C-Reactive Protein
Initiator or Product of Inflammation?

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C-Reactive protein (CRP) is a member of the pentraxin family of proteins and is highly conserved throughout evolution. In humans, CRP is a major acute phase protein with well-defined roles in innate and adaptive immunity. CRP expression is induced by inflammatory cytokines; primarily interleukin-6 (IL-6) with other factors, including IL-1β and tumor necrosis factor-α acting to enhance expression. In response to the presence of pathogenic bacteria and apoptotic cells, CRP binds C1q and activates the classical complement cascade. In addition to roles in opsonizing pathogens and assisting in pathogen clearance, CRP binds FcγRI, FcγRIIa, and FcαRIIb receptors and activates neutrophils. CRP also stimulates uptake and presentation of bacterial antigens by dendritic cells as part of the adaptive immune response. Binding of CRP to the FcγRI receptor on macrophages induces the production of the anti-inflammatory cytokine IL-10, leading to the downregulation of inflammation.

As an acute phase protein, circulating levels of CRP are associated with multiple proinflammatory states including atherosclerosis. The association of higher CRP levels with the presence of subclinical atherosclerosis and clinical cardiovascular disease has been documented by numerous studies. Based on these associations, a hypothesis was put forward that CRP may have a direct role in atherosclerosis progression or conversion to clinical events. CRP has been reported to support the initiation and progression of atherosclerosis through CRP-mediated effects on several vascular cells. Among these, CRP has been reported to stimulate production of inflammatory cytokines in monocytes and reactive oxygen species, chemokines, and adhesion molecules in endothelial cells. CRP has also been reported to activate smooth muscle cells.

Infusion of exogenous CRP into humans has also been reported to have proinflammatory effects. CRP infusion into healthy volunteers activated peripheral leukocytes, coagulation, and inflammatory pathways as measured by increased IL-6 and serum amyloid A (SAA) post infusion. However, these apparent proinflammatory roles are controversial, and it is not clear whether CRP itself was responsible for the documented effects or whether cell perturbation and inflammation resulted from contaminants and adjuvants present in recombinant CRP preparations produced in bacteria. In vitro studies using purified, natural human CRP have not reproduced the results of studies using recombinant material. In support of a noncausal role for CRP in atherosclerosis, genetic studies applying Mendelian randomization analysis have found no association of gene variants that affect CRP levels with cardiovascular disease risk. By contrast, and entirely consistent with the inflammation hypothesis of atherosclerosis, gene variation of the IL-6 receptor (IL6R) supports a causal relationship for this receptor in atherothrombosis.

To further address the question of a causal relationship underlying the association of CRP with cardiovascular disease risk, Lane et al report an elegant in vivo study examining the potential for CRP to directly stimulate inflammatory pathways. In their study, purified, natural human CRP was infused into 7 healthy adult human volunteers. These were nonsmoking males aged 18 to 25 years with body mass index <25 kg/m². Levels of inflammatory cytokines, the anti-inflammatory cytokine IL-10, and SAA, an acute phase protein highly sensitive to inflammatory stimuli, were measured preinfusion and at multiple time points after infusion. Levels of the inflammatory cytokines IL-1β, tumor necrosis factor-α and IL-6, and the anti-inflammatory cytokine IL-10 did not seem to be altered by CRP infusion ≤24 hours post infusion. In addition, circulating SAA did not increase with CRP infusion. Several other biomarkers were measured with results provided in the online-only Data Supplement, showing no impact on coagulation markers as well (von Willebrand factor antigen, D-dimer, prothrombin fragment 1–2, and plasminogen activator inhibitor-1 antigen). The authors conclude that, in these healthy men, CRP infusion did not result in a measurable proinflammatory response, indicating that CRP is more likely a product of the inflammation response rather than a direct mediator of the response.

Similar to genetic studies and previous work by this group, results of the current study do not support a causal role for CRP in atherosclerosis. However, this study is not without some limitations. Most of the cytokine measurements were below the detection limits of the assays used, making it difficult to assess more subtle CRP effects on the cytokines that initiate the inflammation response, although lack of change in circulating SAA provides some evidence that IL-6, IL-1β, and tumor necrosis factor-α levels did not respond to CRP infusion. In addition, IL-1β, IL-6, and tumor necrosis factor-α precede CRP and SAA expression in the inflammatory pathway, so it is uncertain whether an effect of CRP on their levels would be anticipated unless there...
was a positive feedback loop or impact on clearance of the cytokines. Nonetheless, others have postulated that CRP is stimulatory of many pathways so there is value in the findings. Although the authors assessed downstream effects of inflammation by measuring coagulation activation, it would have been interesting to examine the potential for CRP infusion to alter levels of downstream markers of inflammation, especially markers of cellular activation given that CRP has been reported to promote cellular responses. For example, CRP has been proposed to induce expression of cellular adhesion molecules, such as vascular cell adhesion molecule-1, intra-cellular adhesion molecule-1, and E-selectin, soluble forms of which circulate at measurable concentrations. However, the study demonstrating this used recombinant CRP which may have been contaminated as Lane et al point out.

From the clinical perspective, it may not be relevant that CRP does not play a causal role in atherogenesis. It is well accepted that inflammation is central to atherothrombosis. The epidemiological evidence linking higher CRP to vascular risk and work demonstrating interrelations of inflammation with cardiovascular risk factors and the anti-inflammation effects of cardiovascular prevention strategies is robust. With a large body of research evaluating inflammation biomarkers and cardiovascular risk, CRP has emerged as the most potentially useful to classifying risk in practice. This is not necessarily because CRP has a more causal role than other biomarkers but relates to analytic properties that make CRP clinically useful, such as relative low within-person variability, precision, ease of measurement using automated platforms, lack of diurnal variability, wide measurement range, and availability of World Health Organization standards. Elevated CRP identifies a group that will experience reduced mortality and cardiovascular events with statin prescription in the absence of other indications for treatment. Clinical trials are underway that may more directly address the inflammation hypothesis. The Cardiovascular Inflammation Reduction Trial (CIRT) is testing whether low-dose weekly methotrexate compared with placebo will reduce vascular events in myocardial infarction patients with either diabetes mellitus or metabolic syndrome, disorders that are associated with inflammation. The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) will evaluate whether inhibition of IL-1β compared with placebo will lower risk of recurrent vascular events in stable coronary patients with CRP ≥2 mg/dL while they are receiving standard secondary prevention treatments.

To conclude, regardless of the limitations of this and other studies, current evidence does not support a direct causal role for CRP in human atherosclerosis through the induction of chronic inflammation. Further work is needed on treatments that might impair CRP activity itself. From the clinical perspective, CRP remains a valuable biomarker and an appropriate surrogate for clinical research studies.

Disclosures

None.

References


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