The Endothelial Protein C Receptor in Vascular Smooth Muscle Cells

For Good or Bad?

To the Editor:

We read with great interest the recent article by Bretschneider et al,1 who studied the protease activated receptor (PAR)-1-dependent protein C signaling in vascular smooth muscle cells (VSMCs). These data add another piece of evidence to the emerging concept that the endothelial protein C receptor (EPCR) exerts pleiotropic cellular effects.

Previous studies from several laboratories have concluded that EPCR ligation with activated protein C (APC) can lead to the proteolytic cleavage of PAR-1 on the surface of endothelial cells (ECs), leading to pleiotropic cellular effects, decreasing inflammation and apoptosis, and enhancing endothelium barrier protection.2–7 Bretschneider et al1 found that simultaneous stimulation of VSMCs with thrombin and the PAR-1 activating peptide (AP) does not result in a synergistic effect on cellular proliferation whereas the combination of APC treatment with thrombin or PAR-1 AP promotes additional proliferation; these data are in agreement with earlier observations by Uchiba et al8 in which APC treatment activates mitogen activated protein kinase pathway (MAPK) signaling in endothelial cells. Uchiba et al8 also observed that an anti-PAR-1 blocking antibody only partially inhibits the MAPK signals initiated by APC whereas the same antibody completely inhibits thrombin-induced MAPK activation.

Two important questions arise from these observations. First, does the EPCR-APC complex initiate PAR-1-independent signaling pathway in VSMCs? EPCR does not possess intrinsic catalytic activity, thus, PAR-1-independent signaling events would be mediated by either the association of EPCR with other receptor or the clustering of signaling proteins with EPCR cytoplasmic domain. Because of the fact that EPCR has a very short intracellular C-terminal tail, many consider it unlikely that APC-ligated EPCR activate other cellular receptors in VSMCs. Experiments show that EPCR ligation with APC can transactivate the sphingosine-1-phosphate receptor-1 in ECs.6,7 Bretschneider et al1 also demonstrated the expression of EPCR in the fibrous cap of human artery plaques, an area rich in VSMC, and suggested that EPCR-mediated signaling might regulate VSMC in atherosclerosis. Rupture of atherosclerotic plaques can trigger acute coronary events, such as myocardial infarction and stroke. Plaque rupture generally occurs in the “shoulder regions” of advanced plaques with thin fibrous caps, often called unstable or vulnerable plaques.9,10 The VSMCs of the fibrous cap in advanced plaques might be exposed to plasma proteins from increased endothelial permeability. Thus, EPCR might trigger VSMC proliferation, and might also alter VSMC production of extra-cellular matrix and matrix metalloproteinases, altering plaque vulnerability. We would like to suggest that further studies should evaluate the effects of EPCR on atherosclerosis and plaque vulnerability.

Shi-Sheng Li
Lihua Wu
José A. Fernández

Department of Molecular and Experimental Medicine
Department of Immunology
The Scripps Research Institute
La Jolla, California

References
The Endothelial Protein C Receptor in Vascular Smooth Muscle Cells For Good or Bad?
Shi-Sheng Li, Lihua Wu and José A. Fernández

Circ Res. 2007;100:e86
doi: 10.1161/01.RES.0000269328.78313.26
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/100/10/e86

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