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Update on the role of Pentraxin 3 in atherosclerosis and cardiovascular diseases

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ABSTRACT

Pentraxin 3 (PTX3) is an acute-phase protein that was recently demonstrated to play pleiotropic activities in cardiovascular (CV) diseases. Tumor necrosis factor and interleukins up-regulates PTX3 transcription in different cell types (i.e. endothelial cells, phagocytes, smooth muscle cells, fibroblasts and glial cells) involved in atherogenesis. By interacting with numerous ligands, PTX3 acts as a modulatory molecule of complement system, inflammatory response, angiogenesis, and vascular/tissue remodeling. Experimental data point to a beneficial role of PTX3 in atherosclerotic plaque development and vulnerability. Animal studies indicated a protective role of PTX3 signaling in ischemic/reperfusion injury and failing heart. Clinical studies have so far provided contrasting results, highlighting a debated role of PTX3 as an active mediator of endothelial dysfunction, atherosclerotic plaque vulnerability and worse outcome after ischemic events. Therefore, substantial evidence suggests a dual role of PTX3 as modulator or amplifiers of the innate immune response. The final result of PTX3 activation might be determined by a fine tuning of time, space and environmental signals. The aim of this review is to provide an overview of biological properties of PTX3 in CV diseases and to discuss the ability of PTX3 to act as a crossroad between pro- and anti-inflammatory pathways.

1. Introduction

Inflammation is nowadays considered a critical determinant of cardiovascular (CV) disease and relative risk factors, including diabetes, hypertension, and dyslipidemia [1]. Among different inflammatory molecules, cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 were suggested pathophysiological players, whereas C-reactive protein (CRP) was currently used as a clinical biomarker [2,3]. CRP is an acute phase protein belonging to the pentraxins, a phylogenically conserved superfamily of multimeric proteins. CRP represents the only reproducible inflammatory biomarker for which a standardized and inexpensive assay was developed [4], and its predictive value was found to be comparable to total and high-density lipoprotein cholesterol (HDL-c) [5]. However, CRP failed to improve the predictive ability of standard Framingham risk model and the true value as specific biomarker of CV risk remains controversial [6]. As acute phase proteins, all pentraxins are mediators of innate immune response, but they are also involved in a wide range of biological responses, including inflammation, angiogenesis, malignancies, and cell adhesion. Among them, pentraxin 3 (PTX3) showed pleiotropic properties in the field of CV diseases [7,8]. The aim of this review is to update recent evidences linking PTX3 to CV disease by discussing experimental and clinical results. This narrative review was based on the papers found on PubMed and MEDLINE up to May 2017. The search terms used were 'Pentraxin 3 and cardiovascular' in combination with 'acute myocardial infarction, stroke, atherosclerosis and pathophysiology'.

2. Structure of pentraxin superfamily proteins

Pentraxins are a group of high conserved proteins characterized by

Abbreviations: PTX3, Pentraxin 3; CV, cardiovascular; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; HDL-c, high-density lipoprotein cholesterol; SAP, serum amyloid P component; NF-κB, nuclear factor kappa B; ECs, endothelial cells; SMCs, smooth muscle cells; TLR, toll-like receptor; FGF2, fibroblast growth factor 2; IKK, IκB kinase; PPARγ, peroxisome proliferator-activated receptor-γ; LXRα, liver X receptor alpha; ABCA1, ATP-binding membrane cassette transporter A-1; Ba, brachial-ankle; Cf, carotid-femoral; PWV, pulse wave velocity; LV, left ventricular; LVEF, LV ejection fraction; MI, myocardial infarction; VAT, visceral fat; SAT, subcutaneous fat; SLE, Systemic lupus erythematosus

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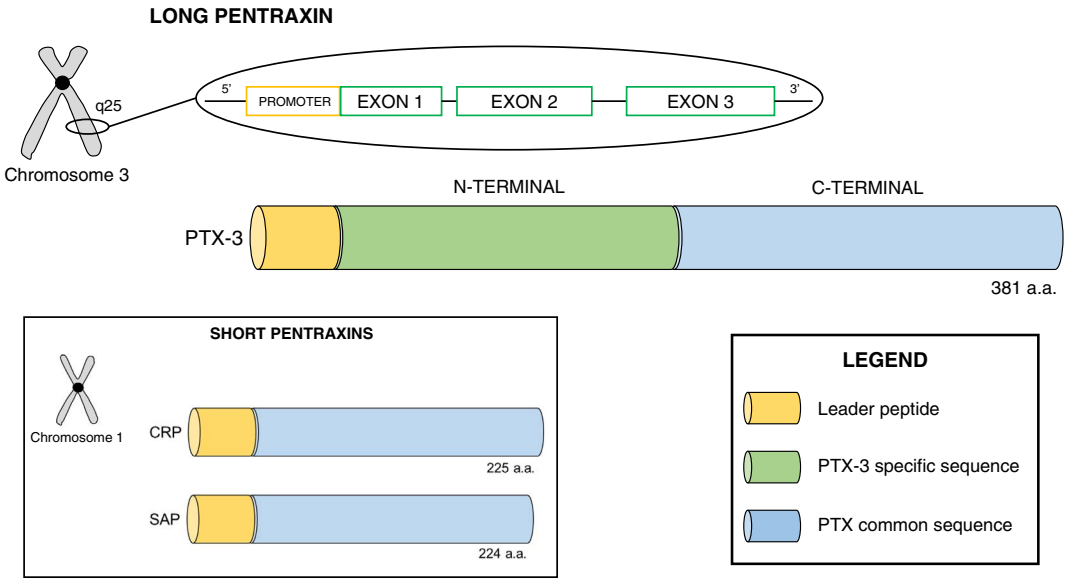

