Targeting Pericellular Proteolysis in Vascular Disease

Michelle P. Bendeck

Proteolytic enzymes released from smooth muscle cells (SMCs) degrade extracellular matrix proteins, and this is thought to facilitate cell migration and neointimal thickening in restenosis and vein graft disease. The plasminogen activator (PA) and the matrix metalloproteinase (MMP) systems play important roles mediating these processes. In the PA system, tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA) cleave plasminogen to release plasmin (Figure A). Many components of the PA system including t-PA, u-PA, and the endogenous plasminogen activator inhibitor (PAI-1) are upregulated in diseased blood vessels, and recent studies using mice with targeted gene deletion point to a role for u-PA in mediating neointimal hyperplasia. u-PA may have a particularly important role in facilitating SMC migration, because it is localized to the cell surface by binding to the u-PA receptor (u-PAR). This potentiates the activity of u-PA by bringing the enzyme into close proximity to its surface-bound plasminogen substrate, permitting plasmin activation within a spatially constrained pericellular environment (Figure A). Plasmin can directly degrade some components of the extracellular matrix and has the potential to activate several of the matrix metalloproteinases including MMP-3, 9, 12, and 13. In fact, there is good evidence that the effects of u-PA/plasmin in tissue remodeling are mediated indirectly via activation of the MMPs.

The MMPs are a family of enzymes that degrade many molecules of the extracellular matrix. MMPs are secreted in a latent zymogen form, with a propeptide tightly coupled to the enzyme active site. MMP zymogens are activated extracellularly when the propeptide is cleaved by plasmin or by other MMPs (Figure A). MMP activity can be inhibited by direct binding of endogenous tissue inhibitors of metalloproteinases (TIMPs) to the active site. MMP-1, 2, 3, 9, 12, and 13 are upregulated in diseased vessels, and MMPs produced by SMCs are thought to clear a path for migration of these cells from media or adventitia to the intima. Taken together, this data suggests cooperative roles for the PA and the MMP systems in mediating matrix degradation and smooth muscle cell migration; however, very few studies have addressed this directly.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada.

Correspondence to Dr Michelle P. Bendeck, Associate Professor, Dept of Laboratory Medicine and Pathobiology, University of Toronto, Medical Sciences Bldg., Room 6217, 1 King’s College Circle, Toronto, ON M5S 1A8, Canada. E-mail michelle.bendeck@utoronto.ca

(Circ Res. 2002;91:861-862.)

© 2002 American Heart Association, Inc.

Circulation Research is available at http://www.circresaha.org
DOI: 10.1161/01.RES.0000043396.97121.9C
ogen are also localized at the cell surface. Furthermore, there is crosstalk between u-PAR and integrin receptors; u-PAR binds to several integrins and also binds directly to vitronectin in the matrix. It is reasonable to postulate therefore that TIMP-1.ATF interferes with these interactions, but this has not yet been investigated.

Another limitation of the present study is that TIMP-1.ATF was not tested in an in vivo model. Past studies using systemic administration of MMP or PA inhibitors, or gene transfection to overexpress TIMPs or PAI-1 in the vessel wall in vivo reduced SMC migration, but it is not clear that long-term neointimal hyperplasia was inhibited in all cases, due to a catch-up effect caused by continued SMC proliferation. The fact that TIMP-1.ATF failed to inhibit SMC proliferation is a significant drawback. Thus, it seems that any strategy to limit neointimal hyperplasia must also target cell proliferation.

At this time, it is not clear whether the MMPs are directly involved in the control of cell proliferation. However, in this context, it is important to note that the MMPs and TIMPs have functions beyond their roles in matrix degradation. MMPs can activate cytokines, release growth factors from matrix, and degrade integrins and cadherins. TIMPs can inhibit these MMP-dependent processes, or independently stimulate cell growth or apoptosis. There is compelling evidence that MMPs may initiate tumor cell growth by releasing growth factors from the extracellular matrix, or by cleaving cadherins, thereby disrupting cell-cell adhesions, leading to β-catenin signaling and increased cell proliferation. This diversity of actions must be taken into account when attempting to elucidate the role of the MMP-TIMP system in any pathological process.

In conclusion, the data presented in this study suggests a unique strategy to curtail cell-surface proteolytic activity in the arterial wall. The results shed light on our understanding of the mechanisms of SMC migration and intimal thickening, and provide support for the hypothesis that pericellular proteolysis is an important component of these responses.
Targeting Pericellular Proteolysis in Vascular Disease
Michelle P. Bendeck

*Circ Res.* 2002;91:861-862
doi: 10.1161/01.RES.0000043396.97121.9C
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. 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/91/10/861

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/