in mice, PTX3 has exhibited therapeutic outcomes such as reduced bacterial burden and inflammation [47, 48]. In addition, in UTIs, uroepithelial cells have been found to rapidly express PTX3 in response to *UPEC* infection in mice and humans, with PTX3 augmenting phagocytosis by, and phagosome maturation in, peripheral blood neutrophils [14]. In agreement with these findings, global PTX3-deficient mice presented a defective capacity to clear bacteria concomitant with an exacerbated inflammatory response, as evidenced by increased production of inflammatory mediators and leukocyte recruitment in the urinary tract [14].

PTX3 binds to outer membrane vesicles (OMV) from *N. meningitidis* and to three selected meningococcal molecules (GNA0667, GNA1030, and GNA2091) [13]. Moreover, global PTX3-deficient mice showed a defective antibody response in vaccination protocols using *N. meningitidis* OMV, while co-administration of PTX3 increased antibody responses relative to controls. Importantly, administration of PTX3 reversed the defective humoral responses to vaccination with OMV of PTX3-deficient mice but also, protected infant rats from infection when challenged with *N. meningitidis* [13]. These results indicate that even if a direct effect of PTX3 in adaptive immune responses has not been described so far, the PTX3-dependent facilitated recognition of microbial components by antigen presenting cells results in improved adaptive immune responses.

The relevance in humans of the results obtained in animal models of bacterial infections has been confirmed by several genetic studies showing a clear association between specific *PTX3* genetic variants and an augmented susceptibility to *Mycobacterium tuberculosis* pulmonary infection [49], acute pyelonephritis and cystitis [14], or *P. aeruginosa* lung infection in cystic fibrosis patients [50].

With regard to viral infections, PTX3 has been proposed to play a protective role in defense against viruses such as human and murine cytomegalovirus (CMV) and influenza virus type A (IVA) [29, 51] (Figure 2). Indeed, increased susceptibility to CMV infection and to specific strains of influenza virus infections have been observed in global *Ptx3*$^{-/-}$ mice [29, 51]. In these cases, PTX3 was found to exert a protective role to the host by binding human and murine CMV, which reduced viral entry into permissive cells and DCs and induced interferon regulatory factor 3 (IRF3) activation in *in vitro* experiments [51]. Accordingly, intraperitoneal injection of PTX3 resulted in therapeutic efficacy against primary CMV infection and CMV reactivation in hematopoietic stem cell transplantation experiments in mice, as indicated by the reduced viral load and tissue damage and increased survival [51]. PTX3 also recognized specific strains of H3N2 subtype IAV by interacting with viral

envelope hemagglutinin and neuraminidase glycoproteins through a sialic acid residue on its glycosidic moiety [29]. In this manner, human and murine PTX3 acted as a “receptor decoy” for the virus preventing viral spread and infection by specific IAV strains [29]. In line with these data, *Ptx3*$^{-/-}$ animals were more susceptible to H3N2 infection than wild type mice, and administration of PTX3 resulted in a protective effect, as evidenced by increased survival and reduced viral burden [29]. In contrast, PTX3 did not result in anti-viral effects against seasonal or pandemic H1N1 and other H3N2 IAV strains because specific amino acid residues of individual viral HA sequences led to a lack of interacting ability with the sialylated residue of PTX3 [52, 53]. Hence, these data suggested selective pressures on HA leading to viral escape from the neutralizing activity of PTX3.

Another study has reported that PTX3 exerts a protective role in defense against coronavirus murine hepatitis virus strain 1 (MHV-1) *in vitro* and *in vivo* [54]. PTX3 was shown to bind to MHV-1 with a resulting reduced infectivity of cell culture. Indeed in this same study, global PTX3-deficient mice were more susceptible than their wild type counterparts to MHV-1 infection [54]. Administration of PTX3 led to protection against MHV-1 because reduced lung injury and inflammation and accelerated viral clearance were observed [54].

Although collectively these results have demonstrated a protective role of PTX3 during microbial invasion, there are other studies where PTX3 has been found to promote immunopathology in a context-specific manner (Figure 2). Indeed, in a model of *K. pneumoniae* infection in mice, PTX3 overexpression was reported to play antagonistic roles depending on the bacterial concentrations used to infect animals [17]. With high bacterial loads, transgenic mice expressing multiple copies of *PTX3* under the control of its own promoter showed faster lethality, reduced lung infiltration of neutrophils and increased bacterial dissemination in blood, when compared to wild type animals [17]. In contrast, with lower *K. pneumonia* pulmonary inocula, PTX3 overexpression conferred protection to mice by increasing the expression of proinflammatory cytokines, the recruitment of neutrophils into lung tissues, and by promoting bacterial phagocytosis [17]. The outer membrane protein A of *K. pneumoniae* (KpOmpA), a conserved major component of the outer membrane of *Enterobacteriaceae*, is in fact one of the few characterized microbial PTX3 ligands [46]. Indeed, KpOmpA has been found to induce PTX3 production and in turn, PTX3 amplifies TLR2-dependent inflammatory responses such as leukocyte recruitment in the mouse air pouch model and footpath swelling, induced upon KpOmpA recognition by scavenger receptors Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and Scavenger receptor expressed by endothelial cells I (SREC-I) [46]. These results suggest that *K. pneumoniae*-induced, amplified PTX3-dependent inflammatory responses either play protective roles for the host, or that they might contribute to immunopathology, depending on microbial load. This underlies the relevance of balanced and finely-tuned inflammatory responses and innate resistance to this type of bacterial infection (Figure 2). And although future research might further clarify whether these type of findings could be influenced by particular experimental conditions, or whether the results hold true for different pathogen infections, the fact remains that PTX3 plays a complex role in immunoregulation.

