Minireview

C-reactive Protein*

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C-reactive protein (CRP) is a phylogenetically highly conserved plasma protein, with homologs in vertebrates and many invertebrates, that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a characteristic that has long been employed for clinical purposes. CRP is a pattern recognition molecule, binding to specific molecular configurations that are typically exposed during cell death or found on the surfaces of pathogens. Its rapid increase in synthesis within hours after tissue injury or infection suggests that it contributes to host defense and that it is part of the innate immune response. Recently, an association between minor CRP elevation and future major cardiovascular events has been recognized, leading to the recommendation by the Centers for Disease Control and the American Heart Association that patients at intermediate risk of coronary heart disease might benefit from measurement of CRP. This review will largely focus on our current understanding of the structure of CRP, its ligands, the effector molecules with which it interacts, and its apparent functions.

CRP was discovered in Oswald Avery’s laboratory during the course of studies of patients with Streptococcus pneumoniae infection (1). Sera obtained from these patients during the early, acute phase of the illness were found to contain a protein that could precipitate the “C” polysaccharide derived from the pneumococcal cell wall. Forty years later, Volanakis and Kaplan identified the specific ligand for CRP in the pneumococcal C polysaccharide as phosphocholine, part of the tachoic acid of the pneumococcal cell wall (2). Although phosphocholine was the first defined ligand for CRP, a number of other ligands have since been identified. In addition to interacting with various ligands, CRP can activate the classical complement pathway, stimulate phagocytosis, and bind to immunoglobulin receptors (FcyR).

In humans, plasma levels of CRP may rise rapidly and mark-
edly, as much as 1000-fold or more, after an acute inflammatory stimulus, largely reflecting increased synthesis by hepatocytes. CRP induction is part of a larger picture of reorchestration of liver gene expression during inflammatory states, the acute phase response, in which synthesis of many plasma proteins is increased, whereas that of a smaller number, notably albumin, is decreased. At least 40 plasma proteins are defined as acute phase proteins, based on changes in circulating concentration of at least 25% after an inflammatory stimulus. This group includes clotting proteins, complement factors, anti-proteases, and transport proteins (reviewed in Ref. 3). These changes presumably contribute to defensive or adaptive capabilities.

**Regulation of CRP Expression**

The CRP gene, located on the short arm of chromosome 1, contains only one intron, which separates the region encoding the signal peptide from that encoding the mature protein. Induction of CRP in hepatocytes is principally regulated at the transcriptional level by the cytokine interleukin-6 (IL-6), an effect which can be enhanced by interleukin-1β (IL-1β) (4). Both IL-6 and IL-1β control expression of many acute phase protein genes through activation of the transcription factors STAT3, C/EBP family members, and Rel proteins (NF-κB). The unique regulation of each acute phase gene is due to cytokine-induced specific interactions of these and other transcription factors on their promoters. Thus, for the fibrinogen genes, STAT3 is the major factor, for the serum amyloid A genes, NF-κB is essential, and for CRP, the C/EBP family members C/EBPβ and C/EBPδ are critical for induction. In addition to C/EBP binding sites, the proximal promoter region of the CRP gene contains binding sites for STAT3 and Rel proteins. Interactions among these factors that result in enhanced stable DNA binding of C/EBP family members result in maximum induction of the gene (5). Extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes (6, 7). The mechanisms regulating synthesis at these sites are unknown, and it is unlikely that they substantially influence plasma levels of CRP.

**Protein Structure**

CRP consists of five identical, noncovalently associated ~23-kDa protomers arranged symmetrically around a central pore. The term “pentraxins” has been used to describe the family of related proteins with this structure. Each protomer has been found by x-ray crystallography to be folded into two antiparallel β sheets with a flattened jellyroll topology similar to that of lectins such as concanavalin A (8, 9). Each protomer has a recognition face with a phosphocholine binding site consisting of two coordinated calcium ions adjacent to a hydrophobic pocket. The co-crystal structure of CRP with phosphocholine (Fig. 1) suggests that Phe-66 and Glu-81 are the two key residues mediating the binding of phosphocholine to CRP (9). Phe-66 provides hydrophobic interactions with the methyl groups of phosphocholine whereas Glu-81 is found on the opposite end of the pocket where it interacts with the positively charged choline nitrogen. The importance of both residues has been confirmed by mutagenesis studies (10, 11).

