

Review

Molecular insight into pentraxin-3: Update advances in innate immunity, inflammation, tissue remodeling, diseases, and drug role



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ABSTRACT

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Pentraxin-3 (PTX3) is the prototype of the long pentraxin subfamily, an acute-phase protein consisting of a C-terminal pentraxin domain and a unique N-terminal domain. PTX3 was initially isolated from human umbilical vein endothelial cells and human FS-4 fibroblasts. It was subsequently found to be also produced by synoviocytes, chondrocytes, osteoblasts, smooth muscle cells, myeloid dendritic cells, epithelial cells, and tumor cells. Various modulatory factors, such as miRNAs, cytokines, drugs, and hypoxic conditions, could regulate the expression level of PTX3. PTX3 is essential in regulating innate immunity, inflammation, angiogenesis, and tissue remodeling. Besides, PTX3 may play dual (pro-tumor and anti-tumor) roles in oncogenesis. PTX3 is involved in the occurrence and development of many non-cancerous diseases, including COVID-19, and might be a potential biomarker indicating the prognosis, activity, and severity of diseases. In this review, we summarize and discuss the potential roles of PTX3 in the oncogenesis and pathogenesis of non-cancerous diseases and potential targeted therapies based on PTX3.

1. Introduction

Pentraxins are a family of evolutionarily highly conserved proteins characterized by a cyclic multimeric structure [1,2]. Besides, pentraxins belong to soluble pattern recognition receptors (PRRs) that are essential components of humoral immunity [2]. The members of the pentraxin family share a C-terminal pentraxin domain that contains an eight amino acid-long conserved pentraxin signature (His-x-Cys-x-Ser/Thr-Trp-x-Ser, where x is any amino acid) [1,3]. Based on their structural differences in subunits, the pentraxin family could be divided into two subfamilies: the short and long pentraxins [1]. The short pentraxins include C reactive

protein (CRP) and serum amyloid P component (SAP) [4–6], while the long pentraxin subfamily consists of neuronal pentraxin 1 (NP1 or NPTX1), neuronal pentraxin 2 (NP2 or NPTX2), neuronal pentraxin receptor (NPR), pentraxin 3 (PTX3), and pentraxin 4 (PTX4) [1].

PTX3 is the prototypic protein of the long pentraxin subfamily [7–9]. It is a 381-amino acid-long glycoprotein comprised of a C-terminal pentraxin domain and a unique N-terminal domain [10]. It was initially discovered in human umbilical vein endothelial cells (HUVECs) and human FS-4 fibroblasts in the 1990s [7,8], which was subsequently detected in many other cells, including smooth muscle cells, myeloid dendritic cells, epithelial cells, and tumor cells [11–14]. MiRNAs,

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cytokines, transcription factors, and drugs could modulate the expression level of PTX3 [13,15–19].

PTX3 plays essential roles in the regulation of innate immunity through exerting opsonic activity, modulating complement activation, forming and regulating neutrophil extracellular traps (NETs) [20–23]. Mice with PTX3 overexpression were protected from severe inflammatory responses such as LPS-induced endotoxic shock and polymicrobial sepsis caused by cecal ligation and puncture (CLP) [24]. PTX3 binds to fibroblast growth factor 2 (FGF-2), an angiogenic factor from the fibroblast growth factor (FGF) family, with high affinity and specificity, acting as a natural angiogenesis inhibitor [25]. In addition, PTX3 could bind to fibrinogen/fibrin and plasminogen at acidic pH and increased plasmin-mediated fibrinolysis, which is a premise for appropriate repair [26]. Interestingly, PTX3 could be synthesized by cumulus cells before ovulation and involved in the organization of the hyaluronan-rich provisional matrix required for successful fertilization [27].

Notably, PTX3 is overexpressed in many types of tumors, such as breast cancer, prostate cancer, lung cancer, hepatocellular carcinoma, glioma, melanoma, and liposarcoma [28–35]. It is also reported that elevated PTX3 levels are associated with tumor stages/grades and maybe a prognostic marker in patients with specific tumor types [32,36,37]. Besides, PTX3 has been proved to be involved in the onset, angiogenesis, metastatic dissemination, and immune-modulation of tumor [14]. Interestingly, PTX3 may play dual (pro-tumor and anti-tumor) roles in cancer, depending on cellular source, tumor type and tumor microenvironment [14]. Furthermore, plenty of studies support that PTX3 is associated with many non-cancerous diseases, including atherosclerosis, acute myocardial infarction (AMI), asthma, hepatic cirrhosis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), acute kidney injury (AKI), chronic kidney disease (CKD), sepsis, systemic inflammatory response syndrome (SIRS), and stroke [38–44].

In this review, we summarize the structure, sources, regulation, biological activities, and receptors/ligands of PTX3. We also discuss the roles of PTX3 in cancerous and non-cancerous diseases. Correspondingly, we illustrate potential targeted therapies based on PTX3.

2. Genetic variants and structure of PTX3

2.1. Genetic variants of PTX3

The human PTX3 gene, located on chromosome 3q25, is 1861 base pairs long and has three exons and two introns [7,45]. The first and second exons encode leader peptide and the N-terminal domain, while the third encodes the C-terminal-pentraxin domain [7]. Besides, it is reported that the enhancer or proximal promoters of PTX3 genes in humans and mice contain many potential binding sites which could interact with transcription factors, such as Pu1, AP-1, NF-κB, SP1, and NF-IL-6 [45,46].

Single-nucleotide polymorphisms(SNPs) in PTX3 are closely associated with susceptibility and development of some infectious and neoplastic diseases [47,48]. In chronic obstructive pulmonary disease (COPD) patients, the rs1840680 AA genotype is significantly associated with an increased risk of pulmonary aspergillosis [47]. Additionally, in non-neutropenic patients, there is a close association between the rs3816527 CC genotype and a higher risk for invasive pulmonary aspergillosis (IPA). Conversely, the rs3816527 AA genotype is possibly related to a lower risk of pulmonary cryptococcus [49]. Donor haplotype h2/h2 (G-A/G-A) in PTX3 impairs the antifungal capacity of neutrophils and may increase susceptibility to invasive aspergillosis in patients treated with hematopoietic stem-cell transplantation [50]. In HIV-uninfected Chinese patients, the rs2305619 polymorphism AA genotype has been proved to cause a higher risk of cryptococcosis [51]. Moreover, in smokers with oral cancer, the rs3816527 CC genotype was closely associated with late-stage tumors and lymph node metastasis [48]. In HCV-infected patients, the polymorphisms rs1840680 and rs2305619 were significantly associated with hepatocellular carcinoma

occurrence [52]. Furthermore, SNPs in PTX3 were related to female fertility [53]. The women carrying rs6788044 show higher lipopolysaccharide (LPS)-induced PTX3 production and a higher number of offspring [53].

2.2. The structure of PTX3

Due to structural differences in subunits, pentraxins could be classified into short pentraxins and long pentraxins [1]. CRP and SAP belong to short pentraxins [4–6], while PTX3 was identified as a prototype of long pentraxins [1]. The human PTX3 protomer is a 381-amino acid-long glycoprotein consisting of a 203-amino acid-long C-terminal domain and a 178-amino acid-long N-terminal domain [10].

About the secondary structure of PTX3, the N-terminal region in PTX3 has four α -helices connected by some short loops. At the same time, the C-terminal domain contains two anti-parallel β -sheets and a single α -helix located on the protein surface [10]. It is reported that long pentraxins share a highly homologous C-terminal domain with short pentraxins [1,3]. However, The N-terminal field in long pentraxins is unrelated to other known proteins, including short pentraxins, making it a unique characteristic of the long pentraxin group [54]. Therefore, there may be overlapping and different biological/ligand recognition properties between the long pentraxin PTX3 and short pentraxins [8,10].

Recombinant human PTX3 is secreted as a mixture of oligomers, the most abundant of which are likely to be octamers [55]. The PTX3 octamer is composed of eight identical protomers linked through disulfide bonds [55,56]. It possesses two domains of different sizes that are connected by a stalk. Thus, the PTX3 octamer is asymmetric [56]. One domain is a tetramer linked by a disulfide bond, while the other is a dimer of dimers (a non-covalent tetramer) [56]. Furthermore, it is reported that interchain disulfide bonds play a crucial role in the formation and stabilization of PTX3 multimeric structure [56]. On the one hand, in the N-terminal domain, three cysteine residues (Cys47, Cys49, and Cys103) form interchain disulfide bonds, which stabilize the assembly of PTX3 subunits into tetramers [56]. On the other hand, Cys317 and Cys318 in the C-terminal domain form an interchain disulfide bond linking PTX3 tetramer pairs into octamers [56].

Notably, PTX3 could bind to diverse ligands/receptors with different structures and sources, which possibly depends on its structural properties. The disulfide-linked tetramer and the tetramer consisting of a dimer of dimers in the N-terminal domain of PTX3 protein could respectively bind to a single FGF-2 molecule [56] (Fig. 1). FGF-2 is a pro-angiogenic factor, and PTX3 could act as an angiogenic inhibitor by antagonizing FGF-2 [56,57]. Moreover, the N-terminal domain of PTX3 interacts with the heavy chains (HCs) of inter- α - trypsin inhibitor(I α I), and this interaction plays a key role in hyaluronan organization in matrix formation of cumulus oophorus [58]. In addition, plasminogen (Plg) [26], fibrin [26], TSG-6 [59], FGF-8b [60], myeloid differentiation protein 2 (MD-2) [61] and conidia of *A. fumigatus* [62] could also bind to N-terminal region of PTX3. Furthermore, P-selectin and complement C1q bind to the C-terminal region of PTX3 [63,64], while complement Factor H (FH) [65] and Ficolin-1 [66] interact with both C- and N-terminal domains of PTX3.

There is also an N-glycosylation site on Asn 220 in the C-terminal domain of PTX3 [67]. It is found that PTX3 was primarily N-linked to complex-type oligosaccharides, which are mainly composed of (biantennary) fucosylated and (variably) sialylated structures [67]. Interestingly, it has been reported that the relative content of bi-, tri-, and tetrantennary oligosaccharides and the level of sialylation is highly variable among PTX3 from different cellular sources, indicating that the glycosylation status of PTX3 might change depending on cell type and inducing stimuli [67,68]. Glycosidic moiety in PTX3 involves in regulating the interaction of PTX3 with many ligands (e.g., hemagglutinin glycoprotein (HAG) of influenza virus, C1q, FH, and P-selectin) and plays important roles in regulating antiviral activities, complement

