The remodeling of blood vessels, characterized by thinning of the vessel wall attributable to neointima formation or changing of the vessel wall thickness and diameter, occurs after injury, dysfunction, or endothelial denudation, resembling the risk associated with endovascular surgery. Upon vascular injury, activated vascular smooth muscle cells (VSMCs) of local or systemic origin contribute to the remodeling processes which may eventually lead to occlusion of the blood vessel. Thus, understanding the molecular aspects of occlusive neointimal proliferation is desirable to promote better therapies for this disease process.

There is substantial evidence that endothelial-derived nitric oxide (NO) is a key regulator of vascular remodeling. Endothelial nitric oxide synthase (eNOS)-derived NO diffuses into the surrounding cell layers of VSMCs to exert various cardiovascular homeostatic functions. eNOS can be stimulated to produce NO by hemodynamic forces, autacoids, hormones, and growth factors. Once NO diffuses into the VSMC layer, NO mediates vasorelaxation but also regulates the balance of VSMC proliferation versus apoptosis, the latter functions governing important aspects of vessel caliber and remodeling. Thus, one can envision the endothelium as a sensor that adjusts to changes in blood flow to regulate NO levels which, in turn, triggers relaxation and eventual remodeling responses in the vessel wall. The canonical mechanism (see Figure, left side) by which NO exerts its functions on vessel relaxation is via activation of the soluble guanylyl cyclase (sGC), thereby elevating cyclic guanosine monophosphate (cGMP) levels. cGMP activates cGMP-dependent protein kinase type I (cGKI) which then phosphorylates downstream targets regulating the actin-myosin cytoskeleton and calcium clearing mechanism leading to vasorelaxation. Indeed, mice deficient in eNOS, sGC, and cGKI all demonstrate impaired endothelium-dependent relaxations in conduit arteries and the latter two knockout strains, reduced responsive to nitrovasodilators. However, the mechanisms by which NO exerts its effects on vascular remodeling are less well understood. For example, in several cell culture–based models of VSMC proliferation and apoptosis, NO has been shown to act as antiproliferative and proapoptotic agent, and in both circumstances work via a cGKI-dependent or -independent manner.

In this issue of ATVB, Lukowski and colleagues provide clear genetic evidence that vascular remodeling in response to flow changes or injury does not depend on the cGMP/cGKI pathway in vivo. They do so by subjecting both wild-type and smooth muscle cell–specific cGKI-null mice to 2 different vascular remodeling models, eg, carotid arterial ligation and wire injury. Both of these models have been shown to rely on endothelial NO production as shown in eNOS-knockout and -overexpression studies. In the present study, in both models the degree of vascular remodeling assessed by comparing neointimal, medial, and luminal diameters was unaltered between wild-type and the tissue-specific cGMP-null mice. Also, the proliferation rate of VSMCs in vivo was unchanged, strongly suggesting that cGKI has little influence on injury-evoked vascular remodeling despite previous data in vitro and in vivo using gene transfer approaches. To assess whether these responses are not only cGKI- but also cGMP-independent, wild-type mice were treated with the phosphodiesterase inhibitor sildenafil, thereby elevating endogenous cGMP levels, and were subjected to carotid arterial ligation. Abnormal vascular remodeling was identical in sildenafil and controls groups suggesting that elevation of cGMP, per se, does not influence arterial remodeling. This result clearly favors a cGKI-independent mechanism for vascular remodeling and leaves little speculation regarding sGC-dependent but cGKI-independent pathways. However, the definitive role of sGC in vascular remodeling has not been tested in mice lacking the \( \alpha \) and \( \beta_1 \) subunits of sGC (see Figure, right side).

Together, Lukowski and colleagues convincingly show that vascular remodeling through VSMC is cGKI-independent and thereby raising an inevitable question. How does NO control blood vessel remodeling if cGKI is not responsible? One possible answer to the question is that NO-dependent, cGMP/cGKI-independent functions during remodeling may occur via protein S-nitrosylation. Initially considered a nonphysiological modification because of the high concentrations of exogenous NO necessary to promote this modification, it is becoming more apparent that nitrosylation occurs at physiologically relevant concentrations of NO and confers a reversible posttranslational modification that changes protein function, stability, and localization akin to protein phosphorylation or ubiquitination. Thus, searching for proteins that are nitrosylated and influence the balance of VSMC proliferation versus apoptosis on vascular injury would be an interesting approach to address potential targets of NO that regulate vascular remodeling.
A second possibility lies in another well known binding partner of NO besides sGC. Very often under-appreciated is the ability of NO to bind with high affinity to mitochondrial cytochrome oxidase, thereby uncoupling the respiratory chain and elevating the production of reactive oxygen species (ROS), which can also impact vascular functions. Thus, it would be interesting to examine how cGKI-null mice in the present study behave under ROS scavenging conditions, which could be achieved for example by overexpression of thioredoxin or other ROS scavenging systems. While this latter possibility might seem remote, the work of Lukowski and colleagues clearly demonstrates that new hypotheses are needed to explain the mechanism(s) of NO-regulated vascular remodeling in vivo.

Disclosures

None.

References

Are the Mechanisms for NO-Dependent Vascular Remodeling Different From Vasorelaxation In Vivo?
Michael Schleicher and William C. Sessa

doi: 10.1161/ATVBAHA.108.167403
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 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/28/7/1207

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/