EDITORIAL COMMENT

Angiogenesis, Arteriogenesis, and Diabetes Paradigm Reassessed:*

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Type II diabetes mellitus is a complex disease with protean clinical manifestations characterized, at its core, by tissue resistance to insulin. This fundamental abnormality leads to increased circulating insulin levels and concomitant hyperglycemia that, in turn, are thought to be responsible for the numerous metabolic derangements seen in this syndrome.

On the cardiovascular side, diabetes has long been associated with accelerated atherosclerosis (1). More recently, a number of abnormalities associated with deregulation of neovascularization have also been recognized. These include abnormally enhanced angiogenesis, defined as capillary vessel growth (2), in the retina, leading to diabetic retinopathy (3) and in the vessel wall, potentially producing atherosclerotic plaque destabilization (4). At the same time, insufficient angiogenesis has been implicated in abnormal wound healing, leading to diabetic skin ulcers (5). Defective arteriogenesis, a process of formation or remodeling of arterioles and arteries (2), has also been reported in diabetic patients (6–8). Impaired release of endothelial progenitor cells from the bone marrow (9) and defective function of these cells (10) are other features of diabetes that further contribute to abnormal neovascularization and increased cardiovascular risk.

The molecular defects underlying these angiogenic abnormalities have generated much interest but, so far, have remained elusive. Diabetic patients have been reported to have a reduced number of circulating endothelial progenitor cells, with the extent of reduction directly proportional to plasma hemoglobin A1c levels (9). There are also reports of reduced vascular endothelial growth factor (VEGF) and VEGF receptors expression in the myocardium of diabetic patients (11) as well as increased production of an angiogenesis inhibitor angiostatin induced by hyperglycemia (7).

This set of observations presents a confusing picture that seems to defy a common molecular mechanism. An important study in this issue of the 

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**groundwork for unraveling this puzzle.** Sasso et al. (12) have examined the expression and function of VEGF and its receptors in patients with advanced coronary disease undergoing coronary artery bypass surgery. In an admittedly somewhat small sample of twenty patients, they demonstrated increased VEGF expression in the myocardium of diabetic patients compared with non-diabetic patients, whereas expression levels of VEGF receptors 1 and 2 (Flt-1 and Flk-1, respectively) were reduced. Most importantly, the extent of Flk-1 phosphorylation, a reflection of its activation status, was severely reduced in diabetic patients compared with non-diabetic patients. This was associated with a reduced activation of serine-threonine protein kinase Akt-1 and endothelial nitric oxide synthase (eNOS), the principal effectors of the VEGF signaling pathway.

These results extend previous observations of abnormal VEGF signaling in diabetic patients first reported by Waltenberger et al. (13), who noted that monocytes from diabetic patients failed to respond to VEGF in a cell migration assay despite activation of the Flt-1 receptor. Taken together, these two studies suggest that whereas Flt-1 activation under diabetic conditions is normal, Flk-1 activation is not. The role of Flt-1 in VEGF signaling remains controversial. Unlike Flk-1, which is expressed almost exclusively in the endothelium and in certain bone marrow cell populations, including endothelial precursor cells, Flt-1, in addition to the endothelium, it is expressed in a wide range of mononuclear cells, including monocytes. It seems to be involved in the regulation of cell migration either via an independent signaling pathway or secondary to Flk-1 activation via an intracellular cross-talk or direct receptor heterodimerization.

Flk-1 is currently thought to be the principal receptor involved in transducing VEGF signaling (Fig. 1). It regulations cell proliferation via activation of the extracellular receptor kinase (Erk-1/2) and Akt-1, a master regulator of cell function. Among many Akt-1 activities, two are the most crucial in this context: activation of eNOS, thereby stimulating nitric oxide production, a step required for endothelial cell proliferation, and inhibition of apoptosis. The latter VEGF/Akt-1 activity is probably necessary for the maintenance of the intact vasculature in adult tissues.

We propose, therefore, the following sequence of events to explain diabetic angiogenic abnormalities (Fig. 2). The abnormal activation of Flk-1 leads to increased levels of circulating VEGF in an attempt to compensate for the perceived deficiency of VEGF signaling. This is similar to the increase in insulin levels seen in patients with defective insulin signaling. High circulating VEGF levels, in turn, lead to increased permeability of vascular structures throughout the body. In the retina, this results in the formation of protein-rich exudates containing VEGF that induces a local inflammatory response resulting in capillary sprouting (14). A similar process might take place in the arterial wall, thereby promoting capillary sprouting and
plaque destabilization. At the same time, the lack of Flk-1 activation in endothelial cells and abnormal VEGF-dependent activation of monocytes impair the arteriogenic response that requires monocyte recruitment and monocyte and endothelial cell migration and proliferation. In addition, VEGF/Flk-1 signaling is thought to be required for bone marrow release of circulating endothelial progenitor cells that might also play a role in arteriogenesis. The abnormal release of endothelial progenitors will further reduce arteriogenic response.

Although this scheme seems reasonable, many questions remain unanswered. What is responsible for elevated VEGF levels in diabetic patients? What cells or organs serve as VEGF sensors and increase VEGF expression in response to declining VEGF/Flk-1 signaling? What is the nature of the intracellular signaling abnormality that inhibits Flk-1 activation? What is the nature of the migration defect in monocytes and endothelial progenitors of diabetic patients?

With a disease as complex as diabetes, other factors are likely to be involved as well. Thus, the presence of advanced glycation end-products might well play an important role in suppressing arteriogenesis (15). For example, glycation of circulating growth factors such as fibroblast growth factor (FGF) has been shown to markedly reduce its biological activity, which, in turn, can inhibit VEGF-dependent signaling (16). It is also possible that intracellular signaling defects in diabetes are not limited to VEGF, but include other important arteriogenic growth factors such as FGFs, platelet-derived growth factors, hepatocyte growth factor, and placenta growth factor.

Clearly, much research remains to be done, although these discoveries have immediate clinical implications, particularly with regard to ongoing trials of therapeutic angiogenesis (2,17). If defective arteriogenesis in diabetic patients is, indeed, secondary to a VEGF signaling defect, therapeutic efforts should be directed not at futile attempts to further increase tissue or plasma VEGF levels, but at restoration of intracellular signaling, a strategy that will likely require small molecule agents.

In summary, the study by Sasso et al. (12) provides yet another important piece in a puzzle that is the arteriogenic defects of diabetes. The emergence of the VEGF (and perhaps other growth factors) defective signaling paradigm in diabetes promises to enhance our understanding of...
cardiovascular complications of diabetes and to redirect therapeutic efforts to search for intracellular drug targets.

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