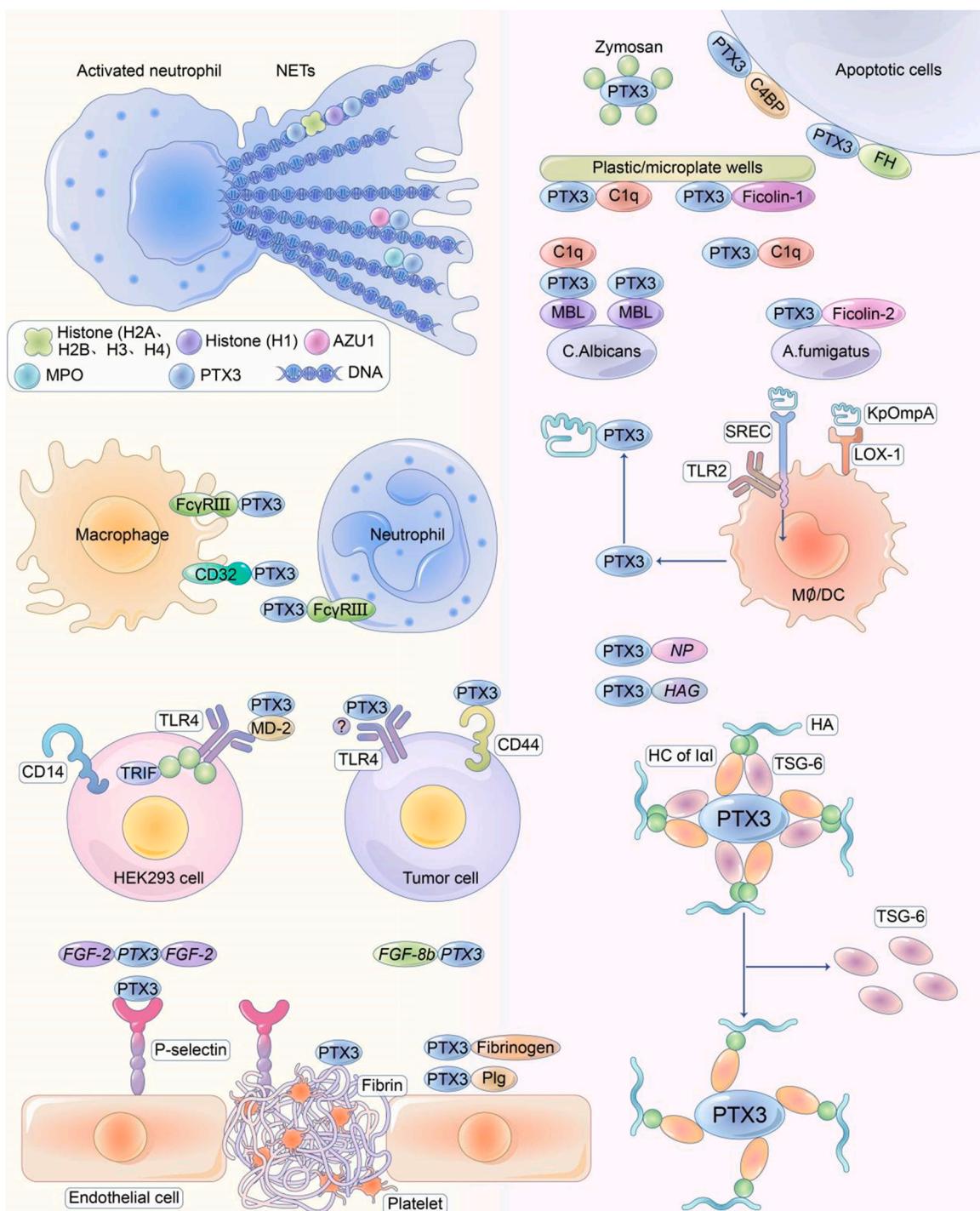


Fig. 1. PTX3 could interact with diverse receptors/ligands (e.g. zymosan, C1q, Ficolin-1, Ficolin-2, MBL, C4BP, FH, histone, AZU1, MPO, KpOmpA, NP, HAG, Fc_γRIII, CD32, TLR4, CD44, P-selectin, FGF-2, FGF-8b, Plg, HC of IαI, and TSG-6), which is crucial for its roles in innate immunity, inflammation, angiogenesis, tissue remodeling, female fertility, and oncogenesis. MBL: mannose-binding lectin; C4BP: C4b-binding protein; FH: Factor H; AZU1: Azurocidin; MPO: myeloperoxidase; KpOmpA: outer membrane protein A from Klebsiella pneumonia; NP: nucleocapsid protein of SARS-CoV-2; HAG: hemagglutinin glycoprotein of influenza virus; MD-2: myeloid differentiation protein 2; FGF: fibroblast growth factor; Plg: plasminogen; HA: hyaluronic acid; HC: heavy chains; IαI: inter-α- trypsin inhibitor; TSG-6: tumor necrosis factor-stimulated gene 6.

activation, inflammation, and tumorigenesis [64,65,67,69,70], which will be discussed in the following '5. Biological activities of PTX3' chapter and '6. PTX3 in oncogenesis' chapter.

Therefore, the complex structural characteristics of PTX3 are closely related to the versatile roles of PTX3 in physiological and pathological processes.

3. The source and expression of PTX3

PTX3, also termed tumor necrosis factor-stimulated gene 14 (TSG-14) and tumor necrosis factor-alpha-induced protein 5(TNFAIP5), was initially isolated from IL-1 β -induced HUVECs and TNF- α -stimulated human FS-4 fibroblasts [7–9].

PTX3 could be synthesized by a variety of cells, including endothelial

cells [7], smooth muscle cells [11], fibroblasts [8], myeloid dendritic cells [12], monocytes /macrophages [71], adipose cells [72], synoviocytes [73], chondrocytes [74], osteoblasts [75], cumulus cells [76] and tumor cells [14]. Moreover, PTX3 is also produced by some epithelial cells, such as proximal renal tubular epithelial cells, lung alveolar epithelial cells, and retinal pigment epithelial cells [13,17,77].

Interestingly, during the acute phase of stroke, reactive astrocytes in the peri-infarct region could produce PTX3 [78]. Furthermore, it is reported that PTX3 is stored in the neutrophil-specific granules and could be rapidly released in microbial recognition and inflammation [79].

4. The regulation of PTX3 expression

4.1. Regulatory factors at the gene level

At the gene level, the inhibition of miR-29c-3p could upregulate the PTX3 level in MEN-117 and MEN-141 meningioma cell lines [80] (Table 1). Inhibiting miR-224 could upregulate the PTX3 expression in the SiHa cell line, thus preventing the progression of cervical carcinoma

Table 1
Regulation of PTX3 expression.

Types		Targeted cells	References
Gene level	MiR-29c-3p	MEN-117 and MEN-141 cell lines	↓ [80]
	MiR-224	SiHa cell line	↓ [15]
		Oocytes, cumulus cells	↓ [81]
	MiR-150	Endothelial cells	↓ [82]
Cellular level Cytokines	MiR-29b-3p	H9c2 cell line	↓ [83]
	LPS, IL-1β, TNF-α	Human peripheral blood mononuclear cells	↑ [71]
	LPS	Human neutrophils and monocyte-derived macrophages	↑ [84]
	TNF-α	A549 and BEAS-2B cells	↑ [77]
	TNF-α, IL-1β	ARPE-19 cells	↑ [17]
	TNF, IL-1β	Amniotic membrane epithelial and stromal cells	↑ [85]
		HASMCs	↑ [88]
	IL-1β	Endometrial stromal cells	↑ [86]
	IL-1β, TNF-α, IL-17, CD40L	Primary proximal tubular epithelial cells and HK-2 cells	↑ [13]
	IFN-γ	Monocytes	↓ [87]
Transcription factors Toxins and drugs	IFN-γ, TGF-β	Synovial cells	↓ [73]
	TGF-β1	Orbital fibroblasts	↓ [18]
	Activin A, GDF-8, BMP2, BMP4, BMP7	SVOG cells	↓ [89–92]
	JUN	U87-MG cells	↑ [93]
	Pneumolysin	A549 cells	↑ [94]
	Atorvastatin	HUVECs and AoSMCs	↓ [95]
	Dexamethasone	HASMCs	↑ [19]
	Gemcitabine	A549 and SPCA1 cell lines	↑ [96]
		MCF-7 cells and glioblastoma stem cells	↑ [101,102]
		PBMCs	↓ [103]
Others	Aerobic training	A549 cells	↑ [104]
	Mechanical stretch	HUVECs	↑ [97,98]
	Inorganic arsenic, fluoride, palmitic acid	Human arterial smooth muscle cells	↑ [99]
	Modified atherogenic lipoproteins	Endothelial cells	↑ [100]
	HDL		

[15]. MiR-224 could also downregulate the NF-κB-induced PTX3 expression to attenuate innate immune response in inner ear inflammation [16]. Moreover, miR-224 hurts ovulation in the mouse model by reducing expressions of PTX3 and Smad4 [81]. In mice with the acute coronary syndrome, miR-150 could decrease the PTX3 expression via the NF-κB signaling pathway, thus facilitating endothelial cell proliferation, migration, and attenuating vascular remodeling [82]. In addition, miR-29b-3p inhibits PTX3 expression in H9c2 cells, thus aggravating the hypoxia/reoxygenation injury of H9c2 cells [83].

4.2. Regulatory factors at the cellular level

LPS, IL-1β, and TNF-α could induce the PTX3 expression in human peripheral blood mononuclear cells (PBMCs) [71]. Besides, LPS was reported to up-regulate PTX3 levels in human neutrophils and monocyte-derived macrophages [84]. IL-1β and TNF-α, but not IFN-γ, could up-regulate the protein and mRNA expression of PTX3 in human retinal pigment epithelial ARPE-19 cells via ERK and NF-κB signaling pathways [17]. TNF-α, but not LPS, could increase the PTX3 gene and protein expression in human alveolar epithelial A549 cells and human bronchial epithelial BEAS-2B cells via the JNK pathway [77]. IL-1β, TNF-α, IL-17, and CD40L could respectively enhance the PTX3 expression in primary human proximal tubular epithelial cells (PTECs) and HK-2 cells [13]. In addition, IL-1β and CD40L could synergistically increase PTX3 production in PTECs and HK-2 cells [13]. In contrast, IL-4 and IL-6 could not increase PTX3 production in the aforementioned two types of cells [13]. The expression and secretion of PTX3 could be up-regulated by TNF and IL-1β in cultured amniotic membrane epithelial and stromal cells [85]. IL-1β has been reported to increase the expression of PTX3 mRNA in endometrial stromal cells [86]. IFN-γ could inhibit the TNF-, IL-1β- and LPS-stimulated PTX3 expression and secretion in human monocytes; however, the inhibitory role of INF-γ has not been detected in human fibroblasts and endothelial cells [87]. The secretion of PTX3 protein from human airway smooth muscle cells (HASMCs) of asthma patients could be induced by TNF and IL-1β, while Th2 (IL-4, IL-9, and IL-13), Th1 (IFN-γ), or Th17 (IL-17) cytokines have no significant impact on PTX3 secretion from HASMCs [88].

Notably, IFN-γ and TGF-β could downregulate TNF-α- and IL-1β-induced PTX3 production in synovial cells in RA patients [73]. Besides, TGF-β1 could suppress the expression of PTX3 via TβRI-SMAD2/3-SMAD4 signaling pathway in orbital fibroblasts in both thyroid-associated ophthalmopathy patients and healthy volunteers [18]. Activin A, a member of the TGF-β superfamily, could inhibit the expression of PTX3 in SVOG cells via the ALK4-SMAD2/3-SMAD4 signaling pathway [89]. Growth differentiation factor 8 (GDF-8), also known as myostatin, belongs to the TGF-β superfamily and could decrease the PTX3 expression in SVOG cells via ACVR2A/ACVR2B-ALK5-mediated SMAD-dependent signaling [90]. Bone morphogenetic protein 2 (BMP2), another member of the TGF-β superfamily, could suppress the mRNA and protein expression of PTX3 in SVOG cells via the SMAD1/5/8-SMAD4 signaling pathway [91]. BMP4 and BMP7 could also down-regulate the expression of PTX3 in SVOG cells through Smad-dependent signaling [92]. It has also been reported that the PTX3 expression in U87-MG cells could be up-regulated by transcription factor JUN [93].

Interestingly, pneumolysin could increase PTX3 expression in human alveolar epithelial A549 cells via the JNK/MAPK pathway [94]. Atorvastatin reduces the synthesis and secretion of PTX3 in HUVECs and human aortic smooth muscle cells (AoSMCs) without effect on PTX3 expression in human monocytes [95]. Dexamethasone could enhance the mRNA and protein expression of PTX3 in HASMCs [19]. Gemcitabine up-regulates the expression of PTX3 in human lung cancer A549 and SPCA1 cell lines, which is mediated by reactive oxygen species (ROS), NF-κB, and hypoxia-inducible factor-1α (HIF-1α) [96]. The single or combined stimulation of inorganic arsenic (iAs) and fluoride (F) have been reported to up-regulate PTX3 expression in HUVECs [97]. Palmitic

acid increases PTX3 expression at the protein and mRNA levels in HUVECs via IKK/IkB/NF- κ B signaling pathway, which could be inhibited by honokiol [98]. Interestingly, modified atherogenic lipoproteins increase PTX3 expression in human arterial smooth muscle cells [99]. High-density lipoproteins (HDL)-induced PTX3 mRNA expression and protein secretion in endothelial cells depend on the activation of the PI3K/Akt pathway [100]. Besides, the hypoxic condition contributes to the up-regulation of PTX3 in the microenvironment of human mammary invasive carcinoma and glioblastoma multiforme (GBM) [101,102]. In older adults, aerobic training could down-regulate the expression of PTX3 in PBMCs [103]. The mechanical cyclic stretch of 20% elongation has been proved to increase the mRNA and protein expression of PTX3 in human alveolar epithelial A549 cells [104].

Thus, the expression level of PTX3 could be regulated by factors at the gene level (miRNA) and at the cellular level (cytokines, transcription factors, toxins, drugs, stress, etc.), and the complex regulatory network needs to be fully deciphered.

5. Biological activities of PTX3

5.1. PTX3 in cell growth, proliferation, differentiation, and survival

PTX3 may have a dual (pro- and anti-) role on cell proliferation, and the mechanisms behind this phenomenon are unknown and remain to be investigated. Knockdown of PTX3, without significant effect on the apoptosis of human glomerular mesangial cells(HMCs), could suppress the proliferation of HMCs via MAPK pathways [105]. The inhibition of PTX3 negatively affected osteoblast proliferation and their ability to form cell clusters and microhydroxyapatite crystals [75]. MiR-29 could promote proliferation and inhibit apoptosis and steroidogenesis of goat granulosa cells by targeting PTX3 via activating the PI3K/AKT/mTOR and Erk1/2 signaling pathways [106]. Heavy chain-hyaluronic acid (HC-HA)/PTX3 dose-dependently suppressed proliferation and epithelial-mesenchymal transition (EMT) of stimulated ARPE-19 cells by down-regulating Wnt (β -catenin, LEF1) and TGF- β (Smad2/3, collagen type I, α -SMA) signaling, respectively [107]. A deficiency of PTX3 could augment vascular smooth muscle cell proliferation after vascular injury [108]. IL-1 β -induced PTX3 could inhibit the proliferation, cell cycle, and invasion of HTR-8/SV neo and JEG3 cells in preeclampsia [109].