Fig. 1. Pentraxin superfamily proteins. Pentraxins (PTXs) are characterized by a conserved C-terminal region including the "PTX signature" sequence. Depending on their length, PTXs are classified in short and long ones. The first described short PTXs are C-reactive protein (CRP) and serum amyloid P component (SAP); their genes are both located in chromosome 1. Differently, the PTX-3 gene is located in chromosome 3 and formed by a promoter region and three exons.

a ≈ 200 aminoacid long domain in their C-terminal region (Fig. 1). This 'pentraxin signature' is made up of: Histidine- x - Cysteine - x - Serine/Threonine - Tryptophan - x - Serine, where x is any aminoacid [9]. Furthermore, depending on the length of the N-terminal region, pentraxins are classified in long or short subfamily. CRP and serum amyloid P component (SAP) are the first discovered pentraxins and belong to the short subfamily. According with their name, they are characterized by a pentagonal structure. CRP is composed by five subunits held by non-covalent interactions, each one characterized by 206 aminoacids and molecular weight of 23 kD. The five subunits composing SAP are instead held by non-covalent bond, and may also form decamers in certain condition. On the other hand, a high-conserved omo-multimeric structure with monomers of 45 kD characterizes PTX3, the prototype of long pentraxin [10,11]. Four α-helic structures connected by short loops compose the secondary structure of the N-terminal portion, thus determining a coiled coil conformation. In this portion, disulphide bonds between cysteine residues further enhance the stability of the protein. Concerning the C-terminal domains, the hydrophobic core is made up of two anti-parallel β-sheets, which determine a jelly roll topology, typical of the family. Finally, disulphide bonds between the two cysteines in position 179 and 357 link the N-terminal tail to the C terminal domain, whereas the asparagine in position 220 is the only N-glicosilation site of the protein. The structure described form a single monomer of the protein. Eight of that, held by disulphide bonds, form PTX3, characterized by a molecular weight of around 440 kDa [11,12].

3. PTX3 and innate immunity

The human ptx3 gene is localized on chromosome 3 band q 25 and is characterized by three exons separated by two introns (Fig. 1). The exons code respectively for the leader peptide, N-terminal and C-terminal domains. Within the nucleus, promoters like nuclear factor kappa B (NF-κB), selective promoter factor 1 and activator protein 1 (AP-1) are involved in PTX3 gene transcription. Specifically, NF-κB up-regulates PTX3 transcription in response TNF-α and IL-1β, whereas AP-1 promotes basal transcription [13,14]. Whereas CRP and SAP are predominantly synthetized by hepatocytes under the stimulation of IL-1 and IL-6, ptx3 transcription may be up-regulated in different cell types in response to a wide range of stimuli. The main cell sources of PTX3 are: endothelial cells (ECs), mononuclear phagocytes, fibroblasts, smooth muscle cells (SMCs), mesangial cells, synovial cells, chondrocytes, adipocytes, alveolar epithelial cells, glial cells and granulosa cells. Different inflammatory signals including IL-1β, TNF-α, toll-like receptor (TLR) ligands and microbial components up-regulate production and release of PTX3 in those cells. Conversely, hepatocytes are not able to synthetize PTX3.

Table 1
Main ligands of PTX3.

Complement components	C1q [15]
	Factor H [16]
	C4BP [17]
	M-, L-ficolin [18,19]
	MBL [20]
Membrane ligands	FcγR [21]
Extracellular matrix proteins	TNF stimulated gene 6 [22]
	Inter trypsin inhibitor [23]
Growth factors	FGF2 [24]
Adhesion molecules	P selectin [25]
Microorganisms	
Bacteria	Pseudomonas aeruginosa [26]
	Klebsiella pneumoniae[27]
Fungi	Aspergillus fumigatus [19]
	Paracoccidioides brasiliensis [28]
Virus	Influenza virus [29]
	CMV [30]

3.1. PTX3 and innate immunity

Once released, PTX3 orchestrates the humoral phase of innate immunity, and its activity is related to the recognition of different ligands (Table 1) [15–30] (Fig. 2). Activation of classical complement pathway may be induced by PTX3 trough the binding with the globular head of immobilized C1q (i.e. when C1q bond to a microbial surface) or the lectine-dependent pathway. Conversely, when C1q is in the fluid phase, the bound to PTX3 suppresses complement activation. PTX3 also prevents complement activation through the interactions with factor H (modulator of alternative complement pathway) and C4b (regulator of the lectin and classical complement pathway) [16,17] (Table 1). Furthermore, PTX3 recognizes pathogen-associated molecular patterns from several classes of Gram-positive and -negative bacteria, fungi (including *A. fumigatus*, *P. brasiliensis*) and viruses (CMV and type A influenza virus) [19,28–30] (Table 1). PTX3 is also a strong