Add Some Fat to Vascular Progenitor Cell Therapy

Jaimy Saif, Christopher Heeschen, Alexandra Aicher

Are cell therapy approaches aiming for the improvement of tissue neovascularization still a big hope for the treatment of cardiovascular diseases? Yes indeed, even after the big hype about cell therapy has settled, now it is apparent that cardiovascular morbidity and mortality is still leading in industrial countries requiring novel advanced therapies to deal with. However, it has become clear now that cell-based treatment strategies require much more strategic advancement than initially anticipated from preclinical studies in mouse models of tissue ischemia. Indeed, we have just achieved to climb up to the very first level of small improvements in tissue perfusion and function that are unlikely to translate into major changes in the clinical outcome of our patients.1

Limited neovascularization, however, is not only a major obstacle for cardiovascular diseases but also affects different kinds of transplants. Apart from whole organ transplants that most likely could also benefit from improved neovascularization to improve long-term graft survival, a clinically very important example represents pancreatic islet transplantation in patients with type I diabetes. Transplantation of human β-cell islets is a procedure that has already helped a number of patients to at least temporarily reduce their demand for insulin. However, long-term engraftment of the infused islets has been a major limitation of this novel treatment approach. Successful islet transplantation does not only depend on the infusion of sufficient numbers of islets but even more on their immediate and adequate neovascularization.2 Compared to the transplantation of whole organs, where perfusion is rapidly obtained by the reconnection of blood supply, β-cell islets completely lack vascularization during the first days after transplantation. Ischemia and insufficient oxygen supply seem therefore to contribute to poor islet survival.3

How can we tackle this problem of limited transplant revascularization? To ensure sufficient perfusion of the jeopardized tissue, the newly created vessels need to generate mature and functional vascular networks. For full functionality, this process of blood vessel maturation requires the stabilizing attributes of mural cells. Blood vessels consist of endothelial tubes ensheathed by mural cells including vascular smooth muscle cells (VSMCs) and pericytes, with the latter displaying a unique distribution along the vessels. Over the past decade, bone marrow, peripheral blood, and vessel wall–derived cell sources for autologous vascular progenitor cells, but also allogeneic sources such as cord blood have been identified and tested in preclinical models.4–6 Adipose tissue–derived progenitor cells derived from surgical liposuction are also receiving a lot of attention, because they have been shown to promote neovascularization attributable to differentiation into endothelial cells and secretion of proangiogenic factors.7–9 In addition, adipose tissue–derived progenitor cells have recently been reported to share characteristic features with pericytes, including vessel stabilizing properties.10 Until now, the challenge of creating adequate neovascularization has been basically tackled by using vascular cell therapy approaches based on single sources of progenitor cells. It is, indeed, a very tempting hypothesis that the diversity of the vascular system could be more sufficiently reproduced by approaches using a dual-cell system. Although recent studies using synergistic cell sources, eg, mesenchymal stem cells in combination with endothelial (progenitor) cells, have already suggested more pronounced and durable effects of the combination concept with respect to tissue neovascularization,11,12 these studies did not investigate the mechanisms involved in cell-to-cell communication of the dual-cell system.

In this issue of Circulation Research, Traktuev et al13 investigated the combination therapy of 2 progenitor cell types with respect to therapeutic synergy and, for the first time, dissected the underlying in vivo mechanisms. The authors combined cord blood–derived endothelial progenitor cells (EPCs) and adipose tissue–derived stromal cells (ASCs) in a ratio of 4:1. Treatment effects were assessed in nonischemic collagen/fibronectin-based gel in vivo neovascularization models. The combination of EPCs plus ASCs revealed a much higher neovascularization capacity resulting in multilayered α-smooth muscle cell actin+ vessels as compared to any single cell type–based approaches. More mature endothelial cells also liaised with ASCs in vascular network assembly. Intriguingly, the reciprocal communication by ASCs and EPCs was associated with vessel proliferation and ASC-mediated reduction of EPC apoptosis.