A host of studies have proved that PTX3 could facilitate cell differentiation in different ways. PTX3 promotes the osteoblastic differentiation of MC3T3-E1 cells via the PI3K/Akt signaling pathway [110]. Exogenous PTX3 could shape osteoclast differentiation indirectly by increasing the RANKL production of precursor osteoblasts(pOBs) [111]. PTX3 could stimulate mesenchymal stem cell (MSC) adipogenesis via the ERK signaling pathway [112]. Besides, PTX3 enhances adipocyte differentiation and lipid synthesis through neuropeptide Y(NPY)/neuropeptide Y receptor (NPYR) signaling [113]. PTX3 could promote human and murine fibrocyte differentiation by an Fc γ receptor I (Fc γ RI)-dependent mechanism [114]. PTX3 facilitates cardiac differentiation of mouse embryonic stem cells (mESCs) via the JNK signaling pathway [115]. However, contrary to the findings mentioned above, High concentrations of PTX3 may suppress endothelial progenitor cell (EPC) differentiation in vitro [116].

Notably, PTX3 may have a positive impact on cell survival. PTX3 knockdown promoted fibroblast cell death characterized by apoptosis and necrosis [117]. The PTX3 overexpression enhances the viability and suppresses the apoptosis of H9c2 cardiomyocytes [83]. Representative micrographs and quantification of TUNEL staining showed that PTX3 reduced A23187-induced apoptosis in HK-2 cells [118]. The pro-apoptotic markers tested in the brain tissues of mice with Parkinson's disease following human recombinant PTX3(hrPTX3) treatment showed that hrPTX3 could prevent apoptosis and degeneration of the dopaminergic neurons [119].

5.2. PTX3 in the regulation of innate immunity

PTX3 is a crucial mediator in innate immunity against selected pathogens, including bacteria, viruses, and fungi [120,121]. Human and murine PTX3 could bind to certain influenza virus strains and mediate a host of antiviral activities, including inhibition of hemagglutination, neutralization of virus infectivity, and inhibition of viral neuraminidase [69]. However, desialylated PTX3 is not recognized by the HAG of influenza virus and thus loses its antiviral activity [69]. Interestingly, PTX3 could act as an opsonin to promote microbial recognition and phagocytosis by macrophages, dendritic cells, and neutrophils in a complement, complement receptor, and Fc γ R dependent way [20,62,122,123]. It was also reported that PTX3 could facilitate phagocytosis in Ig-depleted serum, demonstrating that the opsonization of PTX3 is independent of Ig [65]. PTX3 induced by *Pseudomonas aeruginosa*-derived GroEL promoted the phagocytosis of *Staphylococcus aureus* into macrophages [124]. Besides, PTX3 could bind to the conidia of *Aspergillus fumigatus*, and higher fungal susceptibility of PTX3-null mice was associated with defective conidia recognition by alveolar macrophages and dendritic cells [122]. Notably, Fc γ RIIA/CD32 is crucial for the opsonic role of PTX3 towards *Aspergillus fumigatus* [62]. Zymosan(Zy) is a particle that derives from yeast and consists mainly of β -glucan and mannan [125]. Zy could activate the phagocytic, cytotoxic, and antimicrobial activities of macrophages [20,126]. It has been proved that PTX3 could bind to Zy particles and yeast cells of *Paracoccidioides brasiliensis* [20]. On this basis, Diniz et al. proposed a model to explain the opsonic activity of PTX3 in dectin-1-dependent internalization of Zy by macrophages [20] (Fig. 2A). On the one hand, PTX3 could result in Zy aggregation for activation of macrophages by binding to Zy [20]. On the other hand, in the presence of PTX3, the cell membranes of macrophages express higher levels of dectin-1 to internalize Zy particles, suggesting that PTX3 may up-regulate the expression of dectin-1 in an indirect way [20]. In addition, the opsonization of PTX3 has an inhibitory effect on the internalization of apoptotic cells by antigen-presenting dendritic cells, which might prevent the onset of autoimmune reactions in inflamed tissues [127].

PTX3 exerts regulatory roles in complement activation by interacting with components and regulators of different complement pathways (Fig. 2B). Notably, PTX3 has a dual role in activating the classical complement pathway by binding C1q [21]. C1q with PTX3 immobilized on plastic wells (a situation that mimics PTX3 bound to a microbial surface) induces the activation of the classical complement pathway with the increased C3 and C4 deposition [128]. Conversely, in the fluid phase, the interaction between PTX3 and C1q inhibits classical complement cascade by competitively blocking relevant interaction sites [128]. Furthermore, PTX3 interacts with components of the lectin pathway, including ficolin-1, ficolin-2, and mannose-binding lectin (MBL) [66,129,130]. The binding of ficolin-1 to PTX3 could trigger the lectin complement pathway activation as measured by C4b deposition [129]. PTX3 and ficolin-2 may recruit each other on the surface of *Aspergillus fumigatus* and synergistically enhance ficolin-2-mediated complement deposition [130]. MBL-PTX3 complex not only recruits C1q but also enhances C4, C3 deposition, and the phagocytosis of *Candida albicans* by polymorphonuclear leukocytes [66]. The interaction between MBL and PTX3 results in communication between the lectin and classical complement pathways via recruitment of C1q, which induces cross-activation of the complement system [66].

PTX3 also interacts with C4b-binding protein (C4BP), the regulator of classical and lectin pathways, on biological surfaces of late apoptotic cells and extracellular matrix (ECM) [131]. The binding of C4BP to apoptotic cells could be enhanced by PTX3, leading to an increased rate of C4b inactivation and reduction in the deposition of the C5b-9 complex [131]. PTX3 also interacts with FH, the primary regulator of the alternative complement pathway, on late apoptotic cells [65]. Notably, PTX3 could modulate the alternative complement pathway via facilitating FH deposition on PTX3-coated apoptotic cells and enhancing C3b

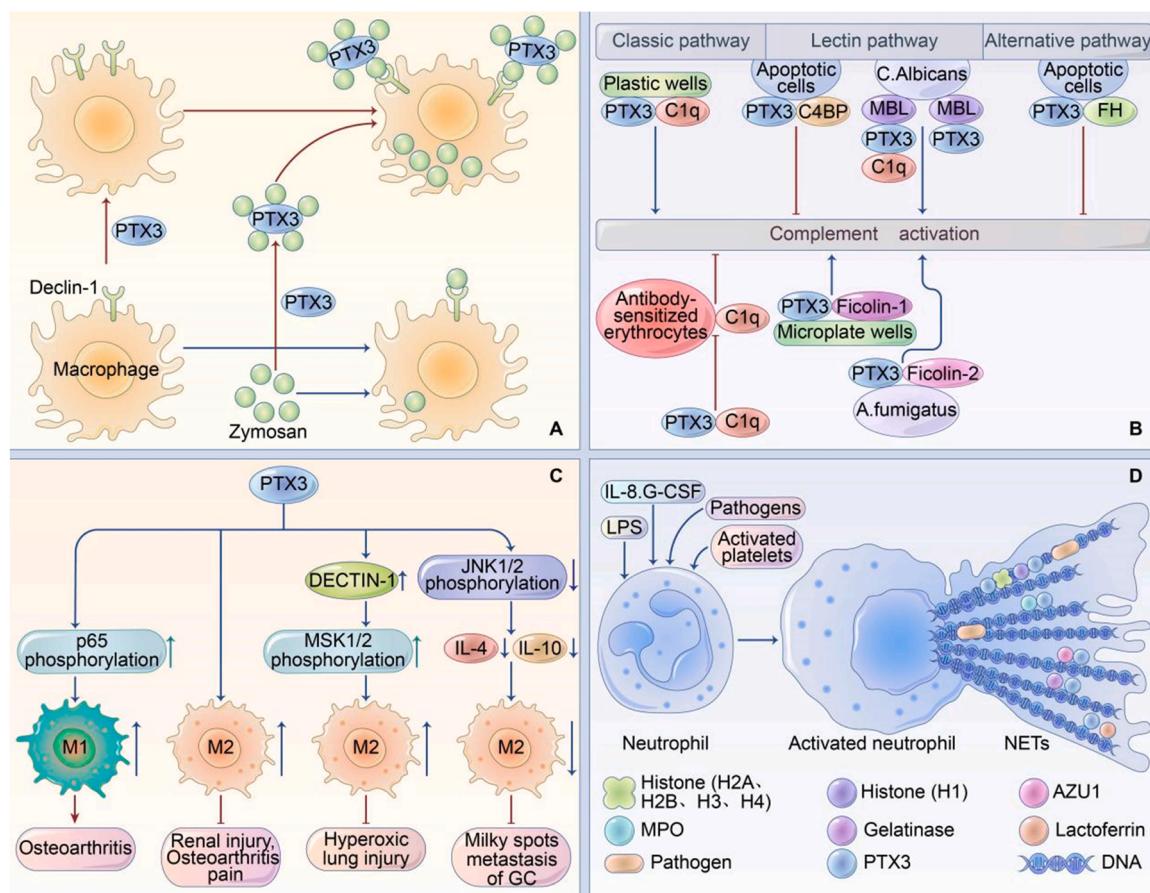


Fig. 2. PTX3 in the regulation of innate immunity. A. A model shows the opsonic effect of PTX3 in Dectin-1-dependent internalization of zymosan by macrophages. B. PTX3 regulates complement activation by interacting with components and regulators of complement pathways. C. PTX3 involves modulating macrophage polarization and related pathological processes. D. PTX3 co-localizes with some components in neutrophil extracellular traps (NETs) and may be a regulator of NETs. C4BP: C4b-binding protein; MBL: mannose-binding lectin; FH: Factor H; GC: gastric cancer; AZU1: Azurocidin; MPO: myeloperoxidase.

inactivation [65]. Therefore, PTX3 prevents excessive complement activation on apoptotic cells and cell lysis by recruiting complement inhibitors C4BP and FH to apoptotic cells [65,131,132]. Compared to native PTX3, enzymatic removal of sialic acid or the entire glycosidic moiety of PTX3 could equally enhance the binding of PTX3 to C1q [67]. Considering that the glycosylation pattern of PTX3 is highly variable, the glycosidic moiety of PTX3 might be useful in regulating PTX3-C1q interaction and fine-tuning both the activating and inhibitory activities on the classical complement pathway [67,68]. However, compared to native PTX3, enzymatically deglycosylated PTX3 bound weaklier to the full-length FH, suggesting that glycosylation is crucial for the stabilization of the PTX3-FH interaction [65]. Therefore, it's noteworthy that glycosylation on Asn 220 of PTX3 could modulate the interaction of PTX3 with components and regulators of complement pathways, thus regulating complement activation.

Interestingly, PTX3 could be secreted by neutrophils surrounded by the splenic marginal zone (MZ) [133]. PTX3 binds to MZ B cells independent of TLR4 and Fc γ Rs, facilitating IgM and class-switched IgG antibody production from MZ B cells in response to microbial capsular polysaccharides (CPS) [133]. Therefore, PTX3, an MZ B cells helper, could be a link between humoral innate and adaptive immune systems [133]. Besides, previous studies have revealed the critical role of PTX3 in the activity of macrophages (Fig. 2C). Increased PTX3 expression regulated by miR-224-5p deficiency could promote M1 macrophage polarization and aggravate osteoarthritis by targeting CD32 and activating the p-p65/NF- κ B pathway [134]. However, in an osteoarthritis rat model, PTX3 secreted by SMUP-Cells could polarize macrophages from M1 to M2 phenotype at the injury site and reduce osteoarthritis

pain [135]. Moreover, PTX3 alleviates renal damage in diabetic nephropathy via facilitating M2 macrophage differentiation [136]. In a hyperoxic lung injury rat model, PTX3 secreted by human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) under inflammatory conditions could promote M2 macrophage polarization via the Dectin-1 receptor by enhancing the phosphorylation of MSK1/2 in NR8383 cells [137]. However, PTX3 was also reported to decrease the expression of IL-4 and IL-10 by inhibiting phosphorylation of JNK1/2 in gastric cancer cells, thus suppressing the M2 macrophage polarization and leading to the inhibition of milky spots metastasis of gastric cancer [138].

Furthermore, the enlightenment of the formation of NETs as a part of the innate immune system sheds new insights into the pathologies of various diseases. NETs are large web-like structures composed of a decondensed chromatin scaffold with associated cytosolic and granule proteins [139]. It could trap different types of pathogens, facilitating their interaction with effector molecules and ultimately resulting in the clearance of pathogens [140]. NETs also participate in the progression of various pathophysiological conditions and diseases, such as innate immunity, thrombosis, atherosclerosis, autoimmune diseases, and cancer [140–144]. In response to microbial recognition and inflammatory regulators, PTX3 is rapidly released by specific granules of neutrophils and localizes in NETs formed by DNA extrusion from viable neutrophils [79] (Fig. 2D). Azurocidin (AZU1) and myeloperoxidase (MPO), two bactericidal proteins associated with NETs, could interact with PTX3 to form complexes [22]. Immunofluorescence analysis revealed a partial co-localization of AZU1 and PTX3 in NETs [22]. Further research suggests that PTX3 is partially co-localized with neutrophil granular

components, including MPO, AZU1, gelatinase, and lactoferrin, on the surface of NETs [145]. Therefore, PTX3 could be a potential component of NETs [146] and may synergistically exert an anti-microbial role with other NET components. Extracellular histones are also significant components of NETs [147], which are toxic to both microbes and host cells [23]. Polyvalent interactions and unfolding of the α -helix of PTX3 could result in histone-PTX3 aggregate formation, enabling PTX3 to bind to histones rapidly and irreversibly [148]. In sepsis, the coaggregation/interaction of PTX3 and histone could inhibit the cytotoxicity of histones towards endothelial cells by preventing the interaction between histones and endothelial cells [148]. Therefore, PTX3 may involve regulating NETs by weakening the adverse effects of extracellular histones on NETs [23].

