CRP - A TARGET FOR THERAPY IN HUMAN DISEASE?

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Abstract
C-reactive protein (CRP) is a widely recognized indicator of inflammation and is known to play an important role in atherogenesis. Recent prospective studies have demonstrated that increased CRP concentrations within the reference interval are a strong predictor of myocardial infarction, stroke, sudden cardiac death, and peripheral vascular disease in apparently healthy adults. The correlation of circulating CRP concentrations with the severity, extent, and progression of many different pathologies, and the prognostic significance of these associations, are consistent with CRP not just being a marker of disease but also contributing to pathogenesis. Knowledge of the structure and function of CRP — including its three-dimensional structure alone and complexed with ligands coupled with experience in developing an inhibitor of the related protein SAP (Amyloid P component, Serum) establishes an excellent platform for drug design

Keywords: CRP; human disease; inflammatory marker; inhibitors of CRP

1. Introduction
Systemic inflammation is associated with leukocyte-mediated endothelial dysfunction1. Proinflammatory cytokines, chemokines, and glucocorticoid hormones are elaborated and stimulate hepatocytes to synthesize a wide array of acute phase proteins2,3. A dominant acute phase protein in mammals, C-reactive protein (CRP) is a 206–amino acid pentameric polypeptide4. Originally isolated from the serum of patients with pneumonia, it has a high binding affinity for pneumococcal C polysaccharide5.

2. Structure
CRP belongs to a family of pentameric proteins known as pentraxins. It is composed of five identical, noncovalently bonded subunits, and each subunit consists of 206 amino acid residues with a calculated molecular mass of 23 017 kDa; therefore, the total molecular mass of CRP is ~118 000 kDa. This arrangement is very similar to that of another acute-phase protein known as serum amyloid P component3. The structure of CRP contains a crystal contact where the calcium-binding loop from one protomer coordinates into the calcium site of a second protomer to form the pentameric structure. This configuration allows for the binding of the ligand phosphocholine and provides information concerning conformational changes related to calcium binding.

3. Synthesis and metabolism
CRP is synthesized and secreted mainly by hepatocytes in response to cytokines such as interleukin-6. Induction of CRP in some models requires both interleukin 6 and either interleukin-1 or TNF-α7. CRP is primarily derived via IL 6-dependent hepatic biosynthesis. Glucocorticoids enhance the stimulatory effects of cytokines on the production of acute phase proteins8. Insulin, on the other hand, decreases their effects on the production of some acute phase proteins9. Efficiency of secretion of CRP is greatly increased during acute-phase response10. During an acute phase response the rate of secretion into the plasma may be relatively constant and the concentration achieved is dependent upon the duration of stimulation and resulting response by the liver11. Newly synthesized CRP is rapidly secreted by liver cells and hence difficult to show within the cytoplasm.

4. Pathophysiology of C-reactive protein
The gene for CRP is on chromosome 1, and about 35 to 40% of the variability of baseline CRP concentrations between different healthy individuals is controlled by genetic
polymorphisms in the CRP gene. Apart from fulminant liver failure, there are no other pathologies and very few drugs (e.g. statins, niacin, fibrates) that will reduce the CRP concentrations, unless they also affect the underlying acute-phase stimulus such as antibiotics for infection or corticosteroids for an inflammatory disease. On the other hand, obesity, smoking, diabetes mellitus, lack of exercise, pregnancy and hormonal therapy (estrogens or progesterones) are associated with a mildly elevated CRP concentration.

5. Conditions or disease states where C-reactive protein is elevated

5.1 Acute inflammation: Bacterial infection, Pneumococcal pneumonia, Acute rheumatic fever, Bacterial endocarditis and Staphylococcal osteomyelitis

5.2 Chronic inflammation: Systemic lupus erythematosus, Rheumatic arthritis, Reiter’s syndrome, psoriatic arthropathy, arthritis following jeuno-ileal bypass, Polyarteritis nodosa, disseminated systemic vasculitis, cutaneous vasculitis, Polymyalgia rheumatic, Crohn’s disease, Ulcerative colitis, Dermatomyositis, Osteoarthritis, Neoplastic diseases, Smokers, Obesity and Diabetes.

