C-reactive protein and cardiovascular disease: linked by complement?

Sir,

We read with great interest the article of Koenig and Wanner regarding the link between C-reactive protein (CRP) and coronary artery disease [1]. CRP is considered to be an independent risk factor for cardiovascular disease. When corrected for established cardiovascular risk factors CRP levels still add to the prediction of adverse cardiovascular events or a worse outcome in healthy individuals as well as in patients with manifest cardiovascular disease. As briefly outlined in the paper by Koenig and Wanner, several hypotheses are proposed to explain the relation between CRP and cardiovascular disease. In most articles in the literature, regarding CRP as a cardiovascular risk factor, this link is considered to be indirect; i.e. that it reflects an epiphenomenon. However, CRP also exerts pro-inflammatory effects in ischaemic heart disease: i.e. that CRP is able to activate complement via the classical pathway after binding to a suitable ligand. Although this ability of CRP has already been described in 1974 by Kaplan and Volanakis [2], in our opinion, too little attention is paid to this aspect of CRP in literature, as is the case in this paper by Koenig et al.

In a recent study we found CRP being colocalized with activated complement fragments in human infarcted myocardium [3]. Koenig and colleagues themselves recently described the same colocalization of CRP and complement in atherosclerotic vessels, indicating that such a pro-inflammatory role for CRP is very likely [4]. Using an assay that specifically detects CRP-mediated complement activation in vivo [5], we also found that patients with acute myocardial infarction (AMI) have increasing plasma levels of CRP-specific complement activation fragments. With the same assay elevated values of CRP-complement complexes were found in homogenates of human infarcted myocardium, taken from patients who died after AMI (manuscripts in preparation). These results together strongly suggest that CRP enhances inflammation in cardiovascular disease by activating complement.

A pro-inflammatory role of CRP could very well explain the observed associations with cardiovascular disease as recently described [6]. Intervention studies should reveal whether our hypothesis that the link between CRP and cardiovascular disease is based on its pro-inflammatory role is correct and clinically relevant.

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1Koenig W, Wanner C. C-reactive protein and coronary artery disease—what is the link? Nephrol Dial Transplant 1999; 14: 2798–2800
2Kaplan MH, Volanakis JE. Interaction of C-reactive protein complexes with the complement system. I: consumption of human complement associated with the reaction of C-reactive protein with pneumococcal polysaccharide and with choline phosphatides, lecithin and sphingomyelin. J Immunol 1974; 112: 2135–2145
6Lagrand WK, Visser CA, Hermens WTh, Niessen HWM, Verheugt FWA, Wolbink GJ, Hack CE. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation 1999; 100: 96–102

Reply

Lagrand et al. underline in their comment the potential direct effects of CRP in the development of atherosclerosis through complement activation, complex binding and deposition in atherosclerotic lesions, and infarcted myocardium. Such a pro-inflammatory effect of CRP has been mentioned in our editorial and its potential role in atherosclerosis is currently investigated by several groups. Indeed, new intriguing experimental data from Griselli et al. [1] support the observations and conclusions by Lagrand et al. [2] and suggest that CRP exacerbates tissue injury during the acute phase of myocardial infarction (MI) by activating the complement system. Injection of human CRP in a rat model of acute MI enhanced infarct size by approximately 40% and in vivo complement depletion abrogated this effect. In addition to these findings, Bhakdi and colleagues [3] recently extended the knowledge in this field by showing that enzymatic non-oxidative, modification of tissue-deposited low density lipoprotein by conferring the CRP-binding capacity onto the molecule. They showed that exposure of native CRP to phosphorylcholine groups from degraded LDL particles generates the targets for binding. Staining of CRP in fatty streaks of human coronary arteries localized the molecule to the deeper part of the fibroelastic layer and in the intima adjacent to the media. Further pathophysiologic effects of CRP might involve the stimulation of monocyte chemotaxis via a specific CRP receptor, a mechanism possibly important in the early steps of atherogenesis, and potentially independent of its complement activating capacity [4]. Additional recent autopsy studies in 62 cases (290 human coronary artery sections, Zhang et al. [5]) confirmed CRP localization at the site of relapsing inflammatory/necrotic process to the coronary intima.

In summary, we agree with Lagrand and colleagues that complement activation might constitute an important pathophysiologic mechanism through which CRP could be directly involved in the pathogenesis of atherosclerosis. We feel, however, that at present direct evidence for such a pro-inflammatory effect of CRP is much less well established than its strong, consistent role as a marker for increased cardiovascular risk in apparently healthy subjects as well as in patients with manifest atherosclerosis.

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