Furthermore, a pathogenic role of PTX3 has been further demonstrated in arthritogenic alphavirus infections induced by Chikungunya virus (CHIKV) and Ross River virus (RRV)

[55] (Figure 2). For instance, the expression of *PTX3* mRNA in peripheral blood leukocytes and PTX3 levels in serum have been found to be increased during the acute phase of alphavirus infection both in patients and animal models [55]. Increased *PTX3* expression was associated not only with enhanced viral load but also with disease severity defined based on temperature, pulse rate and platelet counts [55]. A murine model of acute RRV infection revealed delayed disease progression assessed based on animal strength and hind-leg paralysis and fast recovery in global $Ptx3^{-/-}$ mice when compared to wild type controls. In addition, reduced leukocyte recruitment, expression of inflammatory mediators and viral replication were reported with PTX3 deficiency. It was proposed that this phenotype could be explained by early RRV and CHIKV viral entry and replication, which were promoted by the binding of PTX3 to alphavirus, through still undefined mechanisms [55]. Interestingly, this suggested that PTX3 might be potentially exploited by viruses to facilitate an increase in viral entrance and replication in host cells [55] (Figure 2).

PTX3 in Tissue Remodeling

In addition to its involvement in immunoregulation, PTX3 has also been implicated in various other biological processes. For instance, it has been postulated that PTX3 also contributes to tissue remodeling in physiological under inflammatory conditions (Figure 1). The involvement of PTX3 in physiological tissue remodeling was first identified in PTX3-deficient infertile female mice [56]. This phenotype was reported to be due to defective assembly of the hyaluronan (HA)-rich matrix that forms around oocytes in preovulatory follicles, a process which is absolutely required for fertilization *in vivo* [56]. Indeed, PTX3 produced by cumulus cells during the preovulatory phase, was found to interact through its N-terminal domain with two HA-binding proteins, tumor necrosis factor α-induced protein 6 (TNFAIP6 or TSG-6) and the serum proteoglycan inter-α-trypsin inhibitor (IαI), which are major functional proteins of the cumulus ECM, thus providing structural integrity to the cumulus matrix [56, 57]. PTX3 is thus required to facilitate murine female fertility.

PTX3 has also been found to bind various FGFs via its N-terminal extension, including FGF2, FGF6, FGF8b, FGF10, and FGF17, [58–60], inhibiting FGF-dependent endothelial cell proliferation *in vitro* and angiogenesis *in vivo* in the model of chick embryo chorioallantoic membranes [61]. PTX3 also inhibited FGF2-dependent smooth muscle cell (SMC) proliferation and suppressed the mitogenic and chemotactic activity exerted by FGF2 on these cells [62]. It has been therefore suggested that PTX3, produced by endothelial and inflammatory cells, which are a major source of PTX3, may affect the autocrine and paracrine activity of FGFs on endothelium and SMCs, providing in turn, a mechanism for finely tuning the neo-vascularization processes and restenosis of carotid arteries after balloon injury [63, 64].

Additional evidence has indicated that PTX3 is involved in modulating inflammation and tissue damage in animal models of sterile injury [22, 65]. For example, in a murine model of cardiac ischemia/reperfusion injury, global PTX3-deficiency was associated with increased tissue damage and neutrophil infiltration in the myocardium [22]. Since higher deposition of complement C3 was observed in the infarct area of PTX3-deficient mice relative to controls [22], it was hypothesized that this phenotype could be attributed to the potential defective

regulation of complement activation via Factor H [27]. Indeed, surface-bound PTX3 was found to enhance the recruitment of Factor H, which retained its cofactor activity leading to C3b cleavage [27]. This indicates that PTX3 participates in the localization of functionally active Factor H in sites of tissue damage [27]. Moreover, PTX3-deficiency of on an apolipoprotein E knock-out background (ApoE mice) was associated with increased atherosclerosis, macrophage accumulation within atherosclerotic plaques, as well as more pronounced inflammatory profiles in vascular walls, as revealed by the increased expression of inflammatory mediators and recruitment of macrophages within the plaque [65]. In addition to regulating complement, PTX3 has been reported to selectively bind P-selectin via its N-linked glycosidic moiety, thus inhibiting leukocyte rolling on endothelium, and providing a negative feedback loop that prevents excessive P-selectin-dependent recruitment of neutrophils and tissue damage in murine models of acute lung injury, pleurisy and mesenteric inflammation [30], as well as in post-ischemic acute kidney injury [66].

