Endothelial Seeding for Abdominal Aortic Aneurysms
Lessons Learned From the Past and Present

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In this edition of Circulation, Franck and colleagues report a novel approach to modulate the growth of aortic aneurysms in an animal model by using endothelial cells (ECs) or outgrowth ECs grown in culture that were then delivered directly into an aortic xenograft before implantation. The authors report that this therapeutic approach resulted in modulation of the inflammatory process in the aortic wall and decreased the rate of growth of the xenograft aneurysms. They propose that endothelial seeding may be a promising technique for managing the growth of aneurysms in humans. This article brings back memories of the herculean efforts initiated by a number of laboratories to seed ECs on vascular grafts with the hope that this technique would improve the patency of the grafts and decrease perianastomotic neointimal hyperplasia and loss of ischemic limbs. In vitro assessment of the growth potential of adult human sources of endothelium suggested that there was adequate in vitro growth of cells to theoretically cover the surface of commonly used grafts. In vitro studies also demonstrated that human EC proliferation and morphology were modulated by both extracellular matrix and growth factors. Human trials of EC seeding gave variable results, none convincing enough to try to bring the technique to widespread use. Because of concerns that the surface of prosthetic grafts would never provide a hospitable environment for EC growth and development, the focus of these efforts changed to first lining the matrix with proteins such as fibronectin or with growth factors that would potentiate EC growth along the luminal surface of grafts. Eventually, as research into endothelial and smooth muscle cell biology progressed, this led to attempts at ex vivo construction of complete living cellular vessels. With the previous efforts of endothelial seeding of grafts in mind, it is useful to consider the similarities and differences of the efforts of Franck et al to seed EC onto aortic xenografts. First, we should discuss the similarities.

The relationship these authors draw between the ability of soluble rat-derived bFGF in culture medium to promote human EC growth in vivo and the ability of bFGF to modulate rat EC growth on the lumen of experimental xenografts is unfounded on the basis of the data presented in the article. There were no experiments done in vivo to block the effect of bFGF or to detect bFGF protein in the matrix of the seeded aortic xenografts. These results would be more compelling if the authors had shown that bFGF protein is deposited in the matrix of the seeded xenografts. Then, it may be plausible that transient seeding of the aortic xenografts with ECs could modulate the matrix characteristics of the xenografts to facilitate and sustain the ingrowth of native endothelium.

To prove their point about the utility of cell seeding, Franck et al also used late-outgrowth ECs to seed aortic xenografts. They harvested peripheral blood monocytes, cultured them, and then selected the colonies that had an endothelial morphology for subsequent passage and seeding experiments. The endothelial lining of blood vessels shows remarkable heterogeneity in...
structure and function.12 Surprisingly, rat ECs isolated from the thoracic descending aorta or obtained as late-outgrowth ECs from monocytes were equally effective for aneurysm repair. It is well known that macrophages can develop an endothelial phenotype and secrete growth factors such as bFGF and vascular endothelial growth factor,13,14 which may explain their near-equivalent capability to modulate the growth of the experimental aneurysms compared with rat ECs. A more important question is, Why did the late-outgrowth ECs not outperform their mature EC counterparts? One of the promises of stem cell therapy is that stem cells offer a superior source of cells for tissue engineering because of their regenerative potential. However, just like ECs, there was no evidence for long-term residence of the seeded late-outgrowth ECs. This is reminiscent of previous studies with early-outgrowth endothelial progenitor cells. The criteria for what defines an endothelial progenitor cell in terms of surface markers remain highly controversial.15,16 Unlike late-outgrowth ECs, endothelial progenitor cells do not give rise to ECs. Instead, the definition of endothelial progenitor cell has been obscured by the uptake of platelet microparticles by monocytes/macrophages,17,18 and the mechanisms for the in vivo improvements observed in preclinical models after endothelial progenitor cell administration remain elusive, with paracrine effects, rather than differentiation, being the most likely explanation. Similarly, the authors in the present study speculate that injected cells secrete paracrine factors that have the potential to modify the endogenous healing process. This conclusion is not specific enough from a mechanistic standpoint.

A common practice in cell therapy experiments is to compare the cell treatment with a saline injection or a plain medium control. Cell culture media are supplemented with growth factors, including bFGF, and, in the case of ECs, conditioned medium from monocytes/macrophages.19 and the mechanisms for the in vivo improvements observed in preclinical models after endothelial progenitor cell administration remain elusive, with paracrine effects, rather than differentiation, being the most likely explanation. Similarly, the authors in the present study speculate that injected cells secrete paracrine factors that have the potential to modify the endogenous healing process. This conclusion is not specific enough from a mechanistic standpoint.

Robertson RL, Thomas DM, Harker LA. Endothelial scaffolds to deliver growth factors for specific matrix proteins or growth factors to achieve serial growth in vitro.

The authors are to be commended for seeking a potential solution to halt the growth of aneurysms in humans. This is a significant clinical problem, and the potential complications associated with interventions for aneurysms are not trivial despite major advances with minimally invasive endovascular techniques. However, for the experiments by Franck et al to have significant clinical relevance, it is important to show that the extracellular matrix lining their aneurysmal xenograft replicates the environment found in human abdominal aortic aneurysms. Proteomic methodology has previously been used for the first detailed analysis of the extracellular matrix in human abdominal aortic aneurysm and identified markers of pathological extracellular matrix remodeling related to matrix metalloproteinase-12 activity.20 This methodology could be used to assess the proteome of the aneurysmal xenograft for comparison with the proteome of human aneurysms. If the matrix of the rat xenograft aneurysm is capable of binding growth factors that the human aneurysm matrix cannot, these studies will remain relevant to rats rather than humans.

Disclosures

None.

References


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