Monomeric C-reactive protein and inflammatory injury in myocardial infarction

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Online publish-ahead-of-print 7 August 2012

This editorial refers to ‘Circulating microparticles generate and transport monomeric C-reactive protein in patients with myocardial infarction’ by J. Habersberger et al., pp. 64–72, this issue.

C-reactive protein, a member of the pentraxin superfamily, is a prototypical ‘acute-phase’ protein that is synthesized at a low rate under physiological conditions but is markedly induced and secreted following tissue injury and inflammation. Rapid secretion of C-reactive protein during the acute-phase response results in up to 1000-fold increases in plasma levels within 24–48 h. As a result, C-reactive protein is a highly sensitive, but non-specific, marker of systemic inflammation. Over the last 20 years, C-reactive protein has emerged as an important predictor of cardiovascular risk in a variety of clinical settings. The development of high-sensitivity C-reactive protein assays greatly enhanced the clinical value of plasma C-reactive protein. In contrast to traditional assays that were only suitable for measurements of acute-phase responses, high-sensitivity C-reactive protein immunoassays allowed quantification of baseline plasma levels of C-reactive protein with high sensitivity throughout its normal range. Elevated plasma high-sensitivity C-reactive protein levels predict cardiovascular risk and may identify patients who benefit the most from risk reduction therapies.

Despite the abundance of evidence on the significance of C-reactive protein as a biomarker in cardiovascular disease, surprisingly little is known about its pathophysiological role. Although a causative role for C-reactive protein has been proposed in atherosclerosis and thrombosis, in vitro and in vivo studies have produced contradictory results. For example, treatment with human native C-reactive protein has been reported to accelerate atherosclerotic disease in apolipoprotein-E-null mice; in contrast, transgenic overexpression of human C-reactive protein had no effects on the development of atherosclerosis or even delayed plaque formation. The conflicting in vivo effects of C-reactive protein may be explained by the contextually regulated formation of C-reactive protein isoforms with distinct functional properties. C-reactive protein is known to undergo dissociation from a native pentameric form (pentameric C-reactive protein) to its monomeric subunits (monomeric C-reactive protein). In contrast to the context-dependent pro- and anti-inflammatory effects attributed to pentameric C-reactive protein, monomeric C-reactive protein is considered a non-soluble, tissue-associated protein that exerts potent pro-inflammatory actions and may serve to amplify and localize inflammation.

In the current issue of the journal, Habersberger et al. report for the first time the identification of monomeric C-reactive protein in the circulation of patients with acute myocardial infarction and propose a novel mechanism for pentameric C-reactive protein dissociation mediated through binding to circulating microparticles. Considering that monomeric C-reactive protein has distinct functional properties not shared by pentameric C-reactive protein, its generation in the site of cardiac injury may be an important regulator of prothrombotic and inflammatory activity following myocardial infarction. However, because most of the evidence on the role of monomeric C-reactive protein is derived through in vitro experiments, our current knowledge raises more questions than answers.

(i) What are the mechanisms of pentameric C-reactive protein dissociation in vivo?

Activated platelets and microparticles may provide a substrate for pentameric C-reactive protein dissociation in the infarcted heart; however, their relative contribution remains unknown. Apoptotic cells, present in abundance in the healing infarct, may also mediate monomeric C-reactive protein generation.

(ii) What are the in vivo actions of monomeric C-reactive protein?

In the absence of direct in vivo evidence, one can only speculate on the potential effects of monomeric C-reactive protein generation in the infarcted myocardium (Figure 1). In the coronary vasculature, formation of C-reactive protein monomers may exert prothrombotic actions by increasing platelet adhesion, by stimulating tissue factor synthesis in endothelial cells, and by inducing formation of neutrophil-platelet aggregates. In addition to actions on thrombus formation, monomeric C-reactive protein may also modulate the cardiac inflammatory reaction to infarction by accentuating pro-inflammatory signalling in endothelial cells and leukocytes. C-reactive protein monomers, transferred from microparticles to activated endothelial cells, may stimulate synthesis of endothelial adhesion molecules, enhancing

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leucocyte infiltration into the infarct. Monomeric C-reactive protein has a wide range of pro-inflammatory actions on neutrophils and monocytes that may promote their adhesive properties while prolonging their presence in the healing infarct. In vitro experiments have demonstrated that monomeric C-reactive protein induces neutrophil-derived chemokine synthesis, stimulates monocyte integrin expression, enhances neutrophil adhesion to endothelial cells, and delays neutrophil apoptosis. Monomeric C-reactive protein-mediated accentuation and prolongation of the post-infarction inflammatory reaction may delay the reparative response, accentuate cardiomyocyte apoptosis, and increase matrix-degrading activity, thus resulting in enhanced adverse remodelling of the infarcted heart. However, the reported effects of monomeric C-reactive protein in vitro are not exclusively pro-inflammatory: inhibitory actions of monomeric C-reactive protein have also been proposed. Monomeric C-reactive protein bound to the surface of necrotic cardiomyocytes may recruit both the complement initiator C1q and the inhibitor C4bp, fine-tuning activation of the complement cascade in the infarcted heart. Moreover, monomeric C-reactive protein associated with endothelial cells was reported to exert potent angiogenic actions; the potential significance of these effects in repair of the infarcted heart remains unknown.

(iii) What are the mechanisms of clearance of monomeric C-reactive protein from the infarcted heart?

Effective healing of the infarcted myocardium is dependent on timely suppression of the inflammatory reaction; multiple regulatory mechanisms and STOP signals prevent uncontrolled inflammation in the infarcted heart. Timely clearance of monomeric C-reactive protein from the infarct may be important to limit pro-inflammatory signalling. Pentameric C-reactive protein dissociation to monomeric C-reactive protein on the surface of apoptotic cells may represent such a clearance mechanism, as these cells are rapidly phagocytosed by infarct macrophages, thus reducing local concentrations of pro-inflammatory C-reactive protein monomers in the infarct environment.

(iv) Could monomeric C-reactive protein serve as a cardiovascular risk predictor?

Because monomeric C-reactive protein may be the ‘active’ form of C-reactive protein in inflammatory conditions, microparticle-bound circulating monomeric C-reactive protein may serve as an indicator of cardiovascular risk. The development of reliable, reproducible, and accurate assays for circulating monomeric C-reactive protein is needed before its relative usefulness as a biomarker can be tested.

(v) Is loss of pentameric symmetry the only conformational change regulating C-reactive protein-mediated actions?

Recent studies have suggested that a reduction in an intrasubunit disulfide bond may follow dissociation of pentameric C-reactive protein to monomeric C-reactive protein, accentuating its pro-inflammatory actions. Clearly, we are just beginning to unravel the biological mechanisms of C-reactive protein actions in inflammatory conditions. More than 80 years after its discovery, this extensively studied acute-phase reactant is as mysterious as ever; its role as a mediator of disease remains enigmatic and controversial.

Conflict of interest: none declared.

Funding

N.G.F.’s laboratory is supported by National Institutes of Health grants R01HL-76246 and R01HL-85440, the Wilf Family Cardiovascular Research Institute, and the Edmond J. Safra/Republic National Bank of New York Chair in Cardiovascular Medicine.
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