Biological Surgery

Synergetic Angiogenic Therapy Using Coadministration of Two Progenitor Cell Populations

Wei Li, Roy L. Silverstein

Despite the many therapeutic breakthroughs in cardiovascular science, ischemic coronary and peripheral vascular diseases are still a major health problem throughout the world, and many patients do not respond or are not candidates for available medical and/or surgical treatments. Recently, identification of adult progenitor cells capable of contributing to tissue regeneration has raised the possibility that cell-based therapy could be used for the repair of ischemic heart or limb. There is compelling evidence that circulating endothelial progenitor cells (EPCs) play a role in tissue repair after a myocardial infarction, and higher levels of circulating EPCs are predictive of better short and long-term outcomes.1 EPCs were initially described as a subset of CD34+ hematopoietic stem cells that coexpress vascular endothelial growth factor receptor-2 (VEGFR-2), also known as Flk-1 or KDR. VEGFR-2–positive cells derived from embryonic stem cells can differentiate into both endothelial cells and smooth muscle cells, reproducing the vascular organization process.2 Smooth muscle progenitor cells (SMPCs) were identified more recently and reported to be present in bone marrow, circulating blood, vascular adventitia, and other tissues.3,4 Both EPCs and SMPCs may be mobilized by stromal cell–derived factor-1, a chemokine whose expression increases in response to tissue hypoxia based on regulation by the transcription factor, hypoxia-inducible factor-1,3 suggesting that EPCs and SMPCs may play pivotal roles in repairing injury to the vascular network. In addition, several cell types, including bone marrow cells, embryonic EPCs, and mesenchymal stem cells, have been tested in vivo for their effect on restoring blood supply and/or muscle function in ischemic heart and limbs. The main mechanism of these cell-based therapies is probably not incorporation of the stem cells into neovessels but, rather, enhanced angiogenesis induced by paracrine secretion of cytokines and growth factors, including VEGF, basic fibroblast growth factor, and placental growth factor.6,7

In this issue of Circulation Research, Foubert et al8 examined the effect of coadministration of human EPCs and SMPCs derived from umbilical cord blood in a nude mouse model of critical hindlimb ischemia. The authors compared the therapeutic effects of intravenous injection of EPCs (0.5×10⁶) or SMPCs (0.5×10⁶) alone or in combination (0.25×10⁶ of each cell type). EPCs induced a significant increase in foot perfusion and angiographic score in the medial thigh, with a further 75% increase induced by coadministration of SMPCs. By histological examination, the authors found a marked increase in capillary and arteriolar densities after EPCs and SMPCs were coadministered. As in previous studies, they found that some EPCs were incorporated into the neocapillaries but did not find any SMPCs in the ischemic tissue. To determine the potential mechanism of the SMPC effect, they showed that knockdown of angiopoietin (Ang)-1 expression in SMPCs or Tie2 expression in EPCs by small interfering RNA blocked vascular network formation in a Matrigel angiogenesis assay, reduced EPC incorporation into neocapillaries, and diminished the therapeutic effect of the cell therapy. They concluded that production of Ang-1 by SMPCs activates Tie-expressing EPCs, resulting in an increase in EPC survival and formation of a stable vascular network.

This study is important because it suggests potential strategies to overcome the limited therapeutic successes seen in early clinical trials of human progenitor cell therapy. Use of multiple cell types, or genetically engineered cells, or combinations of progenitor cells with cytokines, growth factors, or transcription factors is likely to be more beneficial than EPCs alone. It has been reported, for example, that coadministration of bone marrow mononuclear cells and granulocyte colony-stimulating factor, which can mobilize EPCs, significantly potentiated angiogenesis compared to cells or growth factor alone.10 In addition, injection of hypoxia-inducible factor-1α cDNA-transfected EPCs into mouse ischemic limb augmented neovascularization compared to EPCs alone.11 Increased expression of VEGF, basic fibroblast growth factor, stromal cell–derived factor-1, and its receptor CXCR-4 was found in these studies, suggesting that signaling pathway mediated by these factors play an important role in tissue repair mediated by progenitor cell based therapy. The present study identifies SMPC-derived Ang-1 and its EPC receptor, Tie-2, as additional important factors.