Mechanistically, the authors built on their previous observation relating to in vitro secretion of platelet-derived growth factor (PDGF)-BB by endothelial cells and vascular endothelial growth factor (VEGF) by ASCs.10 Considering the notion that the stabilization process of newly formed vessels is mediated by PDGF-BB, which triggers VSMCs/pericytes to release proangiogenic mediators such as VEGF and fibroblast growth factors,14,15 the synergistic effects of ASCs and EPCs
can be well rationalized. PDGF-BB and its receptor PDGFR-β expressed by mural cells play a crucial role in the recruitment of pericytes to newly formed vessels and promote proliferation and migration of mural cells during vessel maturation. Indeed, the relevance of vessel stabilization for vascular development has been demonstrated in mice with targeted disruption of pdgfb, resulting in lack of pericytes, subsequent endothelial hyperplasia, and perinatal lethality. Of note, in contrast to widely used early EPCs, late outgrowth EPCs as used in the present study by Traktuev et al do not produce functionally relevant VEGF levels. By using PDGF neutralizing antibodies in the implanted gels, which inhibited assembly into lumen-containing structures, the authors showed a crucial role for PDGF in cooperative vessel assembly by ASCs and EPCs in vivo. Eventually, the combination therapy of ASCs and EPCs established a functional vascular network in implants carrying pancreatic islets, which could not be achieved by either of the cell types alone.

Are the provided mechanistic insights involving PDGF and VEGF sufficient to explain the therapeutic synergy? A very recent study combining PDGF and VEGF gene therapy in an ischemic setting showed very similar data corroborating the crucial and interacting role of these 2 factors. The combination of these 2 factors resulted in longer-lasting improvements in perfusion of ischemic hindlimbs, even though no improved pericyte coverage was detected. However, we have to keep in mind that VEGF has also been reported to counteract vessel maturation if recombinant VEGF and PDGF are coadministered in neovascularization models in vivo. Does this observation teach us that a cell-based system is the favorite treatment approach? A dual-cell system is much more intricate than the combination of 2 genes or 2 growth factors. Reciprocal stimulations in vivo might occur in a very timely and locally controlled fashion, involving coplayers we may not even have anticipated yet. PDGF is not only inducing the secretion of VEGF in VSMC but also stimulates the release of other stabilizing factors, which have to be elucidated in future studies to understand the benefits of dual-cell crosstalk versus the administration of genes or recombinant proteins.

Are the used cell sources ideal? The use of allogenic cell sources with all their limitations needs to be justified, but apparently this is less of an issue for patients undergoing tissue/organ transplantation, which requires immunosuppressive therapy anyway. On the other hand, vascular progenitor cells can be also derived from autologous sources such as peripheral blood but cells obtained from, for example, diabetics may be functionally impaired. More importantly, we have to be aware that liposuction to obtain ASCs itself bears inherent risks that question their routine use. In addition, it has been reported that in vitro expansion of human adult stem cells can result in spontaneous transformation of the cells. Of note, an ischemic environment and different routes of administration might also affect the outcome of cell therapies so that future studies have to address this issue as well. These findings underline the importance of biosafety studies of stem cell biology for any newly introduced or modified cell source before their full clinical evaluation in our patients.

Taken together, Traktuev et al provide important new incentives for future cell-based therapy approaches through first mechanistic insights favoring the use of a more advanced dual-cell therapy system. Further combination therapies, eg, combining multicell therapies along with gene therapy could be used as future therapies in regenerative medicine. However, we have to carefully examine the benefits and risks for each new cell type or growth factor combination that may offset the benefits that presently can be achieved with these novel therapies.

Sources of Funding
Supported by a Healthcare and Bioscience iNet HECF grant funded by enda (to A.A.) and the Fresenius Foundation (A23) (to C.H.).

Disclosures
None.

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**Key Words:** vasculogenesis ■ proangiogenic growth factors ■ vascularization
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Circ Res. 2009;104:1330-1332
doi: 10.1161/CIRCRESAHA.109.200469
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/104/12/1330

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