Very recently, PTX3 has been demonstrated to play a non-redundant role in tissue repair, through a novel mechanism [5]. In different murine models of tissue damage including skin wound healing, chemically-induced sterile liver and lung injury, as well as arterial thrombosis, global PTX3-deficiency was associated with increased clot formation, as well as fibrin and collagen deposition/persistence in the site of damage. Under these conditions, macrophages and mesenchymal cells produced PTX3 in response to TLR activation and amplification by IL-1, localizing to the pericellular matrix of macrophages and mesenchymal-remodeling cells [5]. Moreover, PTX3-deficient mesenchymal remodeling cells exhibited defective pericellular fibrinolysis *in vitro* and impaired directional collective migration in the provisional fibrin-rich inflammatory matrix in mice *in vivo*. It was proposed that this phenotype resulted from the interaction of PTX3 N-terminal domain with fibrin and plasminogen proteins at an acidic pH, and that this occurred *in vivo* as a consequence of cell metabolic adaptation under conditions of tissue damage-associated hypoperfusion and hypoxia [5]. Furthermore, this work argued that the tripartite interaction between PTX3, fibrin and plasminogen at sites of tissue repair facilitated plasminogen-dependent fibrinolysis [5]. Deposited fibrin in damaged tissues acts as a provisional matrix component and its timely remodeling is essential for normal tissue repair [67]. Consequently, the phenotype of *Ptx3-/-* mice described by Doni *et al*. [5] demonstrates that the PTX3-dependent promotion of fibrin-rich inflammatory matrix remodeling contributes to tissue repair. Along the same lines, in another study, PTX3-deficient mesenchymal stromal cells have been found to be impaired in their ability to promote skin wound-healing in the mouse and have also been associated with defective pericellular fibrinolysis and cell migration through fibrin [68]. These studies provide further evidence of the interaction between humoral pattern recognition molecules and ECM components and underscore the evolutionary link that exists between microbial and ECM recognition in the humoral arm of innate immunity [3, 69].

With regard to the involvement of PTX3 in inflammatory processes, other studies have provided interesting data. For example, in a model of mouse cardiomyocyte death resulting from coxsackievirusB3 (CVB3) viral infection, global PTX3-deficiency increased heart injury as evidenced by increased serum creatine kinase activity and cardiomyocyte apoptosis, albeit, without affecting viral titers [70] and through a poorly defined mechanism.

In this context, it was suggested that the catalytic activity of the immunoproteasome that prevents exacerbation of CVB3-induced myocardial destruction, regulated the timely availability of factors (ERK1/2 and p38) controlling PTX3 mRNA expression and protein production during the infection [70]. This suggests that the cardio-protective function of immunoproteasome-dependent *PTX3* expression was a crucial mechanism of stress-induced damage response in myocardial inflammation during CVB3 viral infection [70].

From a different perspective, PTX3 has also been shown to play a protective role in different brain disorders. For example, in a murine model of limbic seizure, PTX3 synthesis was induced in the brain, exerting a protective role in seizure-induced neurodegeneration as evidenced by a lower number of degenerating neurons in wild type mice compared to PTX3-deficient mice [71]. In a cerebral ischemia mouse models, PTX3 production was induced in neurons and glia, and although PTX3-deficiency did not affect acute ischemic brain injury, it did however, compromise blood-brain barrier integrity and resolution of brain edema during recovery, as well as impaired glial scar formation and neurogenesis [72, 73]. As such, PTX3 has been proposed to support blood-brain barrier integrity [74].

PTX3 induction in association with tissue damage has also been identified in other pathological contexts [70] (Figure 3). For instance, in a mouse model of superior mesenteric artery ischemia and reperfusion, PTX3-deficiency was associated with inhibition of local and remote inflammation and tissue injury, whereas genetic *PTX3*-overexpression, or PTX3 i.v. administration worsened tissue injury and lethality [75, 76]. Accordingly, in another murine study, PTX3-overexpression resulted in increased inflammatory responses as well as faster decline in a model of ventilator-induced lung injury [77]. PTX3 overexpression also led to increased hypertrophic responses and ventricular dysfunction following increased pressure overload in a murine cardiac injury model [78]. More recently, PTX3 has been found to induce mouse endothelial cell dysfunction by inhibiting acetylcholine-evoked vasorelaxation in an *in vitro* model of vascular reactivity of resistance vessels and by inducing morphological changes in ECs [79]. These effects were reported to be mediated by a P-selectin/matrix metalloproteinase-1 - dependent pathway leading to impaired phosphorylation of eNOS and nitric oxide production *in vitro* [79]. In agreement, PTX3 iv administration caused hypertension in wild type animals, but not in P-selectin-deficient mice [79]. These results suggest that PTX3 may have a possible direct role on blood pressure homeostasis and endothelial function.

PTX3 in Cancer

Inflammation is an essential component of tumor microenvironments in cancer, sustaining tumor development and growth [80]. Yet, the role of the humoral arm of the innate immune system in cancer is poorly understood.

Different reports have associated increased plasma levels of CRP with cancer risk [81–83], and furthermore, elevated local or systemic PTX3 levels have been observed for several cancers including glioma, liposarcoma, lung cancer, prostate carcinoma, pancreatic carcinoma, breast cancer bones metastates, correlating with either grade of malignancy, or a poor prognosis [18, 84–88]. Indeed, gene expression profiling has identified *PTX3* as one of

the expressed genes associated with the stromal response/extracellular matrix signature and poor prognosis in human ovarian cancer [89]. In addition, *PTX3* genetic variants have been associated with increased PTX3 plasma levels and a risk of developing hepatocellular carcinoma in hepatitis C virus-infected subjects [90].

