Diabetic Monocyte and Vascular Endothelial Growth Factor Signaling Impairment

Michael Simons, MD

Diabetes mellitus has emerged as a major health problem affecting >20 million Americans and 200 million people worldwide. Diabetes complications are often debilitating and affect the function of multiple organs. Although many complications of diabetes mellitus, including uncontrolled capillary proliferation in the retina, have received extensive attention, a poorly understood complication is an impaired arteriogenic response to macrovascular obstruction. This is manifested in patients with peripheral and coronary arterial occlusion as reduced collateral density and impaired wound healing.1–4

The seemingly paradoxical decrease in arteriogenic responsiveness and increase in angiogenesis observed in diabetic patients5 present a distinct challenge to vascular biologists but also provide a grand opportunity for a deeper understanding of the fundamental biology of these 2 processes and their regulation. Angiogenesis, a process of capillary growth, is a relatively well-understood event. It is most often encountered in tissue injury settings such as wound healing or in ischemic settings after a proximal arterial occlusion or stenosis. Angiogenesis is driven largely by vascular endothelial growth factor (VEGF) released either by ischemic tissues or by inflammatory cells. The result is acceleration of tissue repair in the case of injury and mild amelioration of ischemia in the case of arterial occlusion.6

Arteriogenesis, on the other hand, is a much more complex and much less understood process that refers to formation of new arterial vasculature. This new vasculature may form de novo, presumably by arterialization of the capillary bed, a process that involves acquisition of arterial identity and maturation of a newly formed artery, or by the expansion of preexisting collateral vessels.7 Both of these processes appear to depend heavily on the presence of blood-derived monocytes, although what these cells actually do to promote arteriogenesis remains a mystery. Functionally, arteriogenesis is the most important adaptive circulatory response to a compromised arterial blood supply, typically leading to nearly complete amelioration of ischemia.8

One striking feature of the arteriogenic process is that, unlike angiogenesis, it takes place in nonischemic tissues. This suggests that although distal ischemia (in adult tissues) is the reason arteriogenesis starts, the proximate cause is likely to be something else. This “something else” may be shear stress in arterial conduits above the site of stenosis.9

The increased shear stress is then likely to result in increased expression of endothelial adhesion molecules that would in turn promote recruitment of blood-derived mononuclear cells to sites of arterial formation.10 Interestingly, although the importance of these cells in arteriogenesis is largely assumed, there is no conclusive proof of their key role in this process, nor is there a clear understanding of what these cells do or even what they are. The preponderance of evidence points to blood-derived monocytes,8,11 whereas the mechanism of action likely involves the paracrine secretion of a factor or factors that facilitate arterial development and/or maturation.

Assuming that the supposition about the importance of monocytes in this process is correct, it is reasonable to think that certain alterations in monocyte biology might impair their ability to drive arteriogenesis. Because monocytes would need to adhere to the endothelium at the site of arteriogenesis, transmigrate across the vessel wall, migrate along the adventitia, and then secrete the mighty arteriogenic “juice,” it is likely that aberrations in one of these processes may affect their ability to perform an arteriogenic role.

Thus, when addressing the impaired arteriogenesis in diabetic patients, we may ask what the functional status of circulating monocytes is. This has long been a controversial subject. Several studies have demonstrated increased monocyte activation and increased transmigration across the endothelium in vitro and in vivo.12–14 At the same time, monocytes from diabetic patients demonstrate decreased migratory responsiveness to VEGF stimulation in vitro,15 perhaps because of a downstream VEGF receptor 1 (VEGFR1 or Flt1) signaling defect.16

The article by Tchaikovski et al17 in this issue of Circulation provides new information on the biology of diabetic monocytes. The authors confirm decreased chemotaxis of diabetic monocytes in response to VEGF (that in monocytes signals via VEGFR1) and to a “pure” VEGF1 agonist, placental growth factor, despite unaltered VEGFR1 expression. At the same time, they demonstrate increased baseline activation (in the absence of VEGF or placental growth factor stimulation) of some of the signaling cascades involved in cell migration, including p38 mitogen-activated protein kinase, p42/44 mitogen-activated protein kinase, and Akt, an observation consistent with the known increase in migratory activity of diabetic monocytes. Thus, we have yet another diabetic paradox:
The migration signaling cascades are activated, yet migration, at least in response to VEGF, is impaired.

The authors attribute the excessive activation of these cascades to increased oxidative stress. Although it is certainly likely that oxidative stress is higher in diabetic monocytes and although it seems logical to link this increase to greater mitogen-activated protein kinase and Akt activation, it is not clear why increased activity of mitogen-activated protein kinase and Akt pathways should result in reduced responsiveness to VEGF stimulation. Furthermore, the baseline activation of these 3 cascades in diabetic monocytes seems similar to that achieved during VEGFR1 stimulation in nondiabetic monocytes, raising further questions about why activation of these kinases paradoxically blunts VEGF signaling in diabetic monocytes.

Thus, we have 2 undoubtedly correct but seemingly unconnected observations: increased activation of certain signaling cascades in diabetic monocytes at baseline and decreased responsiveness of these monocytes to VEGF. One potential explanation for this paradox is that VEGF activates monocyte migration via a different pathway such as Rac1. Nonetheless, perhaps the more critical question is the extent to which diabetic monocyte resistance to VEGF-induced migration is actually important for arteriogenesis because these cells’ overall migratory capacity is actually increased. This issue might be particularly relevant because monocyte migration is likely a stromal cell–dependent factor– and not a VEGF-dependent process in these settings.

We are left to consider 2 important questions: Why is arteriogenesis decreased in diabetic patients despite increased monocyte activation, adhesion, and migration, all events that presumably should result in arteriogenesis? And what is the link, if any, between the decreased responsiveness of diabetic monocytes to VEGF and impaired arteriogenesis? A hypothesis worth considering is that diabetes mellitus results in a generalized VEGF signaling dysfunction and that poor monocyte VEGF responsiveness is simply a biomarker of that event. Why VEGF signaling is abnormal in diabetes mellitus, what effect it has on various cell types involved in the arteriogenic process, including endothelial cells and monocytes, what all diabetic monocytes, and whether that ailment actually contributes to impaired arteriogenesis are critical issues that require further investigation.

Source of Funding
This work was supported in part by National Institutes of Health grant HL53793.

Disclosures
None.

References

Key Words: Editorsials I angiogenesis I collateral circulation I diabetes mellitus I growth substances I signal transduction
Diabetic Monocyte and Vascular Endothelial Growth Factor Signaling Impairment
Michael Simons

Circulation. 2009;120:104-105; originally published online June 29, 2009;
doi: 10.1161/CIRCULATIONAHA.109.873794
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/120/2/104

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