Therefore, PTX3 may involve in the regulation of innate immunity by exerting opsonic role, modulating complement activation and the NETs. Besides, it could link the humoral arms of the innate immunity and adaptive immunity by binding to MZ B cells. Notably, above-mentioned properties of PTX3 are crucial for its anti-pathogenic roles.

5.3. PTX3 in the regulation of inflammation

PTX3 might be an anti-inflammatory factor under specific conditions. Vitro stimulation of human PBMCs with PTX3 increased the production of anti-inflammatory cytokine IL-10, while the production of the pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α was not affected [149]. Exogenous PTX3 reduced the LPS-induced production of pro-inflammatory cytokines IL-1 β , TNF- α , and monocytes chemoattractant protein 1 (MCP-1, also named CCL2) and induced active TGF- β production in THP-1 cells [150]. In a model of murine hepatitis virus 1(MHV-1)-induced lung injury, administration of recombinant PTX3 significantly increased viral clearance, dampened MHV-1-induced lung injury, and reduced early neutrophil influx and elevation of the inflammatory cytokines in the lung [151]. In an ovalbumin-induced asthma model, PTX3-deficient mice have augmented mucus production, IL-17A-dominant pulmonary inflammation, and airway hyperresponsiveness [152]. Further, PTX3 deficiency increases the infiltration and activity of CD11c $^+$ CD11b $^+$ dendritic cells in the lung, aggravating airway inflammatory responses [39]. In an LPS-induced acute lung injury(ALI) model, PTX3 deficiency could also augment intrapulmonary LPS-induced tissue factor expression/activation and up-regulate the plasma levels of TNF- α and MCP-1 [153]. In a postischemic acute kidney injury model, PTX3-deficient mice showed increased TNF and IL-6 mRNA expression and aggravated neutrophil and macrophage infiltration into the postischemic kidney [154].

PTX3 could protect against sustained inflammation in adipose tissue by modulating NF- κ B and p44/42 MAPK (Erk1/2) signaling pathway activation [155]. In the CLP-induced murine sepsis model and LPS-induced cell inflammation model, PTX3 reduced inflammatory responses and intestinal mucosal barrier damage through the TLR signaling pathway [156]. Notably, PTX3 could restrain complement-mediated inflammation during granuloma formation [157]. In a chemical carcinogenesis model, PTX3 deficiency was associated with increased cancer-related inflammation due to a defect of complement regulation [158]. Interestingly, PTX3 could bind to the adhesion molecule P-selectin, but not E-selectin and L-selectin [64]. In the pleurisy or ALI model, PTX3 derived from activated leukocytes or exogenous administration could dampen neutrophils' recruitment at inflamed sites by interacting with P-selectin [64]. Notably, enzymatic deglycosylation of PTX3 and site-directed mutagenesis of its Asn220 contributed to a 70 % reduction of PTX3-P-selectin interaction, suggesting that the glycosidic moiety of PTX3 may mediate its regulatory role on inflammation [64]. Besides, PTX3 could bind to MD-2 and thus activates the anti-inflammatory TLR4/TRIF signaling pathway, resulting in the decreased inflammatory burden following fungal infection [61].

However, PTX3 was also reported to have a pro-inflammatory effect. In BV-2 cells treated with A β , PTX3 knockdown has an inhibitory effect

on the production of inflammatory proteins and cytokines (TNF, IL-1 β , IL-6, CD86, iNOS, and COX-2), and the phosphorylation of I κ B α [159]. In a model of murine ischemic AKI, compared to wild type (WT) mice, PTX3 knockout mice had reduced endothelial expression of cell adhesion molecules at 4 h of reperfusion, possibly leading to a decreased early maladaptive inflammation in kidneys [160]. In an intestinal ischemia and reperfusion model, PTX3 deficient mice showed decreased neutrophil influx, reduced production of CXCL1, TNF- α , and reduced lethality [161]. In another intestinal ischemia and reperfusion model, PTX3-overexpressed mice were observed with increased neutrophil influx, up-regulated expression of TNF- α , IL-1 β , CCL2, and CXCL1, and reduced survival rate [162]. PTX3 silencing could suppress LPS-induced inflammation and MUC5AC production via the inhibition of the PI3K/Akt pathway [163]. Moreover, PTX3 could interact with outer membrane protein A from *Klebsiella pneumoniae* (KpOmpA) [164], a pathogen-associated molecular pattern (PAMP) from the outer membrane protein (OMP) family [165]. OmpA, recognized by monocytes and DCs, could induce a TLR2-dependent pro-inflammatory response [165] that promotes PTX3 production, while PTX3 binds to OmpA and enhances the pro-inflammatory response in turn [164]. OmpA-induced inflammation was significantly reduced in PTX3-deficient mice, and administration of exogenous PTX3 restores partial inflammatory response [164]. Besides, complement activation is involved in PTX3-mediated enhancement of OmpA-induced pro-inflammatory response [166].

Therefore, PTX3 may involve in the regulation of inflammation by modulating the levels of pro- and anti-inflammatory cytokines, influencing inflammatory cell infiltration, and interacting with inflammation-associated ligands, which closely correlates with its regulatory roles on complement activation.

5.4. PTX3 in angiogenesis and thrombosis

Angiogenesis is a process of forming new blood vessels from pre-existing vessels, which exerts an essential role in inflammation, wound healing, embryogenesis, and tumorigenesis [167]. The balance between pro-angiogenic and anti-angiogenic factors is crucial for angiogenesis [168]. Several FGF family members, such as FGF 1–5, 7, 8b, 9, 10, have been proved to possess the angiogenic property in some pathophysiological conditions [57]. PTX3 could exert an anti-angiogenic role by interacting with certain FGF family members. FGF-2 is a prototypic heparin-binding angiogenic growth factor that facilitates neovascularization in wound healing and inflammatory responses [57]. As mentioned above, the PTX3 octamer has two independent FGF-2 binding sites in the N-terminal domain [56]. PTX3 and FGF-2 could bind to each other independent of their free or ECM-immobilized status [25], and PTX3 prevents FGF-2 from binding to heparan-sulfate proteoglycans (HSPGs) and tyrosine kinase FGF receptors (FGFRs) in the surface of endothelial cells, leading to the inhibition of angiogenic property of FGF-2 [25]. Both exogenous and endogenous PTX3 could inhibit the FGF-2-induced autocrine stimulation loop in endothelial cells, thus inhibiting cell migration, proliferation, and morphogenesis in angiogenesis [25]. In addition, PTX3 prevents FGF-2 from binding to FGFRs on human coronary artery smooth muscle cells (HCASMCs) for inhibition of angiogenesis [169]. Specifically, exogenously administrated PTX3 inhibits FGF-2-induced proliferation and chemotaxis of HCASMCs, while endogenously overexpressed PTX3 suppresses FGF-2-induced proliferation and survival of HCASMCs [169]. Compared to exogenous PTX3, endogenously overexpressed PTX3 exhibits a more potent role in inhibiting FGF-2-induced angiogenesis [169]. Interestingly, TSG-6 could revert the inhibitory effects exerted by PTX3 on FGF-2-mediated angiogenesis via the competition of PTX3/FGF-2 interaction [59].

FGF-8b has the most potent angiogenic and tumorigenic abilities in all FGF-8 isoforms and is detected with high expression in breast, prostate, and ovarian cancers [170,171]. PTX3 binds to FGF-8b with high affinity and prevents it from binding to FGFR1 (IIIc), thus

inhibiting FGF-8b-induced ERK1/2 activation, cell proliferation, and chemotactic migration of endothelial cells [60]. PTX3 also significantly suppresses the FGF-8b-induced neovascularization *in vivo* [60]. So far, there is no evidence of the interaction between PTX3 and two FGF family members, FGF-1 and FGF-4 [25]. Furthermore, PTX3 does not affect VEGF, EGF, TPA, and DAG-induced endothelial cell proliferation because of its limited binding capacity to these mediators [25].

PTX3 may exert an anti-thrombotic effect in certain conditions. Though the interaction between PTX3 and P-selectin represses neutrophils' recruitment at inflamed sites [64], PTX3 does not affect P-selectin-mediated platelet aggregation [172,173]. However, it was observed that the pre-incubation of fibrinogen with PTX3 decreased platelet aggregation in the presence of collagen, which primarily depended on the N-terminal region of PTX3 [172]. Similarly, collagen pre-incubation with PTX3 repressed platelet aggregation in the presence of fibrinogen, which mainly relied on the C-terminal domain of PTX3 [172]. Thus, PTX3 was proposed to localize between the damaged vascular endothelium and the thrombi, which could dampen the pro-thrombotic effects by reducing fibrinogen and collagen induced platelet aggregation [172]. In FeCl₃-induced injury models, hrPTX3 treatment prevented carotid artery occlusion in PTX3-knockout and WT mice, demonstrating a protective role of PTX3 in arterial thrombosis [172].

However, several studies showed that PTX3 might play a thrombophilic by enhancing TF expression, which is paradoxical to the outcome above. PTX3 enhances tissue factor (TF) activity and antigen from LPS-stimulated monocytes and LPS-, IL-1 β -, and TNF- α -stimulated HUVECs in a dose-dependent way [174,175]. The regulation of TF synthesis by PTX3 depends on the increased phosphorylation, degradation of I κ B α , and increased migration of c-Rel/p65 into the nucleus [174]. Besides, PTX3 dose-dependently reduces the whole blood coagulation time and increases TF expression in human monocyte-derived dendritic cells (moDCs) under low-shear conditions [176].

5.5. PTX3 in tissue remodeling

It has been reported that innate immunity coordinates a host of physiological and pathological processes, contributing to tissue repair [177,178]. After tissue injury, PTX3, a component of the humoral arm of innate immunity [179], was induced by TLR sensing and IL-1 β amplification, in which MyD88- and TRIF-dependent signaling pathways were involved in the process [26].

Timely fibrin degradation after fibrin deposition and fibrosis is crucial for tissue repair [180,181]. PTX3 could bind to fibrinogen (FG), fibrin, and Plg at acidic PH (optimal interaction at PH5.5–6.5) but not at neutral PH, and the interaction among PTX3, FG/fibrin and Plg could facilitate fibrin degradation [26]. Specifically, the N-terminal domain of PTX3 was proved to interact with fibrinogen, fibrin, and Plg, while the C-terminal region could only bind to Plg with low affinity [26]. The acidic environment needed for binding PTX3 to fibrin and Plg suggests that the interaction is restricted to wounding sites and thrombi [26, 182]. Therefore, the acidic pH could be regarded as a “switch-on” signal for the role of PTX3 in fibrinolysis [182].

Notably, after tissue injury, the conversion of Plg to plasmin is crucial for tissue remodeling and removal of blood clot [183]. Mapping experiments suggest that PTX3 binds to Plg Kringle 5 domain to initiate Plg conformational changes, leading to closed-inactive Plg transition to an open form [26, 184–186]. Then the tissue-type Plg activators (t-PAs) and urokinase-type Plg activators (u-PAs) could cleave and convert the open form of Plg to plasmin [186]. Administering mesenchymal stromal cells (MSCs) to acute or chronic wound sites could promote wound healing by increasing granulation tissue formation, re-epithelialization, and angiogenesis [187]. Activated MSCs could produce, secrete and even store PTX3 [188,189]. Compared to control wounds, PTX3-deficient MSC-treated skin wounds had more fibrin deposition, indicating impaired pericellular fibrinolysis in PTX3-deficient MSC [187]. Due to impaired fibrinolysis, PTX3-deficient MSCs were less

recruited and invasive at the wound sites, ultimately causing reduced granulation tissue formation and delayed wound closure [187]. Interestingly, plasminogen-conversion inhibitors (APR and PAI-1) could drastically prevent the fibrinolysis of MSCs, suggesting that a plasmin-mediated fibrinolysis mechanism occurred in this model [187]. Thus, PTX3 could create an environment that fosters the recruitment of MSCs and other remodeling cells [187], depending largely on its role in potentiating plasmin-mediated fibrinolysis.

