Gene-Environment Interaction in the Expression of Antioxidant Status: A Role for Genes in the Relationship Between Smoking and Coronary Disease

John E. Hokanson

doi: 10.1161/hq0701.093718
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 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/21/7/1102

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/
Editorial

Gene-Environment Interaction in the Expression of Antioxidant Status

A Role for Genes in the Relationship Between Smoking and Coronary Disease

John E. Hokanson

Both environmental determinants and underlying genetic susceptibilities are undoubtedly involved in complex diseases such as atherosclerosis. However, determining the relative contributions of environmental and genetic factors of complex diseases is difficult. Adding to the difficulty is the possibility of gene-environment interaction in the expression of these traits. That is, the genetic contribution to a disease may vary by a person’s level of environmental exposure, and conversely, environmental exposure may have differential effects depending on one’s genetic background. Valuable insights into the causation of complex diseases will come as we learn to dissect these complicated gene-environment relationships.

See p 1190

Over the past decade, the role of oxidative stress in atherosclerosis has been extensively studied. It is now well established that LDL oxidation is important in foam cell formation, a crucial step in the early atherosclerotic process. Animal models have shown the importance of oxidative stress on plaque formation. It has been more difficult to show a direct link between oxidative stress and atherosclerosis in humans. Nonetheless, evidence is now accumulating to support a role for oxidation in coronary heart disease, including recent studies showing that antibodies to oxidative epitopes are associated with an increase in coronary disease.1,2

A number of environmental factors that modify oxidative potential have been identified. Dietary factors such as α-tocopherol, ascorbate, and β-carotene are associated with an increase in antioxidant status in humans. Clinical trials, however, have not convincingly shown a benefit on coronary disease events associated with these antioxidants. Smoking is one potent stimulus of the oxidative process. Its relationship with coronary disease may be, at least in part, through increasing oxidative stress.

Until now, a genetic contribution to the variability in antioxidant status in humans had not been established. Specific gene products are known to promote or inhibit oxidation, and recent transgenic animal models indicate a primary role for these genes in oxidative stress. The role of human genetic variation, however, is less clear. In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Wang and colleagues3 report that a significant portion of total antioxidant status (TAS) in humans has a genetic component, with the magnitude of this genetic contribution to TAS being dependent on smoking status. This work adds antioxidant status to the list of complex traits affected by genes, environment, and gene-environment interaction. It is a reminder that we need to simultaneously consider environmental and genetic factors, and their potential interaction, to understand the etiology of complex diseases.

Wang and colleagues3 used a statistical genetics modeling technique called variance components analysis. This technique partitions the total phenotypic variation of a trait into genetic and environmental components. This requires family data. Known covariates such as age and sex, interaction terms, and even specific genetic markers can also be included in this flexible, multivariate model.

In families from the San Antonio Family Heart Study, Wang et al1 found that a significant proportion of the variation in antioxidant status could be attributed to genetic factors. Among smokers, genes accounted for 80% of the variation in TAS. Among nonsmokers this contribution was only 26%. Although the amount of TAS variation caused by genes is quite different between smokers and nonsmokers, their data suggest that the variation can be attributed to the same gene or set of genes regardless of smoking status.

The mechanism accounting for the difference in the genetic contribution to TAS between smokers and nonsmokers is not clear. It may relate specifically to smoking-induced oxidation or the general decrease in antioxidant status among smokers. It is possible that the mechanism by which smoking induces oxidative damage is under genetic control or that antioxidant compensation of smoking-induced oxidative stress is genetically regulated. It is also possible that the oxidative stress of smoking depletes antioxidants, thereby revealing the residual intrinsic (genetic) antioxidant capabilities. Of course, these potential mechanisms are neither exhaustive nor mutually exclusive.

It is tempting to speculate which genes may be responsible for the genetic variation in antioxidant status. One interesting candidate would be paraoxonase (PON1). Originally identified on the basis of its ability to hydrolyze organophosphorous compounds, PON1 is now known to be an important antioxidant enzyme associated with HDL particles. Low levels of PON1 activity are associated with carotid artery disease and the extent of coronary stenosis.4,5 Common
polymorphisms in the PON1 gene associated with coronary disease reduce PON1 activity and account for 70% to 80% of the variation in PON1 activity.4,5 The variation in PON1 due to polymorphisms in the PON1 gene may account for genetic variation in TAS.

Another potential candidate is myeloperoxidase (MPO). MPO is capable of forming a variety of reactive oxygen species that can promote the oxidation of LDL,6 and it can specifically convert metabolites from tobacco smoke into reactive oxygen species. A common promoter polymorphism in the MPO gene (MPO−463G→A) modifies an Sp-1 binding domain that alters the expression of MPO7 and oxidative damage due to smoking. This polymorphism could account for the greater amount of genetic variation in antioxidant status among smokers.

There are other potential candidate genes that may contribute to the genetic variation in antioxidant status, such as lipoxygenases, superoxide dismutases, and others. In addition, there are as-yet-to-be-identified genes that will likely contribute to the genetic variation in antioxidant status. Just as there are a number of environmental factors influencing antioxidant status, it is likely that multiple genes will also influence the susceptibility to this complex trait.

Oxidative damage appears to be important in the degenerative processes of aging and plays a crucial role in atherosclerosis. Much work has focused on environmental factors that inhibit oxidation, such as consumption of antioxidant vitamins, and on deleterious environmental factors that promote oxidation, such as smoking. The work by Wang and colleagues3 is the first to show genetic susceptibility to antioxidant status in humans. Equally important, it demonstrates that gene-environment interaction must be considered in studying the etiology of complex diseases.

References

Key Words: genetics ■ antioxidants ■ smoking