Role for Complement as an Intermediate Between C-Reactive Protein and Intercellular Adhesion Molecule-1 Expression?

To the Editor:

The link between C-reactive protein (CRP) and cardiovascular disease (CVD) often is considered to be indirect in that it reflects an epiphenomenon. A direct proinflammatory role of CRP, however, may also explain the associations between CRP and CVD.1 The recent article by Pasceri et al2 regarding the proinflammatory effect of CRP on human endothelial cells provides additional arguments for such a proinflammatory role for CRP. It also raises several intriguing questions, however.

In the study by Pasceri et al,2 the CRP-induced expression of intercellular adhesion molecule-1 (ICAM-1) by endothelial cells appeared to be dependent on the presence of human serum, which implies the involvement of a serum factor. Though it remains to be identified, this serum factor may be activated complement, in view of the fact that upregulation of ICAM-1 by complement in vivo has been described previously.3 Also, our observations regarding ICAM-1 expression in human infarcted myocardium4 fit with such a role of complement, inasmuch as this expression was only found in areas that were positive for complement.

A role for complement as an intermediate between CRP and ICAM-1 expression requires that the former is able to activate complement. Indeed, a number of studies have provided evidence for this effect of CRP. For example, CRP and activated complement show similar localization patterns in human infarcted myocardium, and patients with acute myocardial infarction (AMI) have detectable plasma levels of CRP-complement complexes; these complexes are specific markers for CRP-mediated complement activation in vivo (personal observations). Furthermore, homogenates of human infarcted myocardium (from patients who died after AMI) contain elevated levels of CRP-complement complexes (personal observations). Finally, Griselli et al5 recently demonstrated that human CRP increases infarction size in a complement-dependent fashion in a rat model of AMI. Together, these data fit with a scenario in which CRP enhances inflammation in CVD by activating complement, which, among other effects, stimulates the expression of ICAM-1.

Pasceri et al2 studied the expression of ICAM-1 in human endothelial cells. In the immunohistochemical study referred to above, we found ICAM-1 localization both in endothelial cells and in cardiomyocytes in infarcted parts of human myocardium.4 Thus, CRP/complement-dependent expression of ICAM-1 in CVD may not be limited to endothelial cells.

The exact explanation for the link between CRP and CVD still is under investigation. The study by Pasceri et al2 once more emphasizes that the proinflammatory effects of CRP may be pivotal in the inflammatory cascades involved in CVD. Interventional studies should reveal whether these proinflammatory effects are clinically important.

Wim K. Lagrand, MD, PhD
Hans W.M. Niessen, MD, PhD
Remco Nijmeijer, MD
Departments of Cardiology and Pathology
University Hospital “Vrije Universiteit”
Amsterdam, the Netherlands

C. Erik Hack, MD, PhD
Department of Clinical Chemistry
University Hospital “Vrije Universiteit”
Department of Immunopathology
CLB, Sanquin Blood Supply Foundation
Amsterdam, the Netherlands

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