PTX3 may exert important roles in the synapse formation and repair of brain injury. Brain ECM, also named perineuronal network (PNN), is crucial in the stability and mobility of AMPA receptor (AMPAR) as well as synapse development [190,191]. PTX3 promotes the remodeling of PNN by the β 1-containing integrin-ERK1/2 signaling pathway, which induces the recruitment of postsynaptic AMPARs and enhances excitatory synaptic activity [190]. Besides, after ischemic brain injury, compared to WT mice, PTX3 knockout mice showed impaired glial scar formation and extracellular matrix deposition [192]. Furthermore, after ischemic/traumatic brain injury, PTX3 could promote neurogenesis both *in vivo* and *in vitro* [193,194].

Bone remodeling includes timely and concordant bone resorption and bone formation induced by mechanical forces and microfractures, regulated by a host of cytokines, prostaglandins, and growth factors [195,196]. PTX3 expression was positively correlated with bone density and the proliferation and maturation of osteoblast, suggesting that PTX3 acts as a promoter of bone deposition and plays a crucial role in normal bone homeostasis [75]. In the fracture healing process, PTX3 expression was detected during both the early (inflammatory) phases and the late (regenerative) phases [195]. During the reparative phase of the fracture healing process, compared to PTX3-sufficient mice, PTX3-deficient mice had reduced callus mineralization and decreased expression of type I collagen (Col1) [195]. Notably, in the early stages after fracture, the osteoprogenitor population composed of non-hematopoietic/non-endothelial cells could induce the expression of both PTX3 and FGF-2 [195]. During bone formation, the N-terminal domain of PTX3 interacts with FGF-2 to reverse the anti-differentiation effect of FGF-2, which is significant for unlocking osteoblast maturation [195]. Besides, PTX3 was reported to promote osteogenic differentiation in an *in vitro* inflammatory environment by activating the HA/CD44/FAK/AKT positive feedback loop, and facilitate bone regeneration after periodontitis [197].

PTX3 could be regarded as an essential molecule in regulating ovarian functions and female fertility [27]. In preovulatory follicles, PTX3 is secreted by cumulus cells surrounding the oocyte under the stimulation of LH or hCG [27]. PTX3 could not directly interact with hyaluronic acid (HA), while it could bind to TSG-6 and HCs of I α I [58, 76]. PTX3 was proposed to potentially stabilize the HA network by interacting with some HCs that covalently bond to HA molecules [27,58, 198]. Additionally, TSG-6 and I α I critically regulate the activity of PTX3 in the HA-rich ECM [199]. Therefore, PTX3 in the cumulus HA-rich matrix is crucial for cumulus matrix stability and female fertility [27]. Besides, after ovulation, endothelial and stromal cells of the corpus luteum could express PTX3, which may involve in vasculature involution during the regression of the corpus luteum by binding to FGF-2 and inhibiting the pro-angiogenic activity of FGF-2 [27, 200–202]. Notably, PTX3, trapping FGF2 from undifferentiated stromal cells, was identified as a critical Menin-H3K4me3 regulated downstream gene in decidual regionalization and pregnancy maintenance by inhibiting the cross-talk between FGF2-ERK1/2 and BMP2 [203].

Together, these studies demonstrate that PTX3 is broadly involved in tissue remodeling and repair, a function that depends on recognition of matrix molecules, highlighting the link and interaction between hemostasis and immunity [182]. Besides, considering its beneficial effects on fertilization and pregnancy maintenance, PTX3 could be regarded as a promising therapeutic target for female infertility.

6. PTX3 in oncogenesis

The over-expression of PTX3 has been observed in multiple types of tumors, including pancreatic carcinoma [37], head and neck squamous cell carcinoma (HNSCC) [204], gastric cancer [205], breast cancer [28], cervical cancer [36], glioma [32], liposarcoma [34], prostate cancer [29,206], lung cancer [30], melanoma [33], multiple myeloma (MM) [207], hepatocellular carcinoma(HCC) [31], colorectal carcinoma [208], diffuse large B-cell lymphoma (DLBCL) [209], clear cell renal cell carcinoma (ccRCC) [210], and ovarian epithelial cancer [211] (Table 2). However, some tumor types also showed a reduction in PTX3 expression levels, such as gastric cancer [212], esophageal squamous cell carcinoma [213], prostate cancer [214], and bladder cancer [215]. Increased PTX3 expression level is significantly related to tumor stages or grades of cervical cancer [36], glioma [32], and lung cancer [30]. In addition, PTX3 is proved as the prognostic indicator in patients with pancreatic carcinoma [37], breast cancer [28], glioma [32], lung cancer [216], HCC [31], colorectal carcinoma [208], DLBCL [209], ccRCC [210], ovarian epithelial cancer [211].

6.1. Pro-tumorigenic role of PTX3

EGF promotes the PTX3 expression in HNSCC cell lines by activating PI3K/Akt- and NF- κ B pathways [204]. In PTX3-deficient HNSCC cells, EGF-induced expression of metastatic molecules, fibronectin, and matrix metalloproteinase-9 (MMP-9) were repressed [204]. Additionally, oleate could promote the PTX3 expression in the HNSCC cells via AKT/NF- κ B pathway [217]. PTX3 derived from oleate-induced autocrine production could up-regulate the expression of EMT markers, MMP-3, and vimentin, which enhances the cell communications between tumor cells and endothelial cells to promote the dyslipidemia-mediated HNSCC metastatic seeding in lung [217]. Besides, TNF- α -induced PTX3 could promote the migration of human gastric cancer HTB135 cells, enhance the chemotaxis of macrophages and the binding of macrophages to HTB135 cells [205]. PTX3 secreted by melanoma cells promotes the invasion and migration of melanoma by TLR4/NF- κ B signaling pathway [33] (Fig. 3A). PTX3 upregulation

induced by a brain-derived neurotrophic factor (BDNF) through the TrkB signaling pathway stimulates the interaction between bone metastatic gastric cancer cells and OBs, enhancing the osteolysis of bone metastatic gastric cancer [212].

PI3K activation up-regulates the PTX3 expression in basal-like breast cancer (BLBC) cells by AKT- and NF- κ B-dependent signaling pathways, and PTX3 could promote cancer stem cell-like traits in BLBC [28]. SH3 domain-containing ring finger 3 (SH3RF3), a scaffold protein with E3 ligase activity [218], facilitates the cancer stem cell-like properties in breast cancer by up-regulating the expression of PTX3 via the JNK-JUN pathway [219]. Besides, knockdown of PTX3 has been proved to suppress cell proliferation in glioma GBM8401 cells by inducing G0/G1 cell cycle arrest [32]. Inhibition of PTX3 also curbs the invasion and migration of GBM8401 cells by down-regulating the expression of MMP-1 and MMP-2 [32]. In addition, knockdown of PTX3 reduces cell viability and colony-forming ability of cervical cancer cells, SiHa and HeLa [36]. Knockdown of PTX3 in SiHa and HeLa cell lines decreases the expression of cyclin B1, cdc2, and cdc25c and enhances the expression of p-cdc2, p-cdc25c, p21, and p27, indicating that PTX3 silencing could induce cell cycle arrest at G2/M phase [36]. Knockdown of PTX3 also suppresses the migration and invasion of SiHa and HeLa cells by down-regulating MMP-2, MMP-9, and urokinase Plg activator (uPA) [36]. In non-small cell lung cancer (NSCLC), the Akt/NF- κ B signaling could up-regulate the expression of PTX3, and the increased PTX3 expression facilitates cell proliferation and inhibits the cell apoptosis in A549 and H1299 cell lines [220]. Besides, PTX3 over-expression enhances the EMT process and promotes proliferation, invasion, and metastasis of Huh7 HCC cells [31]. On the contrary, knockout of PTX3 shows the opposite results in MHCC97h HCC cells [31].

In human esophageal carcinoma KYSE450 cells, PTX3 knockout arrested cells in G0/G1 phase, suppressed cell proliferation, and promoted cell apoptosis [221]. PTX3-knockout KYSE450 cells also had lower migration ability and higher sensitivity to chemotherapy and radiotherapy [221]. Interestingly, after PTX3 was knocked out, the cell glycolysis ability was impaired, while the oxidative phosphorylation capacity tended to be enhanced in KYSE450 cells [221]. Chemotherapeutic drugs (Doxorubicin)-induced up-regulation of small extracellular vesicles (sEV) secretion and sEV-associated PTX3 expression was reported to promote the metastasis of breast cancer [222]. Further, Cisplatin (CDDP) or 5-Fluorouracil (5-FU) could induce the up-regulation of CCAAT/enhancer-binding protein delta (CEBD). At the same time, CEBD could increase the expression of PTX3 by binding to its promoter region to activate its transcription in M2 macrophages and myofibroblasts/cancer-associated fibroblasts (CAFs) [70]. Recombinant PTX3 proteins purified from insect cells (bvPTX3) promoted CEBD-mediated sphere formation, anticancer-drug resistance, and migration/invasion of human breast cancer MB231/mCDRM231 cells [70]. However, the recombinant bvPTX3 mutant of Asn220 (mbvPTX3) could attenuate bvPTX3-induced stemness, drug resistance, and migration/invasion of breast cancer cells, suggesting that the glycosylation status of PTX3 is crucial for its tumorigenic role [70]. Besides, Hsiao et al. found that TGF- β 1 induced PTX3 expression via activating CEBD in stromal fibroblasts [223]. PTX3 could directly interact with CD44, which activates the downstream ERK1/2, AKT, and NF- κ B signaling pathways, leading to the metastasis, invasion, and stemness of MDA-MB-231 triple-negative breast cancer (TNBC) cells [223] (Fig. 3B).

6.2. Anti-tumorigenic role of PTX3

As mentioned above, the N-terminal domain of PTX3 interacts with certain members of the FGF family (FGF-2 and FGF-8b) to inhibit their pro-angiogenic activity [56,60]. Dihydrotestosterone (DHT) up-regulates the expression of FGF-2 and FGF-8b, thus activating an FGF-induced autocrine loop of stimulation [60,214]. The over-expression of PTX3 suppresses the tumor proliferation triggered by DHT or FGFs in prostate cancer cell line TRAMP-C2 and breast cancer

Table 2
The expression of PTX3 in certain cancer types.

Expression	Systems	Tumor types	References
Over-expression	Respiratory system	Lung cancer	[30,216,220,36]
		Pancreatic carcinoma	[37]
	Digestive system	Hepatocellular carcinoma	[31,52]
		Gastric cancer	[205,212]
	Urinary system	Colorectal carcinoma	[208]
		Renal cell carcinoma	[210]
	Hematologic system	Diffuse large B-cell lymphoma	[209]
		Glioma	[32]
	Central nervous system		
	Motor system	Multiple myeloma	[207]
Down-expression	Reproductive system	Breast cancer	[28,365]
		Cervical cancer	[36]
	Others	Ovarian epithelial cancer	[211]
		Prostate cancer	[29,206]
	Digestive system	Head and neck squamous cell carcinoma	[204]
		Liposarcoma	[34,35]
	Reproductive system	Melanoma	[33]
		Gastric cancer	[212]
	Urinary system	Esophageal squamous cell carcinoma	[213]
		Prostate cancer	[214]
		Bladder cancer	[215]

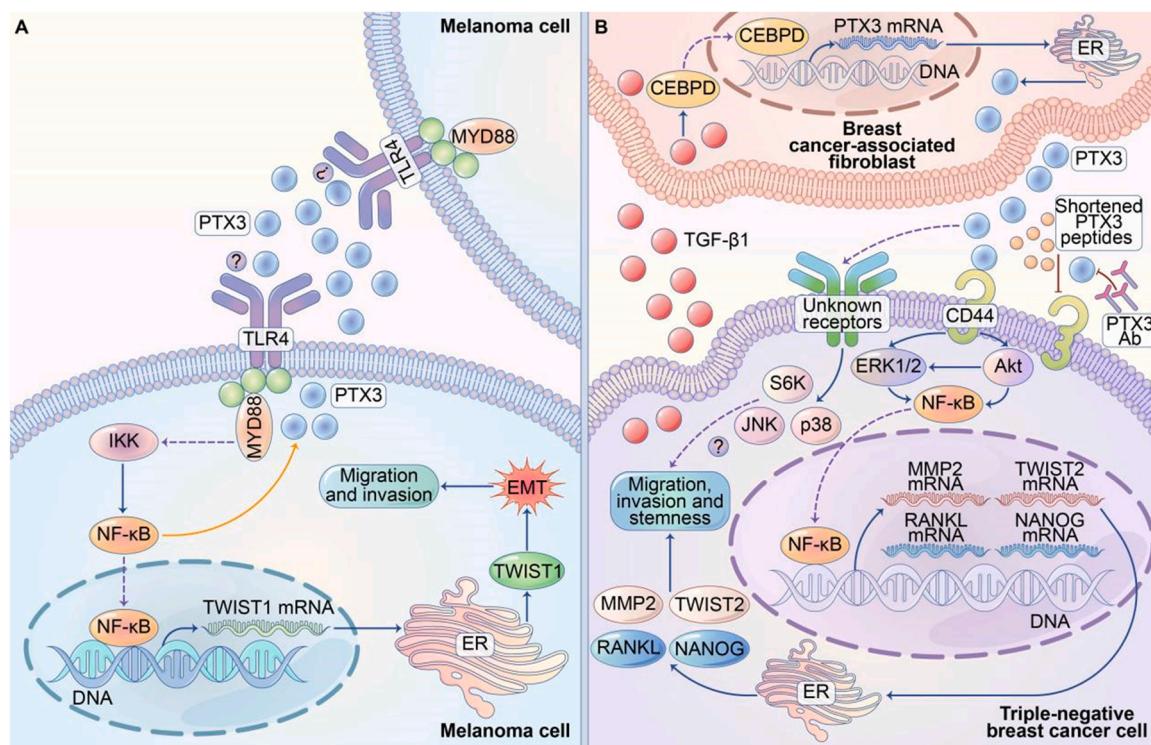


Fig. 3. PTX3 interacts with receptors to promote the migration and invasion of tumors. A. Autocrine/paracrine PTX3 promotes melanoma migration and invasion by TLR4/NF-κB/TWIST1 axis. B. TGF- β 1 induces PTX3 expression by activating CEBPD in breast cancer-associated fibroblasts (BCAFs). BCAF-derived PTX3 directly interacts with CD44 to activate ERK1/2, Akt, and NF-κB signaling pathways, contributing to the migration, invasion, and stemness of triple-negative breast cancer cells. PTX3 antibodies and shortened PTX3 peptides could disrupt the PTX3/CD44 interaction and restrict the metastasis, invasion, and stemness of TNBC. Besides, PTX3 could activate the JNK, S6K, and p38 MAPK pathways by CD44-independent regulation. ER: endoplasmic reticulum; EMT: epithelial-mesenchymal transition; CEBPD: CCAAT/enhancer-binding protein delta.

