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Linking inflammation and thrombosis: Role of C-reactive protein

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Abstract

C-reactive protein (CRP) is a biomarker of inflammation. Increased plasma levels of CRP are associated with an increased risk of myocardial infarction. However, the correlation between plasma CRP concentration and atherosclerotic plaque burden is poor. Based on these observations, it has been hypothesized that CRP increases the risk of myocardial infarction by promoting thrombosis. This article reviews available data that link enhanced CRP expression to increased risk of thrombosis, with a focus on the effects of CRP on hemostasis, platelet function, and fibrinolysis. Overall, the available data support the hypothesis that CRP is an important mechanistic link between inflammation and thrombosis.

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Key words: C-reactive protein; Thrombosis; Inflamma-

INTRODUCTION

Inflammation is defined as a localized protective reaction of tissue to irritation, injury, or infection, which is characterized by pain, redness, swelling, and loss of function. Inflammation plays a central role in the pathogenesis of atherosclerosis^[1]. C-reactive protein (CRP) is an acute phase reactant plasma protein that is present in plasma of healthy humans and whose plasma concentration increases significantly during acute and chronic inflammation^[2]. Several studies have demonstrated that plasma CRP concentration is independently associated with the incidence of atherothrombotic events in humans, most notably myocardial infarction^[3,4]. However, whether CRP plays a causal role in atherosclerosis and its complications, or is simply an important clinical marker of inflammation and cardiovascular risk, continues to be debated^[5]. Plasma CRP levels are only weakly associated with the extent of atherosclerosis in humans^[6]. The Dallas Heart Study, which measured coronary artery calcification and aortic

plaque size in > 2000 individuals, concluded that CRP is a poor predictor of atherosclerotic burden^[7]. These results are consistent with recent experiments in which CRP-transgenic mice were crossed to atherosclerosis-prone, hyperlipidemic mice to test directly the hypothesis that enhanced CRP expression drives atherosclerosis formation. Although an initial report was positive^[8], two subsequent studies have found no apparent effect of CRP on atherosclerotic plaque development^[9,10], and another study has found that CRP retards atherogenesis in mice^[11]. However, transgenic mice that express human CRP demonstrate accelerated thrombosis after arterial injury compared to non-transgenic control mice^[12], and administration of highly purified preparations of CRP to humans activates the blood coagulation system^[13]. These observations support the hypothesis that CRP increases the risk of ischemic vascular events, such as myocardial infarction, not by promoting atherosclerotic plaque size, but rather by activating the blood coagulation system and increasing the risk of thrombosis. The regulatory systems that control hemostasis and thrombosis, although functioning in a highly coordinated manner, can be subdivided into three major components, namely: (1) blood platelets; (2) blood coagulation proteins present in plasma and the vascular wall; and (3) the fibrinolytic system. In this article, the scientific evidence that links CRP to the regulation of each of these systems is reviewed. As a whole, the available data support the hypothesis that CRP is an important mechanistic link between inflammation and thrombosis.

STRUCTURE AND BIOLOGIC ROLE OF CRP

CRP belongs to the pentraxin family of plasma proteins^[2]. Native CRP consists of five identical subunits, each composed of 206 amino acids with a molecular weight of 23 000, which bind non-covalently to form a symmetrically shaped, pentameric molecule with a molecular weight of 118 000. Pentameric CRP can be dissociated into monomers *in vitro*^[14] and *in vivo*^[15], with pentameric and monomeric forms exerting significantly different biological effects^[16-18]. CRP binds to phosphocholine residues in bacterial cell membranes, thereby playing an important role in the innate immune response by facilitating the recognition and clearance of bacteria^[19-21]. CRP also binds phosphocholine residues in apoptotic eukaryotic cells and to several mammalian proteins^[22]. Aggregated or ligand-bound CRP activates the complement cascade, which suggests an additional mechanism by which CRP participates in host defense^[23]. CRP is synthesized predominantly in the liver, where its production is controlled by several cytokines^[2].

CRP ACTIVATES VASCULAR CELLS

CRP is detectable in the walls of diseased blood vessels, including atherosclerotic plaque^[24,25]. Although vascular