The opposite face of the pentamer is the effector face, where complement C1q binds and Fcy receptors are presumed to bind. A cleft extends from the center of the protomer to the central...
ions are from Brookhaven Protein Data Bank (PDB entry 1B09). The calcium
the x-ray crystal structure of CRP-phosphocholine complex obtained
(Accelrys, San Diego, CA) was used to generate the ribbon diagram of
phosphocholine from Thompson
is bound (11). Changes appear to differ depending on the ligand to which CRP
changes in the CRP structure (14). These conformational
optimal C1q binding is accompanied by slight conformational
spans the central pore of CRP and interacts with two of the five
discharged central pore of the CRP pentamer. In this model, which
displays shape complementarity, the globular head of C1q
interacts. Phosphocholine is found in a number of bacterial
groups of these phospholipids are inaccessible to CRP in nor-
damaged and apoptotic cells (15–18). In addition to phospho-
activates complement and enhances phagocytosis. CRP
up-regulates the expression of adhesion molecules in endothelial
cells, inhibits endothelial nitric-oxide synthase expression
in aortic endothelial cells (23), stimulates IL-8 release from
several cell types, increases plasminogen activator inhibitor-1
expression and activity, and increases the release of IL-1, IL-6,
IL-18, and tumor necrosis factor-α (24). Although some of these
in vitro properties are consistent with the net in vivo effects of
CRP observed in mice and described below, it is likely that the
function of CRP is context-dependent and that it can either
enhance or dampen inflammatory responses depending on the
circumstance.

Complement—The complement system, consisting of about
30 proteins, plays an important role in host defense mecha-
nisms against infectious agents and in the inflammatory
response. Three pathways through which complement can be activate-
d are currently recognized: the classical, alternative,
and mannose-binding lectin pathways (reviewed in Ref. 25).
C1–C9 are the major components of the classical activation
cascade, most commonly initiated by binding of immune com-
plexes to C1q. The initial stage of activation generates cleavage
products of C3 and C4, which act as opsonins. The later stage
of classical complement activation involves C5–C9, which are
highly inflammatory, generating powerful chemotactic pept-
ides and forming the membrane attack complex, which can
result in lysis of the bacteria or cells to which it binds.

Complexing of ligand-bound CRP to C1q leads to formation
of C3 convertase (26), which assembles in a fashion similar to
that initiated by antibody-antigen complexes. However, exam-
ination of individual complement components suggests that
CRP-mediated complement activation is limited to the initial
stage of complement activation involving C1–C4, with little
activation of the late complement proteins C5–C9 (26). This is
in contrast to the complement cascade initiated by antigen-
antibody complexes, in which late phase components are acti-
ated. The difference between complement activation by CRP
and that resulting from immune complexes is presumably due
to the ability of CRP to interact with factor H, leading to
inhibition of the pathways that result in formation of C5
convertases. As a result, the strong inflammatory responses typi-
cally associated with C5a and the C5–C9 membrane attack
complex are limited. An additional mechanism through which
CRP may limit the amount of complement activation has re-
cently been described, in which CRP up-regulates endothelial
cell expression of three complement inhibitory factors: decay-
accelerating factor, membrane cofactor protein, and CD59 (27).
The net effect is that CRP can participate in host defense
systems while limiting the potentially damaging inflammatory
effects of the late stage complement components.

