Deposition of Modified or Native C-Reactive Protein in Atherosclerotic Arteries?

To the Editor:

Accumulating evidence suggests a predictive role of elevated serum concentrations of C-reactive protein (CRP) for atherosclerosis and its thrombotic complications.1,2 These findings apparently reflect an inflammatory component of the multifactorial atherosclerotic process. Furthermore, it is increasingly recognized that CRP may not merely represent an indicator of inflammation but may also, because of its known functional properties, be actively involved in the initiation or perpetuation of local inflammatory reactions.2,3 A direct approach in the study of the latter hypothesis is the search for CRP in atherosclerotic lesions.4,5

In this context, the recent publication of Torzewski et al.6 in Arteriosclerosis, Thrombosis, and Vascular Biology is of actual relevance. By means of immunohistochemistry, the authors clearly demonstrate deposits of CRP beside terminal complement proteins in the arterial wall of patients with early atherosclerotic lesions. Because ligand-bound CRP activates the classical pathway of complement, the authors suggest that the colocalization of terminal complement proteins with CRP might reflect complement activation by CRP in situ. Even if we share the hypothesis that CRP may contribute to local complement activation, this conclusion is not unequivocally supported by the presented findings. The monoclonal antibody against CRP used in that study (clone CRP-8 from Sigma) exclusively recognizes a modified form of CRP (mCRP) and not the native CRP molecule. This restricted specificity of clone CRP-8 against mCRP described by the manufacturer (Sigma) was recently confirmed experimentally by us.8 Differentiating between both CRP variants may be functionally relevant, because mCRP, contrary to its native counterpart, is not able to activate complement.9,10 Additionally, the denatured reduced form of CRP (mCRP) differs from native CRP in many biological and physicochemical properties,7 which may be important for the local prevalence and function of the CRP molecule. One might reconcile the findings and hypotheses of that study1 by the assumption that native CRP may reach an appropriate ligands (phospholipids, lipoproteins, or nuclear debris), and may finally be transformed into mCRP under acidic conditions of an inflammatory microenvironment. The significance of mCRP is under investigation. Our data have identified mCRP as a natural component of normal blood vessel intima.8 Its presence and in vitro activities suggest that it may be a part of the physical signaling pathway of the extracellular matrix.9

Peter Vaith
Abteilung Rheumatologie und Klinische Immunologie
Medizinische Universitätsklinik
Universitatslinikum
Freiburg, Germany
Lawrence A. Potempa
Next Era Therapeutics, Inc
Vernon Hills, Illinois


Comment on ‘Deposition of Modified or Native C-Reactive Protein in Atherosclerotic Arteries’

In their letter ‘Deposition of Modified or Native C-Reactive Protein in Atherosclerotic Arteries’ Peter Vaith and Lawrence Potempa comment on our recent publication ‘C-Reactive Protein Frequently Colocalizes With the Terminal Complement Complex in the Intima of Early Atherosclerotic Lesions of Human Coronary Arteries.’1 In that article, we demonstrated deposition of C-reactive protein (CRP) in early human atherosclerotic lesions and its colocalization with the terminal complement complex C5b-9. On the basis of that finding, we suggested that CRP in early atherosclerotic lesions may promote inflammation in the arterial wall by activating the complement system.

The authors of this valuable letter pointed to the fact that CRP in the arterial wall, owing to acidic conditions in inflamed tissue, may be modified into a denatured and reduced form (mCRP) displaying other biological and physiochemical properties than the native form. In the light of increasing evidence for a pivotal role of CRP in atherosclerosis, we agree with the authors’ notion that mCRP and its functional properties are most important to study. However, we do not agree with their statement that the antibody that we used for CRP staining (clone CRP-8 from Sigma Chemical Co) ‘...exclusively recognizes a modified form of CRP (mCRP) and not the native CRP molecule.’ At this point, we would like to cite the specification sheet of the antibody provided by Sigma, which states ‘monoclonal anti-human C-reactive protein (CRP) recognizes an epitope located on the 24-kDa subunit of denatured reduced CRP applying the immunoblotting technique. It does not cross-react with human serum amyloid P component (SAP), human haptoglobin, human α-1 acid glycoprotein, and human IgG, nor with CRP from Limulus. The product displays its reactivity against CRP (native and denatured-reduced) applying ELISA, dot-blot, and immunoblotting technique’ (italics added by us for emphasis). In addition, we have addressed the point raised by Vaith and Potempa in a conversation with the manufacturer, who confirmed the information given in the specification sheet.

On the basis of this information, we suggest that the antibody used in our study is able to detect both the native and the modified form of CRP. In this context, we would like to emphasize that we were not able to demonstrate CRP staining in coronary arteries without any signs of atherosclerotic lesion development. The question remains which form of CRP is the dominating one in early atherosclerotic lesions. Although we did not address this question in our study, extensive costaining with C5b-9 suggests the presence of considerable amounts of native CRP. Furthermore, very recently we demonstrated that native CRP binds to degraded LDL, enhancing complement activation.2 Immunohistochemical studies complemented these findings in showing that CRP colocalizes with enzymatically modified-LDL in early human atherosclerotic lesions.2 However, it is most likely that CRP becomes modified in the lesion, at least in intermediate and advanced lesions with increasing acidic conditions, and the significance of this modified CRP needs to be investigated further.
Jan Torzewski, MD, MPhil
Department of Cardiology
Internal Medicine II
University of Ulm
Ulm, Germany

Michael Torzewski, MD
Department of Clinical Chemistry
University of Regensburg
Regensburg, Germany


Deposition of Modified or Native C-Reactive Protein in Atherosclerotic Arteries?
Peter Vaith and Lawrence A. Potempa

doi: 10.1161/01.ATV.20.4.1173
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/20/4/1173

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/