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Review

Biological actions of pentraxins

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ABSTRACT

The innate immunity is the first defense reaction against microorganisms or altered self-components upon tissue injury. Such exogenous or modified endogenous molecules present conserved molecular structures that are recognized by the immune system via pattern-recognition receptors or molecules. Within the soluble pattern-recognition molecules pentraxins play an important role in humoral innate immunity. Pentraxins branch off into the short and long pentraxins. Short constituents include C-reactive protein (CRP) and serum amyloid P-component which are synthesized in the liver mostly upon IL-6 stimulation. Long constituent pentraxin3 (PTX3) is produced by several immune and vascular cells in response to pro-inflammatory signals (but not IL-6) and by toll-like receptor engagement. The ability of pentraxins to interact with numerous ligands (microorganisms, the complement system, dead cells, modified plasma proteins, cellular receptors, extracellular matrix components, and growth factors) supports their involvement in multiple biological functions. As such, the capability of CRP and PTX3 to modulate inflammation through the complement system and innate immunity suggests their contribution in atherosclerosis, thrombosis, and ischemic heart disease. In this review we will overview the key properties of pentraxins and discuss the major relevant findings that attribute to pentraxins, particularly CRP and PTX3, a biological role in the pathogenesis of cardiovascular disease.
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Contents

1. Pentraxins: fluid-phase endogenous modulators of the humoral innate immune response

The innate immune system comprises the first line of defense mechanism against invading pathogens or endogenous molecules exposed and/or released upon tissue injury. Such exogenous agents or altered self-structures present highly conserved molecular configurations, collectively referred to as pathogen-associated molecular patterns (PAMPs), which are recognized by the immune system via pattern recognition molecules (PRMs) or pathogen recognition receptors (PRRs) [1]. PRMs and/or PRRs may either be cell-associated or fluid-phase molecules. Cell-associated molecules include toll-like receptors, scavenger receptors, and nucleotide-binding oligomerization domain-like receptors, whereas fluid-phase molecules consist of ficolins, collectins, and pentraxins. The latter play a key role in the humoral innate immune

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response and the resulting inflammatory process both critical components of cardiovascular disorders [2].

2. Pentraxins structure, synthesis, and regulation

Pentraxins are a superfamily of multimeric proteins characterized by the presence of a ≈200 amino acid domain (*pentraxin signature*) in their C-terminal region [3]. Depending on the length of the N-terminal region pentraxins are classified as being constituents of the short [C-reactive protein (CRP) and serum amyloid P component (SAP)] or long [pentraxin 3 (PTX3)] pentraxin subfamily. CRP was identified in 1930 [4], SAP was discovered in 1965 [5], and PTX3 in the early 1990s [6]. Since then, other long pentraxins have been identified including neuronal pentraxin-1 and -2, neuronal pentraxin receptor, and most lately pentraxin 4 [7].

CRP is mainly found in the circulation as a pentamer formed by five identical non-glycosylated and non-covalently associated 23-kDa protomers (206 amino acids long) arranged in an annular configuration with cyclin pentameric symmetry [8]. However, upon dissociation of its pentameric quaternary structure, CRP subunits undergo a spontaneous and irreversible conformational change. The resulting molecule, termed modified or monomeric CRP (mCRP) has reduced aqueous solubility and becomes a tissue-based rather than a soluble-based molecule [9]. As such, mCRP has been detected in human aortic and carotid atherosclerotic plaques although not in healthy vessels [10,11]. SAP is a glycoprotein also made up of five non-covalently associated structures (23-kDa each) which may form a decameric structure under certain conditions but not in serum [12,13]. Finally, PTX3 forms an octamer structure with intra-molecule disulfide bonds.

Inflammation, infection or tissue damage triggers a non-specific acute phase response in which the synthesis of a number of plasma proteins (around 40) is rapidly augmented in response to inflammatory mediators originated at the site of the pathology. Among them CRP and PTX3 are the most characteristic acute phase proteins in humans. Other acute phase proteins include coagulation proteins (fibrinogen, prothrombin, Factor VIII, plasminogen), complement factors (C1s, C2, C3, C4, C5, B, C1 inhibitor), proteinase inhibitors (alpha-1 antitrypsin, alpha-1 antichymotrypsin), and transport proteins (haptoglobin, hemopexin, ceruloplasmin) [8]. Conversely, other plasma proteins have shown to markedly diminish their presence in the acute phase response [albumin, high-density lipoprotein (HDL), low-density lipoprotein (LDL), properdin, and transthyretin]. Pentraxin SAP has been shown to remain invariant in humans (30–50 mg/L) although markedly rises in the acute phase response in mice [14].