In order to investigate the role of PTX3 as either a marker of cancer-related inflammation and malignant transformation and/or as an active player in pathogenesis, our group addressed the susceptibility of PTX3-deficient mice to mesenchymal and epithelial carcinogenesis in models of 3-Methylcholanthrene (3-MCA)-induced carcinogenesis, and 7,12-dimethylbenz [α] anthracene/terephthalic acid (DMBA/TPA)-induced skin carcinogenesis [12]. In these models, global PTX3-deficiency was associated with more pronounced cancer-related inflammation relative to controls, presenting a higher number of tumor-infiltrating macrophages which showed upregulated expression of genes associated with macrophage M2-like polarization, as well as increased angiogenesis, secretion of pro-inflammatory cytokines, and complement activation (with increased C3 and lower factor H localization in tumor tissues in addition to higher C5a levels in tumor homogenates) [12] (Figure 4). Moreover, PTX3-deficient tumors were also characterized by enhanced genetic damage as indicated by increased *Trp53* mutations, oxidative DNA damage and expression of DNA damage markers, in line with the hypothesis that inflammation contributes to genetic events that can lead to cancer and to the genetic instability observed in tumors [91]. Importantly C3 deficiency in mice or inhibition through a blocking antibody of the chemokine CCL2, led to a reduction in tumor macrophages, an outcome that was sufficient to revert the increased susceptibility to chemically-induced carcinogenesis of PTX3-deficient mice. These results indicate that at least in mice, PTX3 exerts a protective role in carcinogenesis and that this effect is based on the regulation of complement activation [12] (Figure 3). The potential pro-tumoral role of the complement system has also been suggested by a recent study showing that deficiency in key components of the complement pathway (e.g., C3, C5, or C5a receptor) can be linked to colitis-associated colon cancer resistance in mice [92]. However, in specific mouse models, cancer-related inflammation was complement-independent [93, 94], indicating that complement activation may contribute to cancer-related inflammation depending upon the tissue context and driving molecular pathways.

The functional relevance of PTX3 in human cancer has been further strengthened by results showing that the *PTX3* promoter and regulatory regions of the locus are highly methylated in human mesenchymal and epithelial tumors, in contrast to normal healthy tissue, and furthermore, that such *PTX3* methylation resulted in silencing of PTX3 protein expression [12]. *PTX3* promoter hypermethylation and reduced PTX3 expression have also been reported in human esophageal squamous cell carcinomas [95]. Taken together, these studies indicate that PTX3, which is an essential component of humoral innate immunity and a regulator of complement activation, also acts as an extrinsic oncosuppressor gene in mouse and man. Moroever, its oncosuppressive role appears to act at the level of complement-mediated, macrophage-sustained, tumor-promoting inflammation inhibition [95].

Of note, since PTX3 binds certain FGFs (i.e. FGF2, FGF8) impairing the interaction with their cognate receptors [60, 61], PTX3 plays a protective role in inhibiting tumor growth by

regulating FGF-dependent effects as well [60, 96] (Figure 4). Indeed, *PTX3* overexpression, under the control of the endothelial-specific Tie2/Tek transcription regulatory sequences has been associated with reduced malignant growth of FGF2-dependent mouse TRAMP-C2 prostate cancer and B16 melanoma, as well as reduced melanoma metastasis and cancer-associated angiogenesis [96]. Furthermore, PTX3 has also been shown to impair cell proliferation and epithelial-mesenchymal transition (EMT) in human melanoma cells *in vitro* [60].

However, contrary to the reports describing a protective role of PTX3 against cancer, other studies have suggested a pro-tumorigenic effect (Figure 3). PTX3 has been reported to promote *in vitro* migration and invasion of human pancreatic tumor cells, breast carcinoma and head and neck squamous cell carcinoma, as well as macrophage chemotaxis, by still poorly defined molecular mechanisms [82, 84, 97, 98]. In another study, *PTX3* silencing was found to promote the gastric cancer cell migratory potential, the recruitment of macrophages and their subsequent binding to gastric cancer cells [98]. In addition, the transcription factor CCAAT/enhancer binding protein delta (CEBPD) was shown to activate *PTX3* transcription by directly binding to its promoter region in response to Cisplatin or 5-Fluorouracil treatment in human and murine M2 macrophages and cancer-associated fibroblasts. As a result, PTX3 was found to promote the growth, metastasis and invasion of drug-resistant human breast cancer cells in immunodeficient mice [19].

These studies in mice and the reports showing a positive correlation between *PTX3* expression and poor prognosis in specific human cancers suggest that the tumor-promoting or tumor-supressing role of PTX3 might very likely depend on tissue, cancer type and cellular source (e.g. cancer cells *versus* tumor-associated macrophages or fibroblasts) and contradict the assumption that PTX3 plays a unique role in cancer (Figure 3 and 4). However, it should be emphasized that hard genetic data in mouse and humans demonstrate that this molecule is a *bona fide* cancer gene acting as an extrinsic oncosuppressor.

