Immunopathogenesis of Atherosclerosis

To the Editor:

We read with great interest the article on acceleration of atherosclerosis by nonspecific stimulation of the immune system. Lehr and colleagues showed data supporting the concept that atherosclerosis has an immunopathological component, making improbable that a single infectious agent should assume particular importance in its initiation or progression.

We tested this hypothesis in 218 patients (119 men; 99 women; mean age 64.6; 29 to 83 years) referred for coronary angiography. We studied the possible association between seropositivity for a particular microbial agent and angiographically proven coronary artery disease (CAD), defined as more than 50% diameter stenosis of at least one coronary artery. Blood was tested for seromarkers of 6 pathogens (Hepatitis-A virus, Chlamydia pneumoniae, Helicobacter pylori, Herpes simplex virus, and Influenza virus type A and type B). Analysis of seromarkers of all 6 microbial agents demonstrated that seropositivity for 1 single pathogen was no predictor of risk for CAD. In contrast, the number of infectious pathogens to which an individual has been exposed (“infectious burden”) correlated well with CAD. Five or six seromarkers were positive in 21.3% of patients with CAD and in 9% of patients without CAD (P=0.03).

Although attractive, the microbial pathogenesis theory for atherosclerosis remains unproven. Over the last century, microbiologists have invoked fulfillment of Koch’s postulates to determine pathogen causality. Certainly a multifactorial disease process such as atherosclerosis unlikely will be due to a single microbial agent.

Our clinical data confirm the results from Lehr and colleagues as well as observations from others that multiple infectious agents contribute to atherosclerosis. We hypothesize that the risk of cardiovascular disease posed by infection is related to the number of pathogens to which an individual has been exposed (the “pathogen burden”). In contrast, seropositivity for a single pathogen is unlikely to represent a predictor of risk for CAD.

Johann W. Auer, MD
Robert Berent, MD
Thomas Weber, MD
Bernd Eber, MD
2nd Medical Department
Division of Cardiology and Intensive Care
General Hospital Wels
Grieskircherstraße 42
A-4600 Wels, Austria
johann.auer@khwels.at


Response

The observations of Auer and colleagues and Rupprecht and colleagues caution against the simplistic notion that an infectious agent may cause atherosclerosis. Rather, the total “infectious burden” influences its progression. This concurs with the Mainz hypothesis, which proposes that atherosclerosis is a novel type of immunopathological disease that is initiated and driven by tissue-stranded LDL.

Our hypothesis evolved in the wake of the realization that complement activation is an important element in atherogenesis. Oxidized LDL does not activate complement, and hence another proinflammatory form of the lipoprotein needed to be sought and was found. The concept proposes that enzymatic, nonoxidative modification of LDL occurs in tissues, generating a lipoprotein that binds C-reactive protein, activates complement, and is taken up by macrophages. Enzymatic transformation of LDL to an immune activator is envisaged to be primarily physiological because small amounts of LDL with its insoluble cargo continuously leak into the vessel wall, and cholesterol can then be removed via the HDL-dependent, reverse transport pathway.

Atherosclerosis develops when this process is exaggerated, and any coactivation of complement and macrophages should then be detrimental. This prediction was fulfilled by the experiment and is corroborated by the clinical observations. But the Mainz hypothesis harbors implications extending beyond the realm of infections. It proposes that any coactivation of innate immune effectors is harmful: smoking and hemodialysis representing two noninfectious examples. Further, while processes that enhance tissue-stranding of LDL are risk factors, it is enzymatically modified LDL that actually causes the disease. Efforts to treat atherosclerosis with antioxidants or antibiotics are thus doomed to fail, whereas decreasing the tissue burden of LDL will be effective. It is satisfying that the central predictions of our hypothesis are currently being fulfilled by clinical trials and observations.

Sucharit Bhakdi, MD, PhD
Institute of Medical Microbiology
University Mainz
Germany

Tolga Attila Sagban
Hans-Anton Lehr, MD, PhD
Department of Pathology
University Mainz
Germany

Christian Ihling, MD
University of Freiburg
Germany

Ulrich Zähringer, PhD
Forschungszentrum Borstel
Germany

Klaus-Dieter Hungerer, PhD
Matthias Blumrich, PhD
Hoechst Marion Roussel
Marburg, Germany

Kurt Reifenberg, PhD
Central Laboratory Animal Facility
University Mainz
Germany

Immunopathogenesis of Atherosclerosis
Johann W. Auer, Robert Berent, Thomas Weber and Bernd Eber

Circulation. 2002;105:e64
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/10/e64

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation 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 Circulation is online at:
http://circ.ahajournals.org/subscriptions/