cell line S115 [60,214]. In addition, the angiogenic and tumorigenic abilities were suppressed in PTX3 overexpressed TRAMP-C2 cells [214]. Besides, PTX3 inhibited the tumorigenic and metastatic activities in human and murine melanoma cells, which agreed with the inhibitory effect on FGF/FGFR-driven EMT [224]. Further, the overexpression of PTX3 markedly reduced the proliferative and tumorigenic activity of fibrosarcoma cells in vitro and in vivo [225]. Notably, PTX3 inhibits FGF2-dependent angiogenesis in MM and has an indirect cytotoxic role on MM cells by repressing the cross-talk between the plasma cells and endothelial cells/fibroblasts in the bone marrow of MM patients [207].

Increased proliferation, clonogenicity, and anchorage-independent growth capacity were observed in PTX3-deficient RT4 bladder cancer cells, with enhanced phosphorylation of FGFR, FRS2, and ERK1/2 proteins [215]. Correspondingly, PTX3 over-expression could reduce proliferation, clonogenicity, motility/wound repair capacity of 5637 cells, and clonogenicity of HT1376 cells, with reduced phosphorylation of FGFR and FRS2 [215]. PTX3 silencing also markedly increased the sphere formation capacity of RT4-shPTX3 cells and the percentage of ALDH⁺ cells in RT4-shPTX3 cells [215]. Moreover, compared to RT4-shNT cells, PTX3 silencing in RT4-shPTX3 cells up-regulated the expression of stemness markers (NANOG, OCT4, and CD47) and stemness-associated multidrug resistance genes (ABCG2 and ABCB1) [215]. In PTX3-overexpressing 5637 cells, the Seahorse Mito Stress Test showed decreased cellular respiration and glycolysis that was accompanied by a reduced production of ATP [215]. Besides, recent research demonstrated that PTX3 was down-regulated by TNF- α in gastric cancer cell lines, BGC-823 and SGC-7901, leading to increased invasion and metastasis of gastric cancer [226].

The cellular effectors and mediators of inflammatory responses are considered a part of the tumor microenvironment [227]. PTX3 could be produced under the stimulation of inflammatory factors and involves in

the regulation of inflammation and innate immunity [182,228,229]. PTX3 deficiency increased the susceptibility to tumor development in the models of 3-methylcholanthrene (3-MCA)-induced sarcoma (mesenchymal tumor) and 7,12-dimethylbenz [α] anthracene/terephthalic acid (DMBA/TPA)-induced skin cancer (epithelial tumor) [158]. In the murine 3-MCA induced sarcoma model, PTX3 was mainly induced by IL-1 [158], of which the deficiency was associated with increased macrophage infiltration, higher levels of pro-inflammatory cytokines TNF- α , IL-1 β , IL-6, chemokine CCL2, and angiogenesis factor VEGF [158]. In addition, PTX3 deficiency unleashed uncontrolled complement activation with C5a production due to the deficient FH recruitment, which subsequently induced the production of chemokine [158, 230]. CCL2 could induce M2-type macrophage polarization [231]. Besides, M2-like markers (Ym1, Fizz1, Arg-1, Il10, Mcr1, and Nos2) were more expressed in MHC II^{high} and MHC II^{low} macrophages and monocytes in PTX3-deficient mice compared to WT mice [158]. Therefore, CCL2 may be downstream of direct complement activation with C5a production and recruit skewed M2-like cancer-promoting tumor-associated macrophages (TAM) in PTX3-deficient hosts [158]. Altogether, PTX3 could act as an extrinsic oncosuppressor gene in mice and men by regulating complement-dependent, macrophage-sustained, tumor-promoting inflammation [158].

DNA methylation is crucial for developing almost all types of tumors [232]. In most esophageal squamous cell carcinoma (ESCC) cell lines, the gene promoter hypermethylation led to the down-regulated PTX3 [213]. In 20 paired samples of ESCC tumor tissues and adjacent non-tumor tissues, 80 % of ESCC tumor tissue samples had statistically different PTX3 promoter region methylation, whereas only 20% of paired adjacent nontumor tissues exhibited [213]. Besides, PTX3 promoter hypermethylation more frequently occurred in the early stages (I and II) of ESCC in comparison to advanced stages [213]. Similarly, in

selected human tumors (leiomyosarcoma, colorectal cancer, and skin squamous cell carcinoma), the transcriptional silencing of PTX3 could be partially attributed to hypermethylation in promoter and a CpG island located in a putative enhancer encompassing exon 2 [158].

Overall, PTX3 may be a crucial molecule in oncogenesis due to its regulatory roles in angiogenesis, cancer-related inflammation, and other properties of tumor cells (proliferation, apoptosis, migration, invasion, stemness, metabolic fitness, and drug resistance). Importantly, PTX3 could be seen as a double-edged sword in oncogenesis, depending on its cellular source, tumor types, and tumor microenvironment [14]. More in vitro and in vivo studies are expected to comprehensively clarify its dual role in cancer.

7. PTX3 in non-cancerous diseases

7.1. Cardiovascular diseases

7.1.1. Atherosclerosis, coronary artery disease, peripheral artery disease, arteritis

Immunohistochemistry results showed that PTX3 was positively expressed in macrophages and PMN cells which infiltrated the atherosclerotic lesions [11,233] (Table 3). Some studies have reported that PTX3 participates in the development of atherosclerotic plaque. Still, biases exist in part of these studies due to the small sample size and the lack of prospective assessment [234]. However, based on two surveys with a large sample size (the Bruneck Study and the PLIC Study), Baragetti et al. concluded that plasma PTX3 level couldn't be used as an independent marker to predict the progression of subclinical atherosclerosis and incident cardiovascular events [235]. Besides, PTX3 has atheroprotective effects in mice [236]. Therefore, the roles of PTX3 in atherosclerosis remain to be further investigated.

Compared with low circulating PTX3 levels, high PTX3 levels correlate with a higher risk of poor outcomes in coronary artery disease patients [237]. Besides, compared to high-sensitivity CRP (hsCRP), PTX3 may be a better predictor of peripheral artery disease in patients treated with hemodialysis [238]. A meta-analysis found that compared to CRP, PTX3 performed better in Takayasu arteritis (TAK) activity assessment [239]. However, it should be cautious when PTX3 is used to assess TAK clinically, considering the high heterogeneity and potential publication bias in the present study [239]. Elevated circulating PTX3 levels could identify giant cell arteritis patients with recent optic nerve ischemia [240].

7.1.2. AMI, cardiac arrest, atrial fibrillation, heart failure

In patients with AMI with ST-elevation, PTX3 could predict 3-month mortality after adjustment for significant risk factors and other acute-phase prognostic markers [241]. Besides, in the murine AMI model, PTX3 is proved with a cardioprotective effect [242]. Early detection of PTX3 level but not hsCRP is an independent marker predicting multiple organ dysfunction syndromes (MODS) and premature death in cardiac arrest patients [38,243]. The local production of PTX3 in the left atrium may reflect the local inflammation of atrial fibrillation [244]. Furthermore, PTX3 may be a novel inflammatory marker indicating the left ventricular diastolic dysfunction and heart failure with normal ejection fraction [245].

7.1.3. Hypertension, pulmonary hypertension, aortic aneurysm, aortic dissection

The rs3816527 AA genotype of PTX3 could be an independent predictor and risk factor of hypertension in CKD patients [246]. Compared to individuals with the PTX3 rs2614 locus C allele, carriers with the PTX3 rs2614 locus T allele were more likely to have essential hypertension (EHT) [247]. PTX3 is increased in neonates with pulmonary hypertension and could be used as a diagnostic marker of neonatal pulmonary hypertension [248,249]. A multiparameter model including galectin-3, PTX3, IL-6, and C-terminal telopeptide of type I collagen

Table 3
PTX3 in other non-cancerous diseases.

System	Category	Related factors	Phenomenon and effect
Cardiovascular	Atherosclerosis		PTX3↑ in atherosclerotic plaques [11,233,236] → the development of atherosclerotic plaque [234], atheroprotective effects in mice [236]
	Coronary artery disease		PTX3↑→ risk of poor outcomes↑ [237]
	Peripheral artery disease	Hemodialysis [238]	PTX3↑
	TAK		PTX3↑ in active TAK compared with inactive TAK [239]
	Giant cell arteritis		PTX3↑→ very recent optic nerve ischemia [240]
	AMI		PTX3→ 3-month mortality prediction [241], cardioprotective effect in mice [242]
	Cardiac arrest		PTX3→ MODS and early death prediction [38,243]
	Atrial fibrillation		PTX3↑ [244]
	Heart failure	Normal ejection fraction [245]	PTX3↑
	Hypertension	Essential [247]	PTX3↑
	Pulmonary hypertension	Neonatal [248, 249]	PTX3↑→ a diagnostic marker
	Aortic aneurysm		PTX3↑
	Aortic dissection	Type A [251]	PTX3→ in-hospital mortality prediction
	Pneumonia	Community-acquired [253–255]	PTX3↑→ disease severity↑
		Ventilator-associated [256]	PTX3→ diagnosis with a moderate accuracy
	Pleural effusion		Pleural fluid PTX3→ differentiation of parapneumonic effusion (PPE) from other types of pleural effusion [257–259]
	Aspergillosis		PTX3→ protection against <i>Aspergillus</i> [260–262]
Respiratory	COPD	[263]	PTX3↑ in BALF and plasma
	Asthma	Allergic [88] Severe [264]	PTX3↑ PTX3→ characterization of the severe asthma phenotype in children
	COPD		PTX3↑→ dyspnea (MMRC scores)↑ [265, 266]
	Emphysema	Smokers [267]	PTX3↑→ disease severity and mortality↑
	Lung injury	LPS [268]	PTX3↑ in BALF→ lung injury↑
		WC-Co [269]	PTX3↑→ macrophage efferocytosis↑ → lung injury↓
		Hyperoxic [137]	PTX3→M2 macrophage polarization↑→lung injury↓
	MHV-1 [151] High-volume ventilation [270]		PTX3→ lung injury↓
	Pulmonary fibrosis	Idiopathic [271]	PTX3→ lung injury↑
			PTX3→ a physiological and protective role

(continued on next page)

Table 3 (continued)

System	Category	Related factors	Phenomenon and effect
Digestive	PE	Acute [272]	PTX3→ a clinical indicator in PE prognostic determination PTX3↑→ endothelial dysfunction†[281]
		Fibrosis [282]	PTX3↑
	Liver injury	Acetaminophen [283]	PTX3↑ in liver
		Chronic hepatitis B [284]	PTX3↓→ liver fibrosis
		Chronic hepatitis C [285]	PTX3↑→ significant fibrosis
	Liver cirrhosis	NASH [286]	PTX3↑→ hepatic fibrosis↑
		Acute decompensation [287]	PTX3↑→ poorer prognosis[40]
		Alcoholic [288]	PTX3↑→ disease severity and case fatality†
		Bowel diseases	PTX3↑→ disease severity†
	Bowel diseases	Acetic acid-induced colitis [289]	PTX3↑→ severer inflammation
		Ulcerative colitis [290]	PTX3→ cell-mediated immune defense in inflamed colon tissue (particularly in crypt abscess lesions)
		Crohn's disease [291]	PTX3↑→ disease activity†
		IBD [292]	PTX3↑→ disease activity†
	Pancreatic diseases	Acute appendicitis [293–296]	PTX3↑→ a diagnostic marker
		Acute pancreatitis [297,298]	PTX3↑→ disease severity†
		Obesity	PTX3→ a dual regulatory role [303, 304]
Endocrine	Metabolic syndrome	Subclinical atherosclerosis [307]	PTX3↑→ disease severity†[305,306]
		Overweight and obese children [308]	PTX3↑→ insulin resistance↓
	Prediabetes and T2DM	Obese patients with NAFLD [309]	PTX3↑
		DR	PTX3↑→ development and progression of DR†
	Diabetic ketoacidosis complicated by pancreatitis	Korean patients with T2DM [310]	PTX3↑→ disease severity†[311]
		RA	PTX3→ inflammation and tissue injury [312–314], an indicator of clinical arthritic activity [315]
		SLE	SNARK/PTX3↑→ SLE pathogenesis, atherogenesis and development of cardiovascular disease [320]; PTX3↑→ disease activity [321,322], cumulative lupus damage[323]
	Autoimmune	Ankylosing spondylitis	PTX3↑→ inflammation [324]