Concluding Remarks

Pentraxins are a phylogenetically conserved superfamily of humoral PRMs exerting common essential functions in innate responses to pathogens and in tissue repair. CRP is a widely used biomarker of inflammation in humans, however the lack of a strict evolutionary conservation between mouse and man has precluded the use of straightforward genetic approaches to explore its functions *in vivo*. By contrast, gene targeting mouse studies have allowed a better definition of the functional role of PTX3 in innate immunity, inflammation and tissue remodeling. In addition, genetic and epigenetic data are consistent with the hypothesis that PTX3 exerts similar functions in humans. From the results described here it has been inferred that upon selective binding of conserved microbial molecules, PTX3 generally exhibits protective antibody-like functions, such as complement activation, opsonization of microbes and glycosylation-dependent regulation of inflammation. Furthermore, studies in tissue repair models have shown that PTX3-dependent promotion of fibrin-rich inflammatory matrix remodeling contributes to tissue repair and underlines the evolutionary link that exists between microbial and ECM recognition in the humoral arm of innate immunity. Thus, genetic evidence in mouse and man indicates that PTX3 is essential

for resistance against selected pathogens and that it also promotes tissue repair. Moreover, the findings described strongly support the promising potential of PTX3 in prophylaxis and therapy against infectious diseases for specific clinical settings. Of note, the regulation of complement activation also appears to be an essential mechanism of action for the oncosuppressive role of PTX3 that has been recently described, suggesting that novel therapeutic approaches could be envisioned.

However, several issues still remain (see Outstanding Questions). For example, it is important to take into account that PTX3 could potentially lead to harmful consequences to an organism under certain circumstances. Consequently, when considering the exploitation of PTX3 by viruses (such as alphaviruses) to facilitate viral entry into host cells [55] (Figure 2 and 3), the interaction of PTX3 with collectins and ficolins that can lead to potent synergic complement activation [32], as well as its potential to induce endothelial dysfunction [79] and inflammation [19, 76] (Figure 3), future clinical trials involving PTX3 administration (or blockade) should carefully assess the possibility of generating unbalanced inflammatory responses and other adverse clinical outcomes. Finally, a call is made to strive to achieve a better understanding of the multiple mechanistic pathways in which PTX3 is involved. Deciphering more clearly the multifaceted functional roles of PTX3 in physiology may indeed facilitate the development of targeted therapeutic approaches in a variety of clinical conditions.

Acknowledgments

The financial support of the European Commission (ERC-PHII), Ministero della Salute (Ricerca Finalizzata, RF-2013-02355470), Cluster Alisei (MEDINTECH CTN01_00177_962865), Italian Cystic Fibrosis Research Foundation and Italian Association for Cancer Research (AIRC, AIRC 5x1000) is gratefully acknowledged.

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Trends

- The long pentraxin PTX3 is an essential component of humoral innate immunity and plays a role in the regulation of inflammation.
- PTX3 has complex effects on vasculature, including interaction with the angiogenic growth factor GFGF and regulation of vessel wall tone.
- By modulating complement-driven inflammation, PTX3 acts as an oncosuppressor gene in mice and selected human tumors.
- By interacting with provisional matrix components, PTX3 contributes to the orchestration of wound healing and tissue repair/remodeling.
- PTX3 and the related pentraxins CRP and SAP can exert dual roles in inflammation and antimicrobial resistance, by exerting protective function or amplifying tissue damage.
- Dissection of the yin-yang role of pentraxins in immunopathology may pave the way towards a better exploitation of these molecules as envisaged disease markers and candidate therapeutic agents.

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Outstanding Questions Box

- What is the impact of PTX3 as a genetic or circulating protein marker on disease management for specific clinical conditions? In what immediate conditions can PTX3 be assessed?
- What is the mechanistic basis of the oncosuppressive role of PTX3 in various forms of cancer? Does PTX3 play differential or redundant roles in diverse forms of cancer? What is the role of Complement in carcinogenesis and human cancer?
- What is the role of PTX3 in antiviral resistance? What impact does it have in mediating antiviral defense versus facilitating viral entry? For which different types of viruses is PTX3 facilitating viral entry?
- What is the therapeutic potential of PTX3 in specific microbial infections (e.g. *A. fumigatus; P. aeruginosa*)?
- What is the mechanistic basis for the observed antagonistic effects of PTX3 in response to varying bacterial burdens during an infection and is there a threshold? Would this phenomenon apply to different pathogens? Is there an underlying functional advantage in response to these different scenarios for the host?

