The Matrix Revolutions

Matrix Metalloproteinase, Vasculogenesis, and Ischemic Tissue Repair

Marie-Ange Renault, Douglas W. Losordo

The matrix metalloproteinase (MMP) family of Zinc dependent extracellular proteinases regulates development and physiologic events, including branching morphogenesis, angiogenesis, wound healing and extracellular matrix degradation. They are synthesized as secreted or transmembrane proenzymes and processed to an active form by the removal of an amino-terminal propeptide. MMP-2/Gelatinsase A, as well as MMP-9/gelatinase B, which belong to the gelatinase subclass of the MMP family, have been shown to play a central role in initiating angiogenesis and to be upregulated after hindlimb ischemia. They are involved in degrading extracellular and basement membrane structures, allowing endothelial migration to occur. In addition, MMPs promote the release of extracellular matrix-bound cytokines, such as vascular endothelial growth factor (VEGF), which can regulate angiogenesis.

Both MMP-2 and MMP-9 expression have been shown to be upregulated in bone marrow and peripheral blood derived CD34 positive cells treated by stromal cell derived factor-1. Only MMP-9 had been shown to be involved in vasculogenesis and more particularly endothelial progenitor cell (EPC) mobilization. First, MMP-9 has been shown to be upregulated in the bone marrow and necessary for VEGF-, placental growth factor- and by stromal cell derived factor-1-induced EPC recruitment. Increased MMP-9 activity in the bone marrow has been shown to induce the release of soluble kit ligand (skitL) promoting the proliferation and motility of hematopoietic stem cell and EPCs within the bone marrow. The role of MMP-9 in EPC mobilization has been confirmed in several studies. For example, it has been shown to be involved in estradiol (E2)-induced neovascularization after myocardial infarction. Indeed, MMP-9 activity is increased in the spleen of E2-treated mice and is essential for EPC mobilization induced by estradiol after myocardial infarction in the mice. Also, angiotensin converting enzyme, or HMG CoA reductase inhibition have been shown to promote EPC recruitment to infarcting myocardium and increase MMP-9 activity within the bone marrow. Reduced MMP-9 expression has also been associated with impaired circulating progenitor cell migration and invasion in the case of hyperglycemia.

In this issue, Cheng et al. investigate the role of MMP-2 in ischemia-induced neovascularization in the limb muscle and disclose several potential mechanisms by which MMP-2 deficiency leads to impaired neovascularization. First the authors confirm that MMP-2 expression is upregulated in ECs (endothelial cells) after VEGF or bFGF treatment, and show that VEGF-dependent angiogenesis in aortic-ring culture as well as VEGF-directed EC invasion are impaired in the absence of MMP-2. After they confirmed the role of MMP-2 in angiogenesis, they report here for the first time that MMP-2 is also involved in post natal vasculogenesis and more precisely in EPC mobilization. The seminal observation is that the number of CD31+, c-Kit+ cells circulating in the peripheral blood 10 days after ligation of the femoral artery is reduced in MMP-2 deficient mice. The importance of this finding, and the deficient ischemic response, is supported by the fact that bone marrow transplant from wild type mice rescues neovascularogenesis in MMP-2−/− mice.

A third mechanism by which MMP-2 participates in ischemia-induced neovascularization is also described in this article: MMP-2 promotes the recruitment of VEGF expressing macrophages and leukocytes into ischemic tissues. This MMP-2 deficiency also leads to reduced VEGF in the ischemic tissue and peripheral blood. MMP-9 has also been shown to promote mast cell recruitment and VEGF release within ischemic tissue.

Both MMP-2 and MMP-9 have thus been implicated in EPC mobilization. A mechanism by which MMP-9 promotes EPC mobilization, involving c-KitL, has been described. The exact mechanism underlying the effect of MMP-2 on EPC remains to be described; nevertheless, like MMP-9, MMP-2 is shown to promote EPC proliferation. Because MMP-9 is overexpressed in MMP-2 deficient mice as well as its activity in the ischemic tissue (results shown in this issue), compensatory mechanisms might occur. Nevertheless both MMP-9 and MMP-2 appear necessary for normal EPC mobilization induced by ischemia. If MMP-9 and MMP-2 belong to the same group of proteinase and are both involved in angiogenesis and vasculogenesis, the regulation of their expression is different: MMP-9 is expressed at higher levels by early EPCs (CD14+), whereas MMP-2 has been shown to be more expressed by outgrowth endothelial cells (OECs) (CD14+). MMP-2 expression is increased after VEGF treatment in both OECs and EPCs even if it stays higher in OECs whereas MMP-9 expression is only upregulated by VEGF in EPCs. Also the localization of MMP-2 on the cell membrane is associated with the integrin α5β3 whereas MMP-9 is associated with CD44.
Outside of MMP-2 and MMP-9, cathepsin L, a cysteine protease, has been shown to be highly expressed by EPCs and promotes matrix degradation and invasion of EPCs. EPC recruitment is impaired in Cathepsin L deficient mice, but it has been shown not to be involved in EPC mobilization but rather in EPC homing. In 1995, Granzyme B, an hematopoietic serine protease, have been involved in G-CSF and chemotherapy induced CD34+ cells mobilization.

Thus the work of Cheng et al provides another pathway by which ischemia modulates the kinetics of EPCs, providing certain insights regarding the regulation of postnatal vasculogenesis as well as raising additional questions regarding the precise molecular pathways involved. These findings have important implications, not only in our understanding of ischemic tissue repair, but may also evolve into important therapeutic targets in other realms such as cancer, fertility, and bone and joint disease.

Acknowledgments

We thank M. Neely for secretarial assistance.

Sources of Funding

This study was supported in part by NIH grants (HL53354, HL77428, HL63414, HL80137, PO1HL-66957).

Disclosures

None.

References


Key Words: angiogenesis ■ vasculogenesis ■ matrix metalloproteinases
The Matrix Revolutions: Matrix Metalloproteinase, Vasculogenesis, and Ischemic Tissue Repair
Marie-Ange Renault and Douglas W. Losordo

Circ Res. 2007;100:749-750
doi: 10.1161/01.RES.0000263398.47653.ef

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/100/6/749

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/