Table 3 (continued)

System	Category	Related factors	Phenomenon and effect
Endocrine	Systemic sclerosis	Systemic sclerosis	PTX3†→ endothelial progenitor cell-mediated vasculogenesis↓, vascular manifestations[116]; PTX3↑→ disease severity†[325]
		Multiple sclerosis and neuromyelitis optica	PTX3†→ inflammation [326]
	Psoriasis	Psoriasis	PTX3↑→ the pathogenesis of psoriasis [327] ; PTX3↑→ disease activity†[328]
		Acute rheumatic fever	PTX3†→ prediction of the carditis development
		Gout	PTX3→ the phagocytosis of monosodium urate crystals↑ →the pathogenesis of gouty arthritis[330]
	Nervous	Stroke	PTX3→ a prognostic marker[44,331,332]
		Ischemic[334]	PTX3†→ disease severity†
		Vasospasm	PTX3 in CSF → early diagnosis of vasospasm
	Prion disease	Brain injury	Serum PTX3 ≥ 10 µg/ml→ hospital mortality
		Seizure	PTX3 mRNA↑ in brain [337]
		Kainite[338]	PTX3†→ a protective role in seizure-induced neurodegeneration
Autoimmune	Parkinson's disease	Parkinson's disease	PTX3†→ activities of daily living↑, motor function†[340]
		Alzheimer's disease	PTX3†→ macrophage-mediated phagocytosis of dying neuron cells↓ →disease pathogenesis [341]
	Psychiatric disorders	Psychiatric disorders	PTX3↓
		Bipolar disorders	PTX3 ↓
	Urinary	Schizophrenia	PTX3 ↓
		UTI	PTX3→ a pivotal innate immune component against UTI[346]
		Lupus nephritis	PTX3†→ the progression of tubulointerstitial injury†[347]
	DN	DN	Serum PTX3†→ the progression of DN stage†[348]
		Renal injury	PTX3 ↓ in kidney →renal injury in DN
		Chronic kidney disease	PTX3†→ GFR↓[350]
Autoimmune	Peritoneal dialysis	Peritoneal dialysis	PTX3→ a biomarker for nonspecific peritoneal inflammation
		End-stage kidney disease[351]	PTX3→ a biomarker of hemodialysis-induced inflammation and of blood-membrane bioincompatibility [352]
	Hemodialysis	Hemodialysis	(continued on next page)

Table 3 (continued)

System	Category	Related factors	Phenomenon and effect
Hematogenous	Sickle cell disease	Vaso-occlusive crisis[353]	PTX3↑
	Thalassemia	Major[354]	PTX3↑→disease activity↑
	Henoch-Schönlein purpura	Children[355]	PTX3↑→ a predictor of subsequent renal involvement
Female reproductive	Gynecologic diseases	GVHD	PTX3↑
		Children given haematopoietic stem cell transplantation [356]	
	Obstetrical diseases	Pelvic inflammatory disease[357]	PTX3↑
		PCOS[358]	PTX3↓
Cardiovascular	Cardiovascular diseases	Histological chorioamnionitis [359]	PTX3↑ in amniotic fluid
		Preeclampsia [360]	PTX3↑

(ICTP) may be helpful in the diagnosis and risk prediction of abdominal aortic aneurysm (AAA) [250]. PTX3 level on admission may be an independent predictor of in-hospital mortality in patients with type A aortic dissection (TAAD) [251].

7.2. Respiratory diseases

7.2.1. Pneumonia, pleural effusion, aspergillosis

Plasma PTX3 level was independently associated with microbial cell-free DNA (mcfDNA) levels in patients with pneumonia [252]. The admission level of PTX3 could be used to predict the severity of community-acquired pneumonia (CAP) (NCT03093220) [253]. PTX3 could also be useful in the diagnosis and clinical assessment of the seriousness of CAP [254]. The serum PTX3 level, particularly the dynamic monitoring results, could be used as a biomarker to monitor CAP [255]. PTX3 has moderate accuracy in diagnosing respiratory tract infections and ventilator-associated pneumonia (VAP) [256]. The pleural fluid PTX3 may be a biomarker for differentiating parapneumonic effusion (PPE) from other types of pleural effusion [257–259]. PTX3 was reported to exert a protective effect against Aspergillus and has a potential for diagnosis and therapy of aspergillosis (e.g., IPA) [260–262]. Compared to COPD patients without IPA, COPD patients with IPA had higher bronchoalveolar lavage fluid(BALF) and plasma PTX3 levels [263].

7.2.2. Asthma, COPD, emphysema

PTX3 expression was increased in bronchial biopsies of allergic asthmatics compared to healthy individuals [88]. In addition, the blood concentration of PTX3 may help characterize the phenotype of severe asthma in children [264]. Serum level and gene expression of PTX3 were significantly higher in COPD patients than in healthy controls [265]. It is also reported that plasma PTX3 level was elevated in COPD patients and positively associated with dyspnea (MMRC scores) but had no association with the severity of COPD [266]. Elevated PTX3 level is related to emphysema severity and mortality in smokers [267].

7.2.3. Lung injury, pulmonary fibrosis, pulmonary embolism (PE)

In a murine LPS-induced lung injury model, PTX3 could reflect the severity of lung injury [268]. Besides, PTX3 could alleviate hard metal-induced ALI through potentiating efferocytosis [269]. In a neonatal rat model, soluble PTX3 from human UCB-MSCs attenuated hyperoxic lung injury via activating macrophage polarization [137]. PTX3 may also be protective in coronaviral infection-induced ALI [151]. In multiple sensitive lung injury models in rats, high-volume ventilation

enhanced PTX3 expression, and increased PTX3 expression was highly associated with the severity of lung injury [270]. Doni et al. proposed that PTX3 had a physiological and protective role during idiopathic pulmonary fibrosis [271]. In acute PE patients, plasma PTX3 level is correlated with PE risk stratification, PE-related cardiac deaths, and the prognosis of recurring PE [272].

7.2.4. Coronavirus Disease 2019 (COVID-19)

In patients with COVID-19, circulating and lung myelomonocytic cells and endothelial cells could express high levels of PTX3 and be regarded as a major source of PTX3 [273]. PTX3 could interact with the nucleocapsid protein (NP) of Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) mainly through its N-terminal domain, and it had no anti-SARS-CoV-2 activity [274]. However, It remains to be investigated whether PTX3 involves in nucleocapsid-mediated complement activation and cytokine production [274].

Plasma PTX3 concentration could serve as an independent, strong prognostic indicator of 28-day mortality in COVID-19 [273]. A machine learning model identified binary combinations of “Age, SARS-CoV-2 RNAemia (serum or plasma SARS-CoV-2 RNA)” and “Age, PTX3” as the best predictors of 28-day ICU mortality [275]. Plasma PTX3 levels were useful in predicting 30-day respiratory failure and mortality risk in COVID-19 patients treated with and without remdesivir and dexamethasone [276]. In a retrospective study of 39 COVID-19 patients from Hunan, China, serum PTX3 level was positively associated with disease severity and coagulopathy [277]. Combinations of the serum inflammatory mediators IFN- β , PTX3, IFN- γ , IFN- $\lambda 2/3$, and IL-6 were associated with long COVID with 78.5–81.6% accuracy [278]. A preliminary study suggested that reduced plasma IL-8 and PTX3 levels on day four following siltuximab treatment correlated with improved survival and ventilatory outcomes in COVID-19 patients in hospital [279]. Therefore, circulating PTX3 level may be a potential biomarker indicating the prognosis or disease severity of COVID-19. Besides, in COVID-19 patients, individuals with PTX3 rs1840680 (1449A/G) AG genotype were more protected from macrophage activation syndrome (MAS) compared to individuals with AA genotype [280].

7.3. Digestive diseases

7.3.1. Non-alcoholic fatty liver disease (NAFLD), liver injury, liver fibrosis, liver cirrhosis

In patients with NAFLD, increased plasma PTX3 level was strongly associated with endothelial dysfunction [281]. Moreover, PTX3 is a predictor of fibrosis and arterial stiffness in patients with NAFLD [282]. Elevated liver PTX3 level in the acetaminophen (APAP)-induced hepatic necrosis could be a marker of acute histological liver injury [283]. Serum PTX3 could be used as a novel marker for the early detection of fibrosis in patients with chronic hepatitis B [284]. In patients with chronic hepatitis C, PTX3 could be used as a single diagnostic marker of significant fibrosis [285]. Plasma PTX3 level could differentiate nonalcoholic steatohepatitis (NASH) from non-NASH and may indicate the severity of hepatic fibrosis in NASH patients [286]. Besides, PTX3 has the potential to predict the prognosis of patients with hepatic cirrhosis [40]. High serum PTX3/soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) levels during hospital admission could predict disease severity and case fatality in cirrhotic patients with acute decompensation [287]. It has also been reported that elevated PTX3 and NO levels correlated with the severity of alcoholic cirrhosis [288].

7.3.2. Bowel diseases

In the mice model, the PTX3 level was significantly higher in the acetic acid-induced colitis group, indicating severer inflammation [289]. PTX3 may contribute to cell-mediated immune defense in inflamed colon tissue, particularly in crypt abscess lesions, of ulcerative colitis patients [290]. Serum PTX3 is superior to CRP in predicting the disease activity of Crohn's disease [291]. Plasma PTX3 level was

dramatically higher in patients with active inflammatory bowel diseases (IBD) than in normal individuals and patients with inactive IBD, in which plasma PTX3 concentration positively correlated with clinical disease activity of IBD [292]. Besides, PTX3 may facilitate the diagnosis of acute appendicitis both in children [293–295] and in adults [296].

7.3.3. Pancreatic diseases

PTX3 could be used for early severity assessment and prediction of acute pancreatitis (AP) [297]. Moreover, growth differentiation factor-15 (GDF-15) and PTX3 could help identify the development of severe AP on admission [298]. However, PTX3 was inferior to CRP and APACHE II scores in predicting the SIRS and death of AP. The combination of PTX3 with CRP couldn't improve the predictive value of CRP [299].

7.4. Endocrine diseases

7.4.1. Obesity

Obesity is a state of chronic, low-grade proinflammation [300–302]. Based on existing research, Slusher et al. summarized that PTX3 could promote anti-inflammatory responses by down-regulating pro-inflammatory proteins from neutrophils and macrophages and up-regulating the production of anti-inflammatory cytokines [303]. They also proposed reasonable speculation that therapies increasing the circulating PTX3 level in obese people could assist in restoring obesity-associated inflammatory imbalances and transforming the systemic and local inflammatory microenvironments into anti-inflammatory microenvironments [303]. However, PTX3 may also participate in the onset of obesity via facilitating inflammation and restricting adipose tissue vascularization [304]. Thus, PTX3 may potentially exert a dual regulatory role in obesity, with more evidence needed to prove the hypothesis further.

7.4.2. Metabolic syndrome, insulin resistance, diabetes, diabetic retinopathy (DR), diabetic ketoacidosis complicated by pancreatitis

PTX3 is associated with the severity of metabolic syndrome [305, 306]. Additionally, PTX3 is higher in metabolic syndrome patients with subclinical atherosclerosis [307]. PTX3 level is negatively correlated with insulin resistance and changes in insulin resistance induced by physical activity in overweight and obese children [308]. In obese patients with NAFLD, compared with individuals with normal blood glucose levels, patients with prediabetes and type 2 diabetes mellitus (T2DM) had higher serum PTX3 level [309]. Compared with hsCRP, PTX3 may be a more accurate marker to predict the development of DR in Korean patients with T2DM [310]. Blood PTX3 level may help evaluate the severity of diabetic ketoacidosis complicated by pancreatitis [311].

