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Pentraxins (CRP, SAP) in the process of complement activation and clearance of apoptotic bodies through Fcγ receptors

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Abstract

Purpose of review—Ischemia/reperfusion injury and organ allograft rejection both entail excessive cell and tissue destruction. A number of innate immune proteins, including the pentraxins, participate in the removal of this potentially inflammatory and autoimmunogenic material. The classical pentraxins, C-reactive protein (CRP) and serum amyloid P component (SAP) are serum opsonins, which bind to damaged membranes and nuclear autoantigens. Understanding the role of pentraxins in inflammation has been advanced by the recent identification and structural analysis of their receptor interactions.

Recent findings—The ligand-binding, complement activating and opsonic properties of pentraxins have been known for some time. However, the establishment of Fcγ receptors as the primary receptors for pentraxins is a recent finding with important implications for CRP and SAP functions. The crystal structure of SAP in complex with FcγRIIIa was recently solved, leading to new insights into function and new opportunities for pentraxin-based therapeutics. In addition, new approaches to inhibit CRP synthesis or binding are being developed based on clinical associations between CRP levels and cardiovascular disease.

Summary—This review will summarize data on the function of pentraxins in clearance of injured tissue and cells and discuss the implications of this clearance pathway for autoimmunity and ischemia/reperfusion injury.

Keywords

CRP; SAP; PTX3; apoptotic cells; reperfusion injury; complement; Fc receptors

Introduction

The pentraxin family is an ancient group of proteins that are evolutionarily conserved. This review will focus on the two classical pentraxins, C-reactive protein (CRP) and serum amyloid P component (SAP). These proteins share a characteristic cyclic pentameric structure composed of identical noncovalently linked subunits of about 23 kDa, each of which contains a calcium-dependent ligand-binding site. A second group of related proteins has been dubbed “long pentraxins”. The long pentraxins contain a C-terminal region homologous to the classical pentraxins attached to an unrelated N-terminal domain. This

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review will focus on CRP and SAP, but we will also mention some recent findings on the long pentraxin, PTX3.

CRP and SAP are soluble pattern-recognition proteins found in serum, which bind to determinants on microbial pathogens and then recruit other elements of host defense. A comprehensive review of innate humoral immunity with an emphasis on pentraxins was recently published [1]. Like other innate recognition molecules, pentraxins also recognize ligands exposed in damaged or altered tissue [2]. In this regard, CRP and SAP are believed to play an important scavenger role in the clearance of membrane phospholipids and nuclear components from dead and dying cells. The classical pentraxins are synthesized by hepatocytes and this synthesis is differentially regulated in different species. In man, CRP is a major acute phase protein with baseline levels less than 5 µg/ml and acute phase levels up to 500 µg/ml. Interleukin-6 (IL-6) is the strongest inducer of CRP synthesis by hepatocytes, with additional contributions by IL-1 and glucocorticoids. SAP is found constitutively in human serum at about 25–30 µg/ml and is not an acute phase reactant [3]. Thus, it has been proposed that SAP provides a baseline scavenger function and CRP is rapidly increased when needed following tissue injury. It should be noted that in the mouse SAP is a major acute phase reactant and CRP is expressed at low levels (2–5 µg/ml). CRP is measured clinically because it is a highly sensitive indicator of inflammation and returns more rapidly to baseline (than for example the erythrocyte sedimentation rate (ESR)) with resolution of inflammation or infection.

There is an extensive literature on the association of small increases in CRP with atherosclerosis and cardiovascular events. The continuing discussion of whether CRP is only a marker or an active participant in cardiovascular disease is beyond the scope of this article, but a recent large study in Copenhagen found that genetically-determined elevated baseline CRP is not a risk factor for cardiovascular disease [4]. This review will focus on the role of the pentraxins following tissue injury including ischemia/reperfusion (I/R) injury, and will not review pentraxin roles in host defense or atherosclerosis.

The cyclic pentameric structures of CRP and SAP dictate their interaction with other elements of the immune system. On one face they bind to ligands through 5 calcium-dependent binding sites. On the opposite face they interact with the immune system by binding the first component of complement C1q to activate the classical pathway and by binding to Fcγ receptors (FcγR) on phagocytic cells. Understanding these interactions with complement and FcγR is essential to defining the physiological roles of CRP and SAP. The solution of the crystal structure of the pentraxin-FcγR complex is a recent important advance in this area [5].