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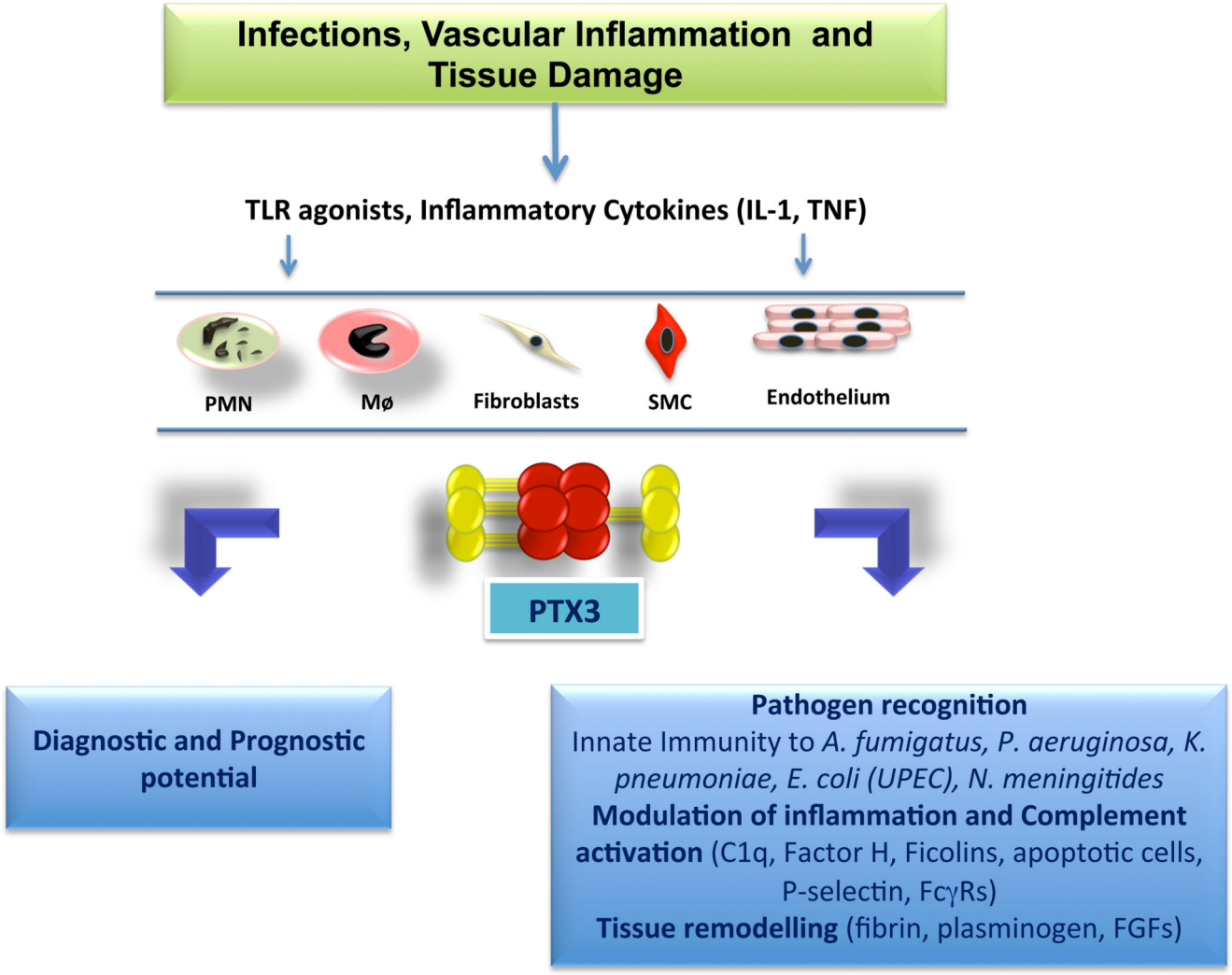

Figure 1. Schematic View of the Functional Roles of PTX3.

After injury or infection, pro-inflammatory cytokines and microbial moieties induce PTX3 production by neutrophils (PMN), macrophages (MΦ) and mesenchymal cells (fibroblasts, endothelium, smooth muscle cells (SMC)). Once released, PTX3 is a potential diagnostic and prognostic marker of inflammation and tissue damage, and player in innate immune responses, regulation of inflammation and tissue remodeling a repair, by interacting with different microbial or endogenous ligands.

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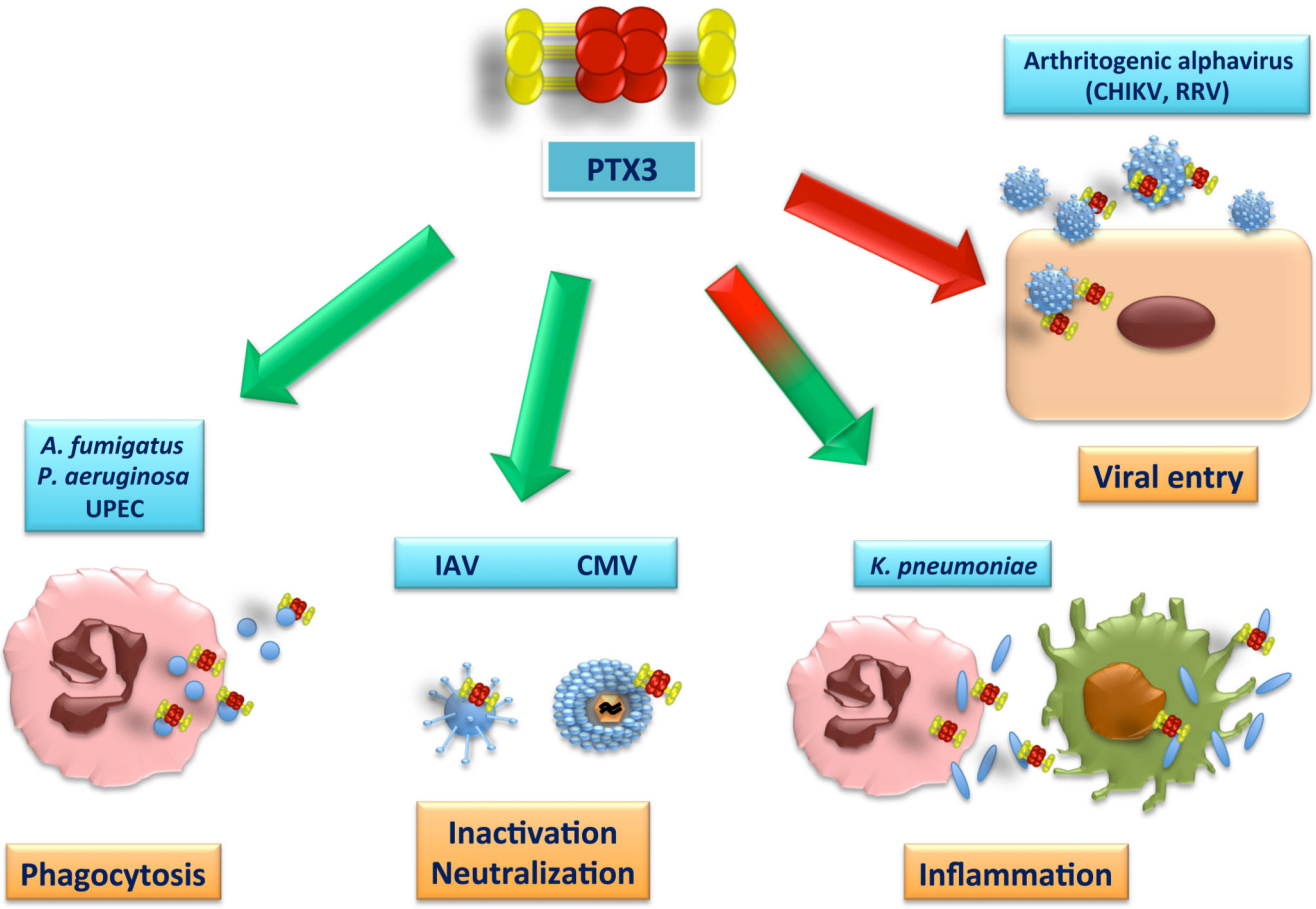