7.5. Autoimmune diseases

7.5.1. RA, SLE

PTX3 was reported to mediate complement-regulated mechanisms, leading to inflammation and tissue injury in RA [312–314]. Besides, PTX3 may be a novel non-invasive marker indicating clinical arthritic activity in patients with RA [315]. However, many studies also revealed that PTX3 had no association with RA activity assessed by neutrophil/lymphocyte ratio (NLR) or disease activity score 28 (DAS28) [316–319], which is paradoxical to the outcome above. The synergistic increase of sucrose non-fermenting AMPK-related kinase (SNARK)/PTX3 via TNF- α /NF- κ B signaling and DNA damage response may mediate SLE pathogenesis, atherogenesis, and development of cardiovascular disease (CVD) [320]. Furthermore, PTX3 significantly correlated with SLE activity [321,322]. However, Skare et al. proposed that PTX3 was associated with cumulative lupus damage of SLE but not with disease activity [323].

7.5.2. Ankylosing spondylitis, systemic sclerosis, multiple sclerosis and neuromyelitis optica, psoriasis, rheumatic fever, gout

Elevated PTX3 levels correlated with inflammation but not disease activity in ankylosing spondylitis patients [324]. High PTX3 levels in patients with systemic sclerosis (SSc) may inhibit endothelial progenitor cell (EPC)-mediated vasculogenesis and facilitate vascular manifestations (digital ulcers and pulmonary arterial hypertension) [116]. Moreover, elevated serum PTX3 levels correlated with the disease severity of SSc [325]. Increased plasma PTX3 concentration is associated with inflammatory responses in patients with multiple sclerosis and neuromyelitis optica [326]. PTX3 may participate in the pathogenesis of psoriasis and could indicate disease activity of psoriasis [327,328]. Elevated PTX3 level during an acute episode of acute rheumatic fever may help predict the clinical course and the severity of accompanying carditis [329]. Besides, PTX3 contributes to the pathogenesis of gouty arthritis by promoting the phagocytosis of monosodium urate crystals [330].

7.6. Nervous diseases

7.6.1. Stroke, vasospasm, brain injury

Several studies support that PTX3 could be a prognostic marker of stroke [44,331,332], with the opposite view proposed by Ceylan el at [333]. Moreover, PTX3 may help assess the severity of ischemic stroke [334]. Acute elevated PTX3 level in cerebrospinal fluid (CSF) but not in plasma correlated with subarachnoid hemorrhage-associated vasospasm, indicating the early diagnostic value of CSF PTX3 in vasospasm [335]. Serum PTX3 levels higher than 10 μ g/ml were independently associated with the hospital mortality of patients with severe traumatic brain injury [336].

7.6.2. Prion disease, seizure, Parkinson's disease, Alzheimer's disease

The mRNA level of PTX3 was elevated in the brain of the ME7 model of murine prion disease [337]. PTX3 could be synthesized in the brain after kainate-induced experimental seizure in mice and may play a protective role in seizure-induced neurodegeneration [338]. However, plasma PTX3 level was not increased in children with epilepsy [339]. Plasma PTX3 correlated with the severity of motor dysfunction and other clinical symptoms in Parkinson's disease patients [340]. CEBPD-activated PTX3 could inhibit the phagocytosis of dying neuron cells by macrophages, which may be a mechanism of Alzheimer's disease development [341].

7.6.3. Psychiatric disorders

Some studies revealed that basal serum PTX3 level was decreased in specific psychiatric disorders (e.g., depression [342], bipolar disorders [342,343], and schizophrenia [344]), suggesting that patients with psychiatric disorders may have impaired immunity [345].

7.7. Urinary diseases

7.7.1. Urinary tract infection (UTI), lupus nephritis, diabetic nephropathy (DN), renal injury

Jaillon el at. concluded that PTX3 is a pivotal innate immune component against UTI [346]. PTX3 level was significantly elevated in patients with active lupus nephritis and may be a potential biomarker for disease progression, particularly tubulointerstitial injury [347]. PTX3 that increases as DN progresses may be a better inflammatory marker than hsCRP [348]. Furthermore, in a rat model, PTX3 level in renal tissue was closely associated with renal damage in DN. It may help quantify the extent of renal damage in DN, early evaluate renal tubular injury in early DN patients, and assess the clinical progression of DN [349].

7.7.2. CKD, dialysis

Plasma PTX3 level increases as glomerular filtration rate (GFR)

declines and is associated with the presence of protein-energy wasting and cardiovascular disease [350]. Moreover, a high PTX3 level was accompanied by higher all-cause mortality in patients with CKD [350]. PTX3 may be a new biomarker of peritoneal inflammation and progressive fibrosis in end-stage kidney disease patients treated with peritoneal dialysis [351]. Besides, PTX3 could indicate hemodialysis-induced inflammation and blood-membrane biocompatibility in hemodialysis patients [352].

7.8. Hematogenous diseases

7.8.1. Sickle cell disease, thalassemia, Henoch-Schönlein purpura, graft-versus-host disease (GVHD)

PTX3 could be considered a subjective predictor for the occurrence and severity of sickle cell disease acute complications [353]. Serum PTX3 levels could help evaluate the vascular endothelial damage in thalassemia patients [354]. High serum PTX3 levels and IgM staining in skin biopsies could predict subsequent renal involvement in child patients with Henoch-Schönlein purpura [355]. Plasma PTX3 levels at GVHD onset also predict disease severity and therapeutic responses in children treated with hematopoietic stem cell transplantation [356].

7.9. Diseases of the female reproductive system

7.9.1. Pelvic inflammatory disease, polycystic ovary syndrome (PCOS), intra-amniotic inflammation, preeclampsia

Plasma PTX3 level has an advantage over CRP in predicting pelvic inflammatory disease and is associated with tube-ovarian abscess (TOA) and length of hospital stay [357]. Plasma PTX3 was decreased in women with PCOS and independently correlated with hyperandrogenism and other endocrine and ovarian features of PCOS [358]. Moreover, PTX3 in amniotic fluid may indicate intra-amniotic inflammation in women with preterm premature rupture of membranes [359]. Compared to women with normal pregnancy, women with preeclampsia have higher circulating PTX3 level [360]. Moreover, raised PTX3 level could be observed before the clinical onset of preeclampsia [360].

8. Targeted therapy of PTX3

8.1. Tumor

The scaling down of PTX3 to PTX3-derived small molecules may be a meaningful attempt to use the anti-tumor properties of PTX3 [14]. A PTX3-derived acetylated pentapeptide Ac-ARPCA-NH2 (ARPCA), corresponding to the amino acid sequence 100–104 in the N-terminal domain of PTX3, was considered the minimal FGF-2-binding peptide which could antagonize the biological activity of FGF-2 [361]. ARPCA could inhibit the FGF-dependent angiogenic and tumorigenic potential of Shionogi 115 mammary carcinoma cells and TRAMP-C2 prostate cancer cells [362]. Besides, ARPCA could suppress downstream FGFR signaling and FGF-2-stimulated proliferation in murine B16-F10 melanoma cells [224]. Additionally, a pharmacophore model of ARPCA/FGF-2 interaction was used for in silico screening of the NCI2003 small-molecule database, which identified NSC12 as an ARPCA mimic [363]. NSC12 suppresses FGFR activation and FGF-dependent tumor growth, angiogenesis, and metastasis in a host of tumor models, showing its therapeutic value for tumor [363,364].

Besides, due to the tumor-promoting properties of PTX3, PTX3 could be a potential therapeutic target for certain types of tumors. Buthus martensi Karsch antitumor-analgesic peptide (BmK AGAP), a typical long-chain scorpion toxin, could inhibit breast cancer cell stemness, EMT, invasion, and migration via down-regulating PTX3 through NF-κB and Wnt/β-catenin signaling pathway in vivo and vitro [365]. Rg3, one of the ginsenosides derived from heat-processed ginseng, could inhibit gemcitabine-induced lung cancer cell invasiveness via ROS-dependent, NF-κB-mediated, and HIF-1α-mediated downregulation of PTX3 [96].

The shortened PTX3 peptide PEGylated retro-inverso peptides AD9 (P2rdAD9) and the PTX3 antibody Ab-10 could interfere with the PTX3/CD44 interaction and suppress the growth and metastasis of TNBC [223]. RI37, a PTX3 peptide inhibitor, was reported to decrease CEBPD/PTX3 axis-induced cancer malignancies and suppress the metastasis and invasion of drug-resistant cancers in vivo [70]. The deglycosylation of PTX3 (dePTX3) by tunicamycin (TM) significantly enhances the sensitivity of lung cancer cells to cisplatin (Cis) and inhibits the growth and metastasis of lung cancer cell [366]. Moreover, dePTX3 by TM in lung cancer cells treated with Cis suppresses the activation of the AKT/NF-κB signaling pathway, facilitating the apoptosis of lung cancer cells [366]. Therefore, dePTX3 in chemotherapy has the potential to be a sound therapeutic strategy against lung cancer [366].

8.2. Non-cancerous diseases

PTX3 may also be a therapeutic target for many non-cancerous diseases. PTX3 could potentially treat chronic lung infection caused by *Pseudomonas aeruginosa* by inhibiting lung colonization, reducing pro-inflammatory cytokines (CXCL1, CXCL2, CCL2, and IL-1b), and suppressing leukocyte recruitment in the airways [367]. In a murine model of traumatic brain injury, exogenously administrated recombinant PTX3 could activate A2 astrocytes, thus improving the recovery of neural function via increasing neuronal survival and enhancing neurogenesis [194]. In lupus-prone New Zealand Black/White (NZB/W) F1 mice, immunization with hrPTX3 could prevent murine lupus nephritis progression from the preclinical stage to the clinical stage, inciting anti-PTX3 antibodies and preventing PTX3 deposition in kidneys [368]. Besides, anti-PTX3 antibodies could delay lupus-like nephritis and prolong the survival of NZB/NZW F1 mice [369]. In an atherosclerotic cell model, Honokiol, an active component isolated from the Chinese medicinal herb Magnolia Officinalis, could repair endothelial dysfunction by inhibiting the over-expression of PTX3 via suppressing IκB phosphorylation and reducing the expression of NF-κB p50 and p65 subunits in the IKK/IκB/NF-κB pathway [98]. Calcium dobesilate (CaD) may suppress PTX3 expression by altering the IKK/IκB/NF-κB pathway, thus ameliorating high glucose-induced endothelial dysfunction in HUVECs, which indicates that CaD has therapeutic potential for diabetic neuropathy [370]. MiR-29b over-expression could dampen the vascular inflammatory response by inhibiting the expression of PTX3 and dipeptidyl-peptidase 4 (DPP4), which could be applied to treat radiotherapy-induced vascular disease in the future [371].

9. Conclusion and perspective

Since the discovery of PTX3 30 years ago, numerous studies have contributed to comprehensively defining its physiological and pathological features, aiming to promote the clinical management of patients based on the known knowledge of PTX3. So far, the clinical applications of PTX3 have mainly been restricted to its diagnostic and prognostic value. The targeted therapy based on PTX3 is limited and has not revolutionized the treatment modality. Notably, there are still several puzzles remaining to be solved.

First, the structures and functional domains of PTX3 must be fully identified. PTX3 is a 381-amino acid-long glycoprotein that consists of a C-terminal domain and an N-terminal domain, which also contains various binding sites of ligands (e.g. FH, P-selectin, FGF-2, inter-α-trypsin inhibitor). The structural characteristics of PTX3 are closely responsible for its regulatory roles in innate immunity, inflammation, angiogenesis, ECM stability, and tissue remodeling. The FGF-2-binding peptides are already proven with anti-angiogenic and anti-tumorigenic potential. Therefore, identifying all structures and functional domains in the PTX3 molecule could help design and produce the corresponding chemicals and antibodies for precision-targeted therapy.

Second, the unknown receptors and ligands of PTX3 are yet to be

explored. Currently, some receptors/ligands (e.g., C1q, P-selectin, histone, TSG-6, fibrin, FGF-2, CD44, CD32, etc.) have been confirmed to interact with PTX3. As PTX3 is a secretory protein, many membrane proteins, such as CD47, were proposed as potential receptors. Besides, the interaction of PTX3 with other NETs components and their potential synergic antibacterial roles are needed for further investigation.

Third, the specific roles of PTX3 on microenvironment cells, such as macrophages, neutrophils, fibroblasts, and DCs, remain to be further investigated. For example, how PTX3 influences the polarization of macrophages are needed for further elucidated.

Forth, the complex roles of PTX3 in cancer development should be entirely determined as PTX3 exerts both anti-tumor and pro-tumor effects. Notably, researches involving the interaction of PTX3 with membrane receptors on tumor cells and relevant downstream signaling pathways are limited and needed for further investigation.

Fifth, selective drugs targeting PTX3 are limited, and more potential drugs targeting PTX3 are needed, such as the drug for deglycosylation of PTX3.

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Hao Zhang and Ruixuan Wang drafted the manuscript and prepared the figures. Hao Zhang, Ruixuan Wang, Zeyu Wang, Wantao Wu, Nan Zhang, Longbo Zhang, Jason Hu, Peng Luo, Jian Zhang, Zaoqu Liu, Songshan Feng, Yun Peng collected the related references and participated in the discussion. Zhengzheng Liu and Quan Cheng designed this review and revised the manuscript. All authors contributed to this manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors have declared that no competing interest exists.

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