Reprogrammed Endothelial Cells
Cell Therapy for Coronary Collateral Growth?

James E. Faber

Myocardial infarction, ischemic stroke, and atherosclerosis of arteries supplying the heart, brain, and lower extremities are leading causes of morbidity and mortality. The abundance of native preexisting collateral vessels in tissues, and their anatomic lumen enlargement induced by arterial obstruction (remodeling or arteriogenesis) are major determinants of the severity of ischemic tissue injury caused by these diseases. Unfortunately, findings in animal studies showing that both of these determinants vary significantly among individuals because of differences in genetic background and environmental factors (eg, cardiovascular risk factors) are beginning to find corroboration in humans.1–6 Although efforts to increase collateral growth in ischemia using small molecules, proteins, and gene therapy have shown some effectiveness in experimental animals, patient trials for therapeutic angiogenesis have been largely disappointing.7–9

Recent preclinical studies suggesting that cell-based therapies may provide a transformative approach to augment vascular growth have generated considerable excitement and have led to initial clinical trials.10–12 A key unanswered question concerns the best cell type to use.12 Since the discovery that four transcription factors, Klf-4, Sox2, Oct4, and c-Myc, could reprogram somatic cells to become induced pluripotent stem cells (iPSCs) capable of differentiating into any cell type of the body,13–15 investigation of cell reprogramming for tissue regeneration has moved forward rapidly.15–19 Although iPSCs offers great promise, their capability to form tumors presents a significant hurdle.15,20 Thus, in a sense, the greatest potential strength of iPSCs for regenerative therapies may provide a transformative approach to augment vascularization, for example, when obtained from vessels used in coronary artery bypass grafting, from endothelial cells harvested from adipose tissue, or from blood or bone marrow-derived mesenchymal stem cells, or native ECs (Figure). Moreover, in contrast to iPSCs, no teratomas were evident even 3 months after implantation. These exciting findings are a major conceptual advance that could ultimately lead to an effective cell therapy for revascularization in obstructive disease.

Where Do We Go From Here?
Yin et al21 provided evidence for migration of the iVPCs away from their point of injection, which was below the coronary occluder, followed by homing to perivascular positions and possible engraftment in capillaries and larger vessels in the ischemic region (see two photon images in the Supplemental Materials). Whether this included homing to collaterals was not determined because of difficulty in identifying these vessels in tissue sections. Future work is also needed to identify the mechanisms underlying the large improvement in collateral flow achieved with iVPC therapy. Do iVPCs act directly or in a paracrine manner to augment remodeling of native collaterals or induce formation of neocollaterals, or to reduce vascular tone in the collaterals or vessels above or below them, or to promote outgrowth of adjacent arterial trees into the ischemic region (distal muscularization), or to increase ischemic capillary angiogenesis? However, this effect alone would contribute only a small effect at best to the improvement in blood flow to the ischemic area.

The findings of Yin et al raise other intriguing possibilities and important questions. Do iVPCs recruit endogenous stem or vascular progenitor cells from cardiac, bone marrow, or extracardiac vascular stem cell niches?10–12 Do ECs from different sources have the same potential after reprogramming, for example, when obtained from vessels used in coronary artery bypass grafting, from endothelial cells harvested from adipose tissue, or from blood or bone marrow-

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derived endothelial progenitor cells? Will implanted iVPCs and their beneficial effect persist for months or years after implantation, without eventually forming tumors or undesirable cells such as bone tissue? And will they do the same in a large animal preclinical model? Studies in experimental animals have found that the presence of certain cardiovascular risk factors and disease cause loss of native collaterals and impair collateral remodeling and capillary angiogenesis.1,2,4,22,23 They also have adverse effects on progenitor cell abundance and function, in part because of reduced responsiveness of vascular tissue to factors released by progenitor cells.23–25 Thus, it will be necessary to demonstrate that iVPCs can still produce collateral growth in preclinical models of cardiovascular risk factors and disease with their associated vascular oxidative stress and endothelial dysfunction. These conditions could complicate the ability of iVPCs to differentiate, proliferate, and survive. Yin et al demonstrate the potential for iVPCs to improve collateral flow in a model of unstable cardiac ischemia-reperfusion. Will similar effects be obtained in acute coronary artery occlusion? An additional important question is whether iVPC therapy can improve collateral function in models of ischemic stroke and peripheral artery disease. Finally, what is the nature of epigenetic and presumably other mechanisms that cause the ECs reprogrammed by the strategy of Yin et al to retain both EC and progenitor cell characteristics? It is conceivable that this commitment to a vascular lineage is why they were better-able to stimulate collateral flow and improve myocardial function than iPSCs or other cell types that were tested.

Stimulating growth of the collateral circulation so that patients can grow their own bypasses is an important goal. A treatment that achieves this could be viewed as prophylactic, insofar as adequate growth of collaterals in the heart, brain, and lower extremities could significantly reduce morbidity and mortality and improve prognosis in patients with ischemic heart disease, stroke, and peripheral artery disease. Recent clinical trials show promising effects of external counterpulsation and exercise training in patients with coronary artery disease.26,27 Compared to the number of trials aimed at myocardial regeneration, there is a paucity of studies testing stimulation of collateral growth in the heart and other tissues (http://clinicaltrials.gov/). The study by Yin et al offers a new approach in regenerative therapy—partial reprogramming of endothelial cells “back” to a progenitor cell that remains committed to the vascular lineage. Hopefully, this observation will stimulate efforts toward therapeutic collaterogenesis in the heart and other tissues.

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**References**


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