Figure 2. Role of PTX3 in innate immunity.

The binding of PTX3 to select microorganisms, including bacteria, fungi and viruses, leads to the activation of different antimicrobial effector mechanisms, such as phagocytosis, viral neutralization and inactivation, but also potential dangerous inflammation, or facilitated viral entry. UPEC: uropathogenic *Escherichia coli.* IAV: Influenza A virus. CMV: Cytomegalovirus. CHIKV: Chikungunya virus. RRV: Ross River virus.

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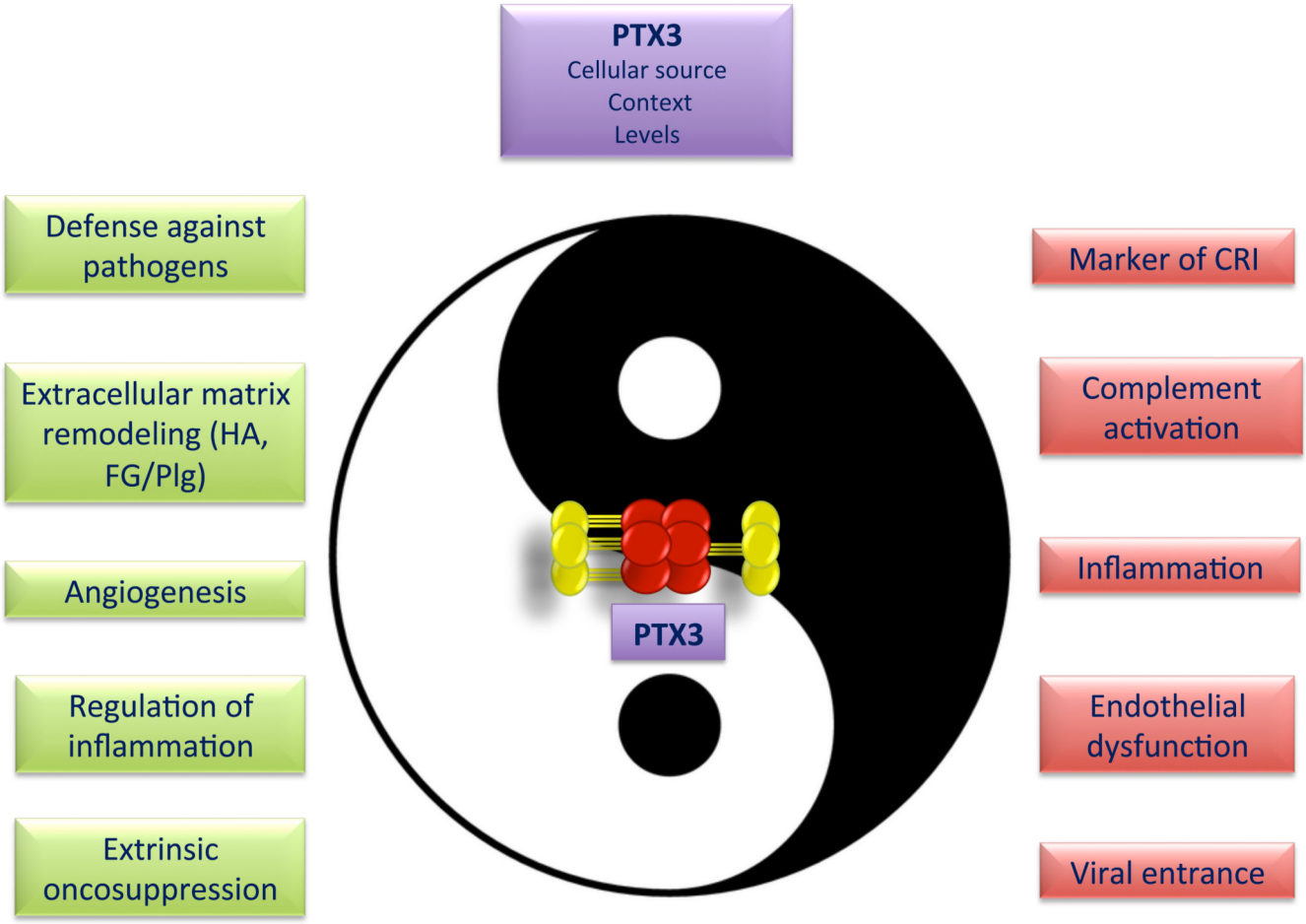

Figure 3. The Yin-Yang of PTX3 in Innate Immunity, Inflammation, Tissue Damage and Cancer.

