PGC-1α: The Missing Ingredient for Mesenchymal Stem Cell–Mediated Angiogenesis

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Diabetes is a vascular disease. As blood vessels become damaged, loss of flow leads to ischemia of critical organs. This results in coronary artery disease (CAD), stroke, and peripheral artery disease (PAD) due to large vessel damage, as well as retinopathy and nephropathy due to small vessel injury. These vascular complications are the greatest contributors to diabetes-associated morbidity and mortality as well as healthcare costs related to diabetes, which are approaching $200 billion. The incidence of cardiac and vascular disease is expected to rise steadily as a result of the current epidemic of diabetes (1). Thus, there is an urgent need for novel therapies targeting large vessel damage.

Therapeutic angiogenesis offers great potential as a strategy to treat large vessel disease. Although the angiogenic factor vascular endothelial growth factor (VEGF) has been tested extensively, results from over two dozen clinical trials in cardiac and limb ischemia have been largely unsuccessful (2). However, improved delivery modalities may enhance VEGF efficacy, although additional angiogenic and growth factors may be required for functional vessel development, since VEGF alone generally induces formation of incomplete, leaky vessels. Approaches to use of mesencymal stem cells (MSCs) that have the capacity to promote angiogenesis are in their infancy, but small clinical studies suggest promise in CAD and PAD (3–5). Bone marrow–derived cells themselves are not incorporated into collaterals. However, these cells have been shown to produce VEGF, basic fibroblast growth factor, and other factors that augment development of collateral circulation and improve hindlimb ischemia (6). Bone marrow–derived MSCs can differentiate into osteoblasts, chondrocytes, and adipocytes, as well as cells with a myocyte phenotype including cardiomyocytes and vascular smooth muscle cells (5). These cells also produce growth, angiogenic and matrix factors, and suppress the action of multiple types of immune cells (7). When MSCs in combination with endothelial progenitor cells were injected into patients with limb ischemia, limb perfusion and ankle brachial index improved as did pain-free walking distance. These benefits were observed for up to 10 months (3). Genetic engineering may further improve utility of these cells by extending their longevity, controlling secreted factors, and regulating their immune function.

In this issue of *Diabetes*, Lu et al. (8) combined the multipotency of MSCs with the angiogenic capacity of the hypoxia-stimulated transcriptional coactivator, peroxisome proliferator–activated receptor-γ coactivator-1α (PGC-1α). PGC-1α is a key regulator of oxidative metabolism and mitochondrial function, and coactivates the estrogen-related α receptor to induce VEGF. Mice transgenic for PGC-1α have been shown to have better blood flow responses to hindlimb ischemia compared with wild-type mice, whereas PGC-1α knockout mice had worse responses (9). Transfection of rat MSCs with PGC-1α green florescent protein to achieve a 1.7-fold increased expression, as performed by Lu et al., led to two- to threefold increases in VEGF, fibroblast growth factor, platelet-derived growth factor, and hypoxia-inducible factor-1α. This resulted in prevention of hypoxia-induced apoptosis of MSCs and improved perfusion up to 2 weeks following hindlimb ischemia in rats treated with PGC-1α transfected MSCs compared with control-transfected MSCs. Further, there was no necrosis in the PGC-1α group compared with controls. These exciting observations raise many questions. For instance, what was the fate of the injected MSCs transfected with adenoviral–PGC-1α green florescent protein? The results by Lu et al. showed that after transplantation, more PGC-1α–transfected MSCs were present than control-transfected cells. Did this translate into sustained improvements in hindlimb perfusion beyond the 2 weeks of the study? These experiments showed that capillary density was improved in mice with PGC-1α–transfected cells. What was the source of endothelial cells and what was the leakiness of the new vessels? Despite these unanswered questions, demonstration of a PGC-1α–induced enhancement of MSC activity applied to a physiologic model strongly supports further investigation of this novel approach.

Recently, circulating levels of total and high-molecular weight adiponectin were shown to be inversely associated with incident PAD in 340 women enrolled in a nested case study within the Women's Health Study. These results persisted after adjustment for traditional cardiovascular risk factors, use of postmenopausal hormone therapy, high-sensitivity C-reactive protein, leptin, HbA$_{1c}$, and fasting insulin (10). Adiponectin has insulin-sensitizing and anti-inflammatory properties mediated by activation of AMP-activated protein kinase (AMPK), SIRT1, and Ca^{2+}/calmodulin-dependent protein kinase kinase-β (11). PGC-1α is activated by AMPK-mediated phosphorylation and by SIRT1-mediated deacetylation of the transcription factor (12). Loss of the adiponectin R1 receptor from skeletal muscle led to impaired adiponectin-induced PGC-1α activation, insulin resistance, and reduced muscle mitochondrial function (13). Both AMPK and SIRT1 are expressed in the vasculature and promote angiogenesis, but a mechanism involving PGC-1α that explains adiponectin-induced adipogenesis and vasodilation has not been considered (14,15). It is possible that low adiponectin predicted PAD in the Women's Health Study because of decreased PGC-1α responses to hypoxia and/or effects on vascular

remodeling. These studies further suggest that mechanisms such as adiponectin that activate PGC-1α should be considered as potential strategies for treatment of ischemia.

A major concern with therapeutic angiogenesis is the possibility of tumor growth because maintenance and expansion of tumor vasculature supplies nutrition to the cancer, thereby allowing its expansion (16). Indeed, adiponectin has been implicated in both growth and inhibition of cancer, and its effects are probably dependent on the characteristics and growth patterns of the tumor itself as well as the tumor's microenvironment (17). Adiponectin is reported to potentially enhance early breast cancer growth through angiogenesis, but in mice lacking adiponectin, tumor growth was more rapid at later stages of disease (18). SIRT1 can act as both a tumor promoter and tumor suppressor (19). Mechanisms of tumor promotion include inhibition of apoptosis and cellular senescence, negative regulation of the tumor suppressor p53, and enhancement of angiogenesis (20). However, little is known about PGC-1α effects in cancer. Despite the promotion of angiogenesis, PGC-1α also increases mitochondrial biogenesis, which can impair carcinogenesis through multiple mechanisms (21). Clearly, further studies are necessary to investigate angiogenic mechanisms in treatment of ischemia and their impact on cancer development, but use of engineered MSCs is highly promising.

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