The work of Foubert et al must be interpreted with caution for several reasons, not the least of which was the use of athymic nude mice; it is likely that factors related to the immune system may be involved in the response to cell therapies in humans. Also, the investigators were not able to determine the fate of the injected SMPCs in this study. SMPCs were not detected in the ischemic tissue, suggesting
that they may circulate or be trapped in normal tissues or organs. A potential risk is that they could accumulate in diseased tissues such as atherosclerotic neointima and have untoward effects.3,4 Future studies using more sensitive tracking methods are thus needed to better understand the potential benefits and risks of these therapies. It will also be useful to examine long-term effects of coadministration of EPCs and SMPCs, as well as their effect on vascular grafts.

Another important issue in this study was the route of cell delivery. The authors used proximal femoral arterial ligation to achieve critical limb ischemia, raising the question of how injected cells found their way to the ischemic zone. Data from Aicher et al12 indicated that ≈1% of intravenously injected EPCs can be found in normal tissues, with up to 2-fold enrichment in ischemic tissues, and in the latter case, these were seen only in the infarction border zone, suggesting that although cytokines such as VEGF and stromal cell–derived factor-1 generated by the ischemic tissue can recruit EPCs toward to the ischemia, microenvironmental factors within the damaged muscle may prevent migration into the ischemic zone. Direct injection of cells into an ischemic area leads to a much higher regional cell concentration, but poor blood supply and local hypoxia in the ischemic zone negatively influences cell survival. An interesting recent study indicated that preconditioning mesenchymal stem cells with hypoxia before injection increased their tissue regenerative potential,13 suggesting that strategies to improve stem cell survival in vivo may be feasible.

What additional tools might be available to support progenitor cell homing to the ischemic zone? Mobilization of EPCs is matrix metalloproteinase-9–dependent; genetic deletion of matrix metalloproteinase-9 or its upstream activator urokinase plasminogen activator significantly impaired scar formation and revascularization in a mouse cardiac infarction model, even after treatment with VEGF.14 We and others have reported that coadministration of trypsin significantly increased gene transfection efficiency in myocardium and vascular grafts.15,16 Whether manipulation of enzyme activities can enhance cell-based therapies in humans remains to be determined.

In summary, in spite of continued accumulation of knowledge about the biology of progenitor cells, the optimal cell type or types, technique of delivery, and combination of adjuvant approaches for cellular therapy for ischemic myocardium and skeletal muscle remains to be determined. In the present study, Foubert et al demonstrate a possible synergistic effect from coadministration of EPCs and SMPCs based on Ang-1/Tie22 signaling and thus provide a new direction for further study. As shown in the Figure, if progress continues to be made in defining optimal cell type and dose, delivery route, and supplementary methods to enhance homing, survival, differentiation, and remodeling, we believe that “biological surgery” (ie, the use of progenitor cell-based angiogenic therapy) will become an important therapeutic tool to improve the quality of life of patients with atherosclerotic coronary and peripheral vascular disease.

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Disclosures

None.

References


Figure. Neovascularization is a complex multistep process requiring precise coordination of multiple cell types responding to many growth factors, cytokines, chemokines, enzymes, and mechanical forces. IGF-1 indicates insulin-like growth factor-1; FGF, fibroblast growth factor; TP, thymidine phosphorylase; MMP, matrix metalloproteinase; uPA, urokinase plasminogen activator; TGF-β, transforming growth factor-β; HIF-1, hypoxia-inducible factor-1; TNF α, tumor necrosis factor α; MOP-1, monocyte chemotactic protein-1; VCAM-1, vascular cell adhesion molecule-1; PDGF, platelet-derived growth factor; GM-CSF, granulocyte/macrophage colony-stimulating factor.


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