Severe ischemic diseases are often caused by atherosclerotic occlusion of arteries supplying blood to the myocardium or limbs. In such cases, transluminal angioplasty or bypass surgery is the most effective strategy for restoring blood supply in the affected arteries. However, in patients with severe ischemic heart disease or peripheral artery disease who cannot undergo bypass surgery or angioplasty, therapeutic angiogenesis is an effective means of preserving the integrity of tissues. Therapeutic angiogenesis is mediated by either injection of angiogenic cytokines, such as vascular endothelial growth factor, basic fibroblast growth factor, and hepatocyte growth factor; or implantation of angiogenic cells, including bone marrow mononuclear cells, peripheral blood mononuclear cells, and endothelial progenitor cells.

Several studies have demonstrated successful therapeutic angiogenesis using autologous bone marrow mononuclear cells in patients with critical limb ischemia, such as the Therapeutic Angiogenesis with Cell Transplantation (TACT) trial. Although the safety and efficiency of the TACT protocols have been established, patients with very severe peripheral artery disease have poor responses to this procedure. Moreover, patients with peripheral artery disease or multiple coronary risk factors have diminished functions of endothelial progenitor cells and poor responses to angiogenic cell therapy. Thus, an alternative source of stem/progenitor cells for therapeutic angiogenesis has been explored. Recently, several studies reported that adipose tissues contain multipotent mesenchymal stem cells termed adipose-derived regenerative cells that have an ability to regenerate damaged tissues. Adipose-derived regenerative cells also secrete multiple angiogenic growth factors, such as vascular endothelial growth factor and hepatocyte growth factor, that directly stimulate angiogenesis and mobilize endothelial progenitor cells from the bone marrow, facilitating so-called vasculoengenesis. In fact, direct implantation of adipose-derived regenerative cells has been shown to stimulate angiogenesis and to mobilize endothelial progenitor cells in the setting of tissue ischemia.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Yoshida et al report that implantation of human omentum adipose tissue–derived microvascular endothelial cells (HOMECs) augmented angiogenesis in a mouse model of hindlimb ischemia. Moreover, a unique and new aspect of their research is that they used an engineered endothelial capillary network based on optical lithographic printing technique. They show that implantation of endothelial capillary structures engineered on decellularized human amniotic membranes into an ischemic hindlimb of nude mice significantly augmented blood perfusion compared with controls with decellularized human amniotic membranes alone. They used HOMECs as an autologous cell source. Because the omentum is normally covered with visceral adipose tissue, the HOMEC may be another adipose-derived regenerative cell for therapeutic angiogenesis.

The same research group previously demonstrated that such engineered capillary networks function in vitro and improve blood perfusion in a mouse model of subcutaneous punch lesion. The novel technique used in that study was based on an offset printing technique and the properties of endothelial cells (ECs). The substrate for cell patterning was devised according to hydrophilicity. When human umbilical vein ECs were seeded and incubated on the fully patterned substrate, human umbilical vein ECs migrated, and they adhered to the linear hydrophilic regions of the printed substrate. For future clinical application, the researchers tested HOMECs as an alternative cell source and decellularized amniotic membrane as a pathogen-free scaffold for the engineered capillary structure, because human umbilical vein ECs cannot be used as an autologous cell source at present. One problem they faced was that HOMECs did not form capillary structures as human umbilical vein ECs did. However, they overcame this issue using sphingosine 1-phosphate, which facilitated the capillary structure formation via the sphingosine 1-phosphate 2 receptor–Rho kinase–ROCK pathway.

Tissue engineering techniques are emerging because coordinated cell and scaffold structure is sometimes more effective than single-cell injection. For example, mesenchymal stem cell or skeletal myoblast cell sheet implantation has been shown to improve cardiac function in severe ischemic cardiomyopathy, but such efficacies were not confirmed in the case of the single-cell injection technique. Currently, an important tissue engineering strategy for the vascular and cardiac regeneration may be cell sheet technology, using either a temperature-responsive polymer or magnetic cell arrangement methods.

Clearly, the tissue printing method demonstrated herein by Yoshida et al is an additional strategy for tissue engineering. For future clinical application, there may be several issues to
be further studied. First, how can capillary structures composed on decellularized human amniotic membranes be implanted? It may still be difficult to place the composed capillary structures on the ischemic tissue without disturbing capillary luminal function. Second, are HOMECs the best cell source for capillary composition? Isolating HOMECs may be an invasive procedure, and additional cell sources, such