Depending on the context, cellular source and levels of production, PTX3 plays protective roles or may contribute to pathogenesis. CRI: cancer-related inflammation; HA: hyaluronic acid; FG: fibrinogen; Plg: plasminogen.

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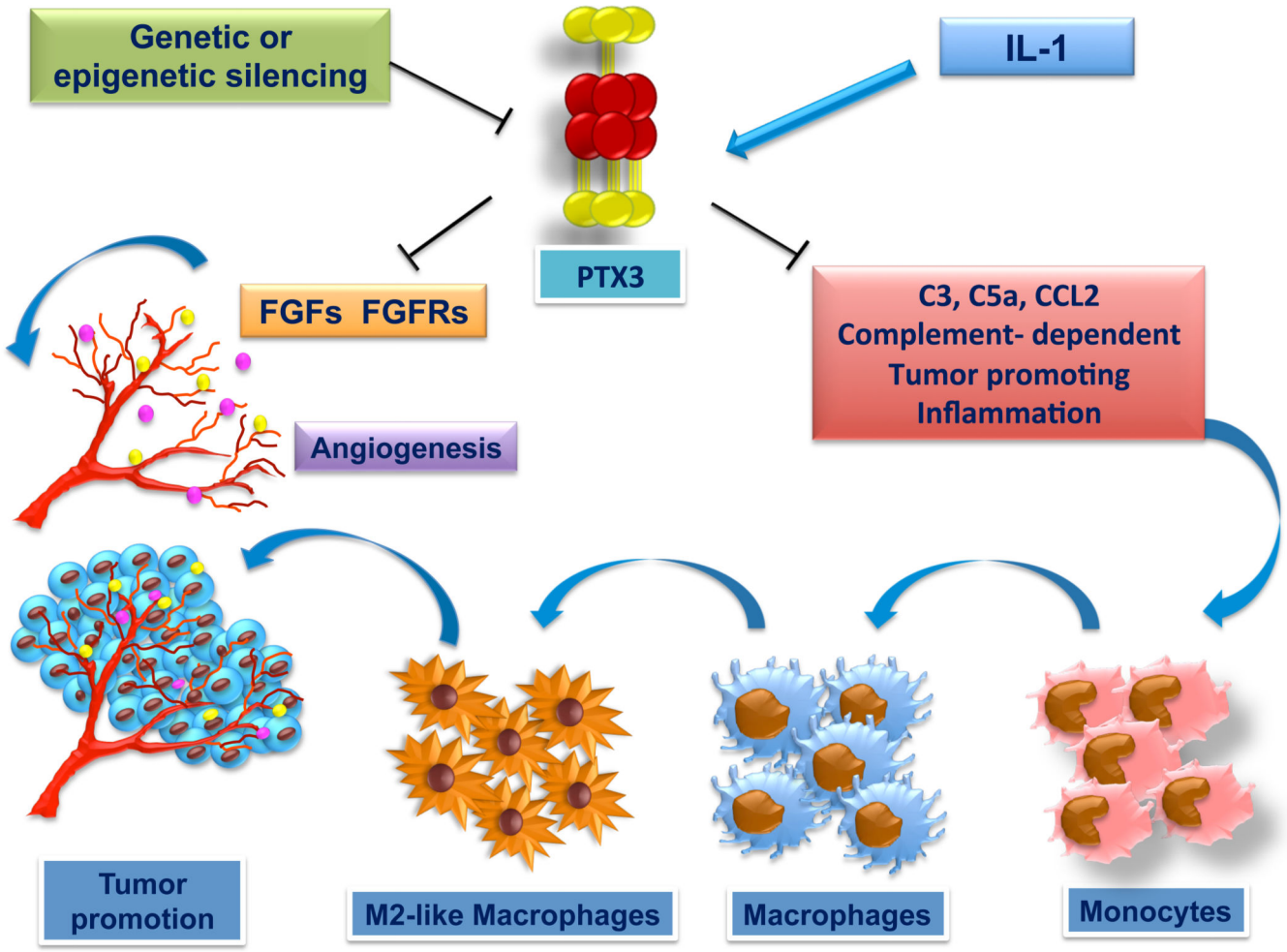

Figure 4. PTX3 as an extrinsic oncosuppressor in cancer.

In cancer, PTX3 expression is under the control of inflammatory mediators (e.g. IL-1) or genetic and epigenetic mechanisms. PTX3 regulates complement-dependent tumor promoting inflammation, including macrophage infiltration and cytokine production, as well as FGF-dependent angiogenesis, which lead to genetic instability and tumor promotion.