5.3 Tissue injury: Tissue injury and surgery and acute myocardial ischemia.

6. Role of CRP in inflammation and cardiovascular disease

Accumulating data pathologically link atherosclerosis and the inflammatory response to vascular injury. Luminal injury associated with hyperlipidemia, hypertension, and/or angioplasty results in endothelial cell dysfunction, adhesion molecule expression, and inflammatory cell infiltration. The autocrine and paracrine effects of cytokines and chemokines promote oxidized lipid deposition with vascular smooth muscle cell proliferation and migration. This chronic vascular wall inflammation leads not only to progressive luminal stenosis but also to plaque instability. Several prospective studies have demonstrated a direct correlation between acute myocardial infarction (MI) rise in CRP, post infarction adverse events and subsequent infarct size.

7. Direct CRP-Mediated Vascular Disease

The evolving concept of CRP acting as a direct pathologic mediator in vascular remodeling may ultimately provide the most clinical relevance. C-reactive protein has been localized to the neointima of atherosclerotic plaque and activates complement in early lesions. Although hepatic production has classically been identified as the primary source, Yasojima and colleagues recently demonstrated that CRP is also expressed by vascular smooth muscle cells and macrophages resident in atherosclerotic lesions. Furthermore, CRP induces endothelial cell expression of adhesion molecules and monocyte chemotactant protein-1. Recently, Fu and Borensztajn demonstrated that CRP promotes the aggregation of low-density lipoprotein, thus contributing to foam-cell formation within atherosclerotic lesions. This local influence, coupled with the well-documented proinflammatory effects of CRP on monocytes and macrophages, supports a direct deleterious role of CRP in the vascular wall itself.

Although systemic markers of focal inflammatory processes are becoming increasingly useful for risk stratification in cardiovascular disease, targeting specific pathologic culprits within the inflammatory cascade may permit a direct therapeutic benefit.

8. Anti-inflammatory therapy

Antiplatelet and/or lipid-lowering agents have traditionally been used for the prevention of acute cardiovascular events. An evolving pharmacologic paradigm links these drugs and serum CRP levels. The Nurses’ Health Study analyzed the incidence of coronary events in more than 80,000 women who were taking aspirin regularly. Overall, 1 to 6 aspirin tablets per week resulted in a decrease in nonfatal MI and fatal coronary disease. These results have been corroborated in several large, randomized studies. Although the risk reduction of MI in this group was 55.7%, the beneficial effect was reduced as CRP levels decreased. These data emphasize the inflammatory component of cardiovascular disease and suggest that aspirin therapy may directly affect endovascular dysfunction, as indicated by CRP production. Furthermore, CRP level may serve as an indicator of patients at risk and as a practical
marker of the efficacy of the preventive strategy. Several large trials 37, 38, 39 have linked the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to the attenuation of serum CRP levels. Recently, the Air Force/Texas Coronary Artery Prevention Study (AFCAPS/TexCAPS) investigators reported the effects of lovastatin on CRP levels in patients with and without hyperlipidemia 40. Apart from its lipid-lowering effects, lovastatin reduced CRP levels by 14.8%. Lovastatin was effective in preventing coronary events in patients with elevated cholesterol levels and was also effective in patients with low cholesterol and high CRP levels. Thus, not only does CRP level reliably reflect inflammation, but its suppression is associated with a reduction in adverse cardiovascular events.

Conclusion
It has been speculated that CRP may have significant proinflammatory effects, and that, by binding to ligands exposed on cells or other autologous structures as a result of infection, inflammation, ischemia, and other pathologies, and triggering complement activation, it may exacerbate tissue damage, leading to more severe disease 41. The rat myocardial infarction model provided the first direct evidence of these processes in vivo 42, but they are not necessarily confined to cardiovascular disease. The excellent correlation of circulating CRP concentrations with the severity, extent, and progression of many different pathologies, and the prognostic significance of these associations, are consistent with CRP not just being a marker of disease but also contributing to pathogenesis. A definitive way to test this concept will be the use of novel drugs that specifically block CRP binding and its proinflammatory effects in vivo 43. If these compounds are effective, they may find very broad applicability. Such drugs would be a powerful tool for determining whether increased CRP production merely reflects atherosclerosis or does indeed participate in its pathogenesis and complications, and they could also have cardioprotective effects in acute myocardial infarction. Knowledge of the structure and function of CRP — including its three-dimensional structure alone and complexed with ligands coupled with experience in developing an inhibitor of the related protein SAP (Amyloid P component, Serum) 44 establishes an excellent platform for drug design.

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