The most controversial area of pentraxin biology is the relative importance of pro-inflammatory and anti-inflammatory effects of CRP. This has led to proposed therapeutic approaches that on the one hand use CRP as an anti-inflammatory treatment or on the other hand induce clearance, or block synthesis of CRP. In this review we will consider activities of CRP and other pentraxins in the context of new structural information and in different clinical situations.

Ligand-binding specificities of CRP and SAP

Pentraxins have a conserved calcium-dependent ligand-binding site on each subunit (Figure 1). The prototypic ligand for CRP is phosphocholine (PC), which binds through phosphate interaction with two calcium atoms and choline interaction with glutamic acid 81 and phenylalanine 66 [6]. The SAP ligand binding site has specificity for phosphoethanolamine (PE) and sugars such as methyl 4,6-*O*-(1-carboxyethylidene)-β-D-galactopyranoside (MOβDG) [7]. The affinity of each ligand-binding site for these small molecules is in the

μmolar range, but the multivalent nature of the pentraxins can result in high avidity binding to bacteria, cells or nuclear antigens displaying multiple determinants. CRP binding to polycations, such as poly-L-lysine, is calcium-independent. SAP binds to polyanions, such as heparin and glycosaminoglycans, and to all types of amyloid.

CRP binding to necrotic fibers in inflamed rabbit muscle was first demonstrated by immunofluorescence [8], and many studies since then have observed CRP localization in inflammatory tissue lesions [9]. A detailed analysis of CRP binding to cell membranes by Volanakis and others [10, 11], showed that phospholipase A₂ cleavage of phosphatidylcholine was sufficient to expose the PC head groups of membrane phospholipids, which provide binding sites for CRP on late apoptotic cells [12]. CRP also binds to oxidized phospholipids, which are found in atherosclerotic lesions and on apoptotic cells [13].

CRP binding to nuclear antigens was first described by Robey et al. who suggested that CRP bound to chromatin and nucleosome core particles [14]. Our laboratory determined the binding specificities for the pentraxins with nuclear antigens, and identified a shared peptide motif on several nuclear autoantigens recognized by CRP [15]. CRP and SAP have overlapping specificities for chromatin and histones, but in intact nuclei CRP binds predominantly to small nuclear ribonucleoproteins (snRNPs) producing a speckled pattern of fluorescence, whereas SAP binds to chromatin and to DNA [16]. Thus CRP and SAP may be scavengers for nuclear material released during or following cell death.

Complement activation by CRP and SAP

Both CRP and SAP bind to C1q to activate the classical complement pathway [17]. Of recent renewed interest is the interaction of CRP with the regulatory protein factor H (fH). CRP activation of complement is restricted to the early classical pathway leading to opsonization through C3b and iC3b with little activation of the final product, membrane attack complex (C5b-9) or generation of C5a, a potent inflammatory mediator. We showed that this pattern of activation results from the ability of CRP to recruit fH to the C3 convertase [18]. Recently, genome screens identified a common fH polymorphism as a strong risk factor for age-related macular degeneration (AMD). The polymorphism is located in one of several binding sites for CRP [19] and, although several earlier papers reported conflicting results, a recent detailed biochemical analysis found that the fH variant associated with AMD has reduced ability to bind to CRP [20]. These findings suggest that in chronic inflammation CRP may act locally at sites of injury to recruit fH and limit complement activation. Both CRP and SAP have also been shown to bind to C4b binding protein and this may regulate classical pathway activation by the pentraxins [21]. Local production and activation of complement also has an important role in I/R injury and allograft rejection [22]. By localizing at sites of tissue damage, CRP has the potential to contribute to the complement activation at these sites, but CRP may also regulate this activation by its interaction with fH and C4bp.

Structure of the pentraxin-FcγR complex

Although many studies showed specific, saturable binding of CRP to monocytes and neutrophils, the identity of the CRP receptor was controversial for many years. We identified FcγRI and FcγRII as CRP receptors and FcγRI, II and III as SAP receptors through binding to transfected cells and in phagocytosis assays [23–25]. Our recently published findings analyzed pentraxin interactions with FcγR in solution and solved the crystal structure of SAP in complex with FcγRIIa [5] (Figure 2). This work not only confirmed our previous identification of FcγR as the major receptors for CRP and SAP, but also determined the stoichiometry to be 1:1. Since FcγR cross-linking initiates signaling

(through either the activating ITAM or the inhibitory ITIM pathway), these results imply that CRP and SAP activation of cells through Fc γ R requires a multivalent ligand or other means of aggregation. The affinity of the pentraxins for the Fc γ R is in the micromolar range, similar to that of IgG binding to the low affinity Fc γ R, which further suggests that multivalent ligation of Fc γ R by the pentraxins will be required for cellular activation.