wall CRP can be deposited from blood^[26], CRP mRNA is detectable in the arterial wall^[25], which indicates that CRP is also produced locally, particularly within atherosclerotic plaque, in which one study has found higher CRP mRNA concentrations than those in liver tissue^[27]. Macrophages within plaques produce CRP^[27]. CRP mRNA and protein are present in vascular smooth muscle cells (VSMCs) within human atherosclerotic plaques, which indicates that VSMCs synthesize CRP *in vivo*^[24,27]. Inflammatory cytokines induce CRP expression by cultured human coronary artery VSMCs^[28]. Exposure of cultured vascular endothelial cells to CRP inhibits nitric oxide synthase expression and upregulates expression of interleukin-8, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1^[29,30]. In addition to phosphocholine residues, CRP binds to protein receptors that are present on plasma membranes of eukaryotic cells. CRP binds to Fcγ receptor I (FcγR I CD64), a member of the IgG Fc receptor family, which is expressed on macrophages^[31,32]. FcγR II a (CD32), which is expressed by macrophages and platelets and plays an important role in the pathophysiology of immune-mediated thrombocytopenia, binds CRP to activate intracellular signaling pathways^[33-35]. One study has suggested that CRP binds to vascular endothelial cells *via* FcγR I and FcγR II a^[30]. However, some studies have concluded that CRP does not bind directly to FcγR II a, and that the observed interactions of CRP with cells that express FcγR II a might have been due to binding of the intact Fc region of anti-CRP antibodies to FcγR II a^[36].

EFFECT OF CRP ON BLOOD PLATELETS

Platelets express CRP receptors FcγR III (CD16) and FcγR II a^[37]. Several studies have found that CRP inhibits platelet aggregation induced by a variety of agonists, including thrombin, platelet aggregating factor (PAF), and immunoglobulin^[38-40]. CRP appears to inhibit PAF-induced platelet aggregation by binding to the phosphocholine moiety of PAF^[41]. However, CRP induces platelet adhesion to endothelial cells and monocytes^[42,43]; interactions that promote thrombosis. The conformation of CRP (i.e. monomeric *vs* pentameric) might play a major role in controlling platelet aggregation. Pentameric CRP binds FcγR II a on platelets, which inhibits binding of platelets to neutrophils^[37,44]. Conversely, monomeric CRP binds to FcγR III, which promotes platelet capture of neutrophils^[37]. Activated platelets convert pentameric CRP to the monomeric form^[44,45]. Hence, CRP-platelet crosstalk is bidirectional; i.e. CRP regulates platelet activation, whereas activation of platelets regulates the conformational status and biological function of CRP. Conversion of pentameric CRP to monomeric CRP by activated platelets leads to activation of monocytes, which potentially provides a mechanism to link platelet activation to monocyte activation and invasion into the vascular wall.

REGULATION OF BLOOD COAGULATION FACTORS BY CRP

Tissue factor (TF) appears to be an important mechanistic link between inflammation, CRP, and thrombosis. TF is a 44000 molecular weight membrane-bound glycoprotein that plays a key role in initiating thrombosis after vascular injury by binding factor VIIa^[46]. The TF-VIIa complex activates factor X and factor IX, thereby initiating proteolytic cascades that result in thrombin formation and blood clotting. TF is synthesized in the adventitia of normal blood vessels^[47], where it functions to maintain hemostasis after vascular trauma. TF is not detectable in the intima of normal arteries, but is abundant in the lipid-rich cores of atherosclerotic plaques^[46,48]. CRP stimulates TF expression by blood monocytes *in vitro*^[49], and it has been proposed that the monocyte is an important target cell of CRP that mediates its prothrombotic effects. CRP also induces TF expression by VSMCs, both *in vitro* and *in vivo*^[50,51], which provides a mechanism by which CRP can promote fibrin formation after endothelium-denuding vascular injury.

EFFECT OF CRP ON THE FIBRINOLYTIC SYSTEM

Plasminogen is converted to plasmin, the enzyme that degrades fibrin clots, by tissue-type plasminogen activator (t-PA). Plasminogen activator inhibitor-1 (PAI-1) is the main physiological inhibitor of t-PA and urinary-type PA. PAI-1 is present in plasma, platelets, endothelial cells, VSMCs, and extracellular matrix. CRP inhibits release of t-PA and stimulates release of PAI-1 from vascular endothelial cells^[52,53]. Therefore, CRP can alter the fibrinolytic balance of endothelial cells so as to promote intravascular fibrin formation.

CONCLUSION

In summary, CRP appears to play an important role in regulating the function of blood platelets, the extrinsic blood coagulation cascade, and the fibrinolytic system. *In vivo*, CRP enhances the thrombotic response to vascular injury. Inflammation upregulates CRP expression; hence, CRP appears to be an important mechanistic link between inflammation and thrombosis. Activation of the blood clotting system - specifically, activation of platelets - regulates CRP structure and biological function. Therefore, the CRP-dependent crosstalk between inflammation and thrombosis is bidirectional. Further studies are necessary to define more precisely the pro-thrombotic functions of CRP. In addition, more research is warranted to determine the impact on thrombosis of pharmacological inhibition of CRP expression level and function, which can be achieved with statins and compounds that specifically target CRP^[54,55].

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