CRP and SAP are primarily produced in the liver in response to inflammatory mediators such as interleukin (IL)-1, IL-17 and most prominently IL-6 (Fig. 1) [15]. In contrast, PTX3 is produced by different cell types (vascular cells and innate immune cells) but not hepatocytes and pro-inflammatory cytokines IL-1β and TNFα (but not IL-6), toll-like receptors agonists, and distinct microbial moieties or intact microorganisms enhance PTX3 production (Fig. 2). Interestingly, atheroprotective HDL and anti-inflammatory IL-10 have also demonstrated to modulate PTX3 expression suggesting a regulatory role of PTX3 in the anti-/pro- inflammatory balance [16–18]. Specifically, HDL_3 subfraction has been shown to induce PTX3 production in endothelial cells and subsequently abrogate cytokine-induced inflammation. This atheroprotective effect likely occurs through PI3K/Akt pathway activation via G-coupled lysosphingolipids receptor-1 (S1P) [16]. On the other hand, anti-inflammatory IL-10 has also shown to amplify PTX3 expression on stimulated immune cells [19].

As an acute phase protein, CRP is barely detectable in the plasma of healthy human adults (levels below 3 mg/L) but rises rapidly (6 h) and markedly (up to 1000-fold) reaching a maximum at 48 h following an acute phase stimulus. CRP quickly drops once the triggering factor has been eliminated. PTX3 also presents low circulating levels under physiological conditions (below 2 ng/mL) and peaks earlier than CRP (at around 6 h) reaching levels of 10 ng/mL after tissue injury [e.g., acute myocardial infarction (AMI)] and of 1500 ng/mL upon inflammatory or septic conditions [20]. The rapid increase in PTX3 is likely derived from its local production by a number of different cell sources as compared to IL-6-related hepatic synthesis of CRP. Moreover, there is also a constitutive form of PTX3 stored in specific granules of

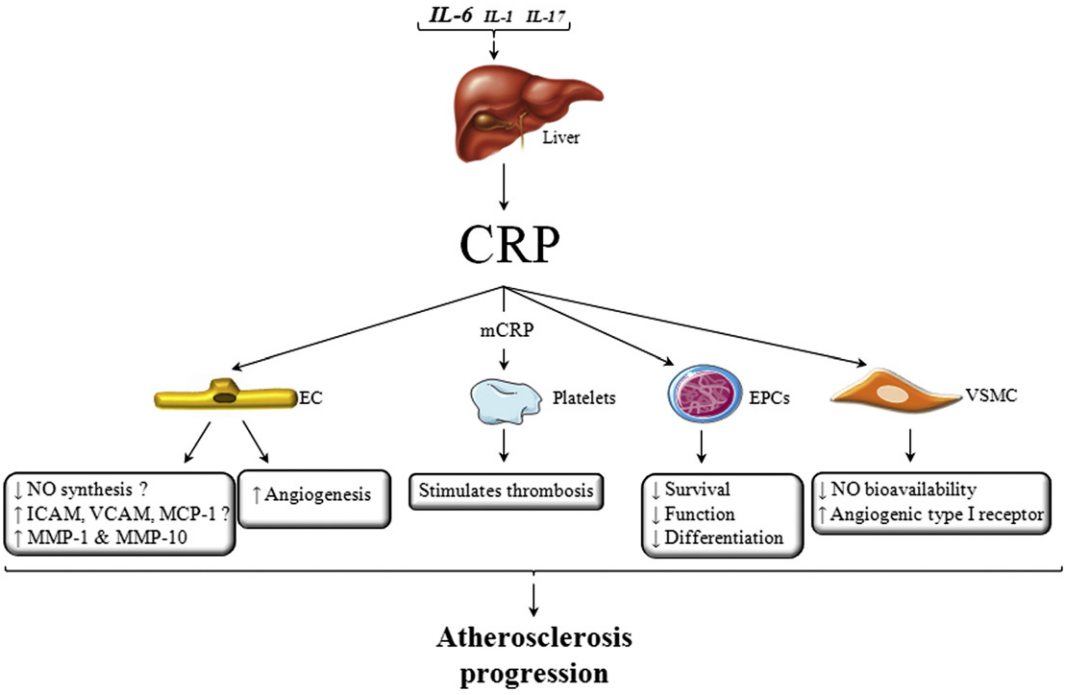

Fig. 1. Mechanisms involved in C-reactive protein (CRP) synthesis and/or release and the subsequent contribution to the etiopathogenesis of atherosclerosis. mCRP: monomeric or modified CRP. EC: endothelial cells; EPC: endothelial progenitor cells; VSMCs: vascular smooth muscle cells; ICAM: intracellular adhesion molecule; IL: interleukin; MMP: metalloproteinases; VCAM: vascular adhesion molecule; MCP-1: monocyte chemoattractant protein-1; NO: nitric oxide; VSMCs: vascular smooth muscle cells.

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