CRP Receptor—Functional effects of CRP on phagocytic cells,
as well as binding of CRP to such cells, have been recognized for
many years. Only recently have the receptors for CRP been
identified as the already known receptors for IgG, FcγRI and
FcγRII. Two general classes of FcγRs are now recognized, the
stimulatory receptors, characterized by an associated cytoplas-
mic immunoreceptor tyrosine-based activation motif (ITAM)
sequence, and an inhibitory receptor, characterized by the

In Vitro Effects

Further insight into the biologic function or functions of CRP
is provided by the ligands and effector molecules with which it
interacts. Phosphocholine is found in a number of bacterial
species and is a constituent of sphingomyelin and phosphati-
dylcholine in eukaryotic membranes. However, the head
groups of these phospholipids are inaccessible to CRP in nor-
mal cells, so that CRP can bind to these molecules only in
damaged and apoptotic cells (15–18). In addition to phospho-
choline, CRP can bind to a wide variety of other ligands, in-
cluding phosphoethanolamine, chromatin, histones, fibronec-
tin, small nuclear ribonucleoproteins, laminin, and polycations
(11, 19). Ligand-bound or aggregated CRP efficiently activates
the classical complement pathway through direct interaction
with C1q. There is evidence that CRP can interact with the
immunoglobulin receptors FcγRI and FcγRII as well, eliciting a
response from phagocytic cells. The ability to recognize patho-
gens with subsequent recruitment and activation of comple-
ment, as well as effects on phagocytic cells, constitute impor-
tant components of the first line of host defense.

Like many mediators of inflammatory processes, CRP has
pleiotropic effects. Both “pro-inflammatory” and “anti-inflam-
matory” activities have been described. In addition to the in vivo anti-inflammatory effects described below, CRP has been
shown to induce the expression of interleukin-1 receptor an-
tagonist (20) and increase release of the anti-inflammatory
cytokine interleukin-10 (21, 22) while repressing synthesis of
interferon-γ (22). However, many other functions that can be
regarded as pro-inflammatory are recognized. For example,
CRP activates complement and enhances phagocytosis. CRP
up-regulates the expression of adhesion molecules in endothelial
cells, inhibits endothelial nitric-oxide synthase expression
in aortic endothelial cells (23), stimulates IL-8 release from
several cell types, increases plasminogen activator inhibitor-1
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function of CRP is context-dependent and that it can either
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circumstance.
Phagocytosis of CRP-opsonized particles and apoptotic cells has been shown to proceed through FcγRs in the mouse (30, 31). CRP has also been shown to induce signaling through human FcγRIIa, an ITAM-containing receptor, in granulocytes (32). As discussed previously, activation of the classical complement pathway can lead to an enhancement of leukocyte phagocytosis, but even in the absence of complement, CRP has been reported to enhance in vitro leukocyte phagocytosis of several pathogenic species, including Staphylococcus aureus, Escherichia coli, and Klebsiella aerogenes (33). The enhancement of phagocytosis by CRP is likely due to its interactions with FcγRs.

**In Vivo Effects**

In contrast to humans, plasma levels of mouse CRP rarely exceed 2 µg/ml following inflammatory stimuli. Ablation of the murine CRP gene by homologous recombination has not been reported. Rather, the murine CRP response represents an evolutionary oddity, a natural knockdown, that has been exploited in a variety of studies utilizing exogenous or transgenic CRP to study the effects of CRP in vivo.

The ability of CRP to protect mice against bacterial infection by various species has been well established. These species include S. pneumoniae (34, 35) and Haemophilus influenzae (36, 37), which have phosphocholine-rich surfaces, and Salmonella enterica serovar Typhimurium, which has no known surface phosphocholine, although its cell membrane is known to be rich in another CRP ligand, phosphoethanolamine (38). Protection is predominantly mediated through CRP binding to phosphocholine or phosphoethanolamine, followed by activation of the classical complement pathway. CRP protection of mice infected with S. pneumoniae has been shown to require an intact complement system (39) but does not require interaction with FcγRs (39, 40).