Another important finding from the crystal structure and competitive binding studies [26] (unpublished) is that C1q and Fc γ R cannot simultaneously bind to a single CRP molecule. The ridge helix and C-terminus of two nonadjacent pentraxin subunits provide the primary contacts with the 2 immunoglobulin domains of the Fc γ R, blocking access to the proposed C1q binding site [26, 27] (Figure 2). However, both complement and Fc γ R could interact with CRP attached to a multivalent ligand, such as an apoptotic cell.

These studies are highly significant as they establish a strong connection between pentraxins of the innate immune system and the Fc γ R, which were previously associated with antibody-dependent functions.

Furthermore they will help to resolve issues concerning the physiological interaction of pentraxins with leukocytes on a molecular level. Finally, they will provide a basis for the development of small molecule inhibitors of these interactions.

CRP and SAP binding and opsonization of apoptotic cells and nuclear antigens

The clinical observation that active systemic lupus erythematosus (SLE) is associated with an interferon signature of peripheral blood cell activation has contributed to an appreciation of the ability of nuclear antigens released from apoptotic cells to activate toll-like receptors (TLR) and promote autoimmunity. Multiple mechanisms are present to clear apoptotic cells, and defects in several of these are associated with SLE [2]. The strong genetic association between rare deficiencies in early complement components (C1qrs, C4) and SLE led to the “garbage hypothesis” [28]. According to this hypothesis, inefficient or defective clearance of apoptotic cells promotes the development of autoimmunity. Several complement-dependent pathways are associated with apoptotic cell clearance, including direct complement activation, and natural IgM antibody and pentraxin activation of the classical pathway [12]. Genetic studies have found associations between low CRP levels and SLE incidence or clinical severity [29, 30]. Most recently a promoter polymorphism associated with low baseline CRP was identified as a risk factor for SLE [31].

CRP and SAP binding and opsonization of apoptotic cells has been demonstrated by several different groups. Both complement-dependent and Fc γ R-dependent uptake can be demonstrated *in vitro*. Interestingly, CRP binding to apoptotic cells resulted in decreased lysis of the cells through fH recruitment, complement-dependent uptake, and release of TGF- β , an anti-inflammatory cytokine [32].

Together the genetic data and functional studies suggest an important role for pentraxins in preventing the development of SLE. Pentraxins probably contribute to clearance of dying cells and released autoantigens and regulation of responses to these autoantigens through interactions with Fc γ R. Furthermore, CRP has important anti-inflammatory activities that directly inhibit renal disease in SLE. It is not known whether apoptotic cells provide natural ligands for pentraxins *in vivo*. However, this possibility is consistent with the ability of CRP incubated with spleen cells to activate Fc γ RI signaling and induce regulatory macrophages [33].

Pentraxins in autoimmunity and inflammation

Studies in experimental models of inflammation and autoimmunity suggest that CRP has broad anti-inflammatory and protective activities in autoimmune diseases through its interactions with Fc γ R. Since CRP is expressed at low levels in the mouse, these studies relied on either transgenic expression or injection of human or rabbit CRP. The findings have consistently shown protective effects of acute phase levels of CRP in a number of acute inflammatory and autoimmune conditions including endotoxin shock [34, 35], SLE [36–38], experimental autoimmune encephalomyelitis [39], nephrotoxic nephritis [40], immune complex peritonitis (unpublished), and immune thrombocytopenia [33]. Where these models were analyzed (endotoxin shock, nephrotoxic nephritis, immune complex peritonitis), the effects of CRP were dependent on macrophages, Fc γ RI and IL-10. In immune thrombocytopenia [33], CRP-treated macrophages were able to transfer suppression, and this effect required Fc γ RI in the donor cells and the regulatory receptor, Fc γ RIIb, in the recipient.

A role for SAP in inflammatory disease has recently been reported. SAP acting through Fc γ R was shown to inhibit renal fibrosis *in vivo* [41]. These effects, like many of the effects of CRP, were at least partially dependent on the induction of IL-10 in macrophages. Since CRP and SAP interact with all of the different Fc γ R with similar affinities, they are likely to have overlapping functions depending on their concentration and the presence of monocytes, macrophages and neutrophils with different receptor expression.

It is difficult to experimentally test the importance of the anti-inflammatory activity of CRP in man. However, as mentioned above, genetic polymorphisms associated with lower baseline CRP levels are associated with increased risk of SLE. In addition, in a study of human volunteers injected with endotoxin, genetically-determined higher baseline CRP levels were associated with lower inflammatory cytokine responses (IL-6, TNF- α) *in vivo* [42].

PTX3 also plays an important role in inflammation. Unlike the classical pentraxins, PTX3 is produced locally, primarily by endothelial cells, macrophages and dendritic cells, in response to TLR activation. Serum levels of PTX3 are in the ng/ml range, suggesting that PTX3 has a special role in regulating inflammation locally at sites of tissue injury. It has recently been reported that PTX3 binds to P-selectin to block neutrophil migration through activated endothelium, suggesting that PTX3 has a feedback role in limiting neutrophil recruitment and inflammation [43].

Pentraxins in vascular injury and allograft rejection

In contrast to the anti-inflammatory effect of CRP acting through Fc γ R on macrophages, most studies of CRP in ischemic tissue have focused on its potential to activate complement at these sites. Complement activation increases I/R injury, although the stimulus and pathway of activation differ depending on the experimental model [22]. Reperfusion injury is also an important consideration in solid organ transplantation and complement activation contributes to allograft rejection [44, 45].

CRP and complement activation products are localized along with IgM to infarcted tissue in human autopsy material following myocardial infarction [46]. Pepys's group reported that injection of human CRP increased I/R injury in rat models of cardiac and cerebral infarct [47, 48]. Human CRP was deposited in the lesions and its adverse effect was eliminated by complement depletion. The interpretation of these results is complicated by the presence of endogenous rat CRP at levels of 200–300 μ g/ml. The authors stated that rat CRP does not

activate rat complement, although other investigators dispute this [49] and report endogenous rat CRP co-localized with complement in an intestinal I/R model [50].

A direct role for CRP participation in vascular injury was described by Szalai's group. Using human CRP transgenic mice in combination with Fc γ R or C3-deficiency, they initially showed that CRP increased neointimal thickening following vascular injury by an Fc γ RI-dependent mechanism [51]. More recently, they have further analyzed this model and report that CRP-induced neointimal thickening is complement-dependent. The proposed mechanism involves interaction of CRP with macrophages through Fc γ RI that results in the synthesis of C3 by the macrophages at the site [52].

Two studies have used genetically-deficient mice to study its role PTX3 in I/R injury with different results. In an intestinal I/R model, PTX3 deficiency reduced the inflammatory response decreasing both local and remote injury [53]. However, in a myocardial infarction model PTX3-deficient mice had increased inflammation, complement activation and myocardial damage [54]. Thus the *in vivo* roles of both the classical and long pentraxins in I/R injury remain unclear.

A role of pentraxin interaction with Fc γ R in complement-mediated allograft rejection is just beginning to be appreciated. In a cardiac allograft model, Fc γ RIII-deficient mice had accelerated rejection associated with increased inflammation and a failure to clear apoptotic material. Mouse SAP and complement were associated with these uncleared apoptotic cells and fragments, suggesting a failure of efficient removal of pro-inflammatory material in the absence of Fc γ RIII and supporting a beneficial scavenger role of pentraxins [55].

Conclusion

CRP and SAP are two important pattern recognition molecules that participate in the clearance and processing of pathogens, effete cells and nuclear autoantigens. The pentraxins have both inflammatory and anti-inflammatory roles, depending on the differential interactions with complement, Fc γ R and complement regulatory proteins. Overall they provide an important function in regulation of events to limit the inflammatory response.

Acknowledgments

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Figure 1. The crystal structure of CRP in complex with phosphocholine (B face)
Surface representation of 1BO9 [6]. Phosphocholine is represented as sticks and the calcium atoms as spheres.

Figure 2. The crystal structure of SAP in complex with Fc γ RIIA (3D5O)[5]
The complex demonstrates a 1:1 stoichiometry of the A face of SAP with the Fc receptor. SAP contacts Fc γ RIIA between the D1 domain of Fc γ R and the A subunit of SAP and between the D2 domain of Fc γ R and the C subunit of SAP.