CRP protective effects are not limited to bacteria. CRP has been shown to play a protective role in a variety of inflammatory conditions, including protecting mice from lethal challenge with bacterial lipopolysaccharide and various mediators of inflammation (41). The former has been shown to require Fcγ receptors (21). In addition, CRP has been found to delay the onset and development of experimental allergic encephalomyelitis, an aseptic animal model of multiple sclerosis (22). In a murine model of chemotactic factor-induced alveolitis, CRP has also been shown to inhibit the influx of neutrophils and protein into the lungs (42, 43). Taken together, these experiments suggest that the net effect of CRP in mice is anti-inflammatory.

It is of interest that CRP may exert an ameliorative effect upon murine models of systemic lupus erythematosus (SLE). SLE is an autoimmune condition, which is characteristically accompanied by antibodies against cellular, particularly nuclear, components, many of which are CRP ligands, and in which CRP levels are often unexpectedly low (44). Two reports have shown that injection or transgenic expression of CRP in a murine strain prone to development of a disease resembling human SLE resulted in a slight delay in mortality (45, 46). In addition to these mouse models, a polymorphism in the human CRP gene resulting in a lower basal level of CRP has been associated with an increased risk of developing systemic lupus erythematosus (47). These findings raise the possibility that decreased amounts of CRP may contribute to the pathogenesis of SLE. It has long been held that an important function of CRP is to target for clearance the cellular debris of necrotic and apoptotic cells by binding to damaged cell membranes and nuclear material. Decreased clearance of such material might well enhance development of autoantibodies to them.

**“Modified” CRP**

Denatured and aggregated forms of CRP (neo-CRP or modified CRP) have been reported to be powerfully pro-inflammatory in a number of experimental systems, although the existence of this material in vivo has not been unequivocally established (reviewed in Ref. 48). It is conceivable that at local sites of deposition, small amounts of modified CRP may be generated with a set of properties distinct from those of the native protein. It has recently been reported that modified CRP increased the release of the inflammatory mediators monocyte chemoattractant protein-1 and IL-8 and up-regulated the expression of ICAM-1 in endothelial cells. In this model, modified CRP was shown to be a much more potent inducer than native CRP (49).

**Minor CRP Elevation**

Although about two-thirds of the American population has plasma CRP levels under 3 µg/ml, circulating CRP levels under 10 µg/ml have historically been regarded as clinically insignificant. In recent years, a plethora of studies have demonstrated an association between slightly elevated CRP plasma levels, between 3 and 10 µg/ml, and the risk of developing cardiovas-
cular disease (reviewed in Ref. 50), metabolic syndrome, and colon cancer. It is felt that many of these conditions involve a low level of underlying chronic inflammation that could be reflected by these minor increases. Minor increases in CRP levels have also been reported to be associated with a number of medical conditions that do not appear to be inflammation-associated, as well as with several genetic polymorphisms of the CRP and other genes, ethnicity, various dietary patterns, and obesity.

**CRP and Atherosclerosis**

Evidence in support of the possibility that CRP itself plays a role in the pathogenesis of atherosclerosis has been summarized in a recent review (6). Examples include the finding that CRP binds the phosphocholine of oxidized low density lipoprotein (18), up-regulates the expression of adhesion molecules in endothelial cells, increases low density lipoprotein uptake into macrophages (51), inhibits endothelial nitric-oxide synthase expression in aortic endothelial cells (23), and increases plasminogen activator inhibitor-1 expression and activity. A recent study utilizing a mouse strain expressing transgenic CRP and deficient in apolipoprotein E reported a modest acceleration in aortic atherosclerosis in male animals expressing high levels of CRP (52). A second report demonstrated increased arterial occlusion in transgenic mice expressing CRP in a model of vascular injury (53). Despite these suggestive findings, a role for CRP in the pathogenesis of atherosclerosis is far from established.

**Summary**

CRP is an ancient protein whose initial role as a pattern recognition molecule may have been to defend against bacterial infections, but whose present biological role appears quite complex. It is protective against a variety of bacterial infections and inflammatory stimuli in mice. It is likely that the activity of CRP in humans, either pro- or anti-inflammatory, is dependent on the context in which it is acting. Recent data have raised the possibility that it may participate in the pathogenesis of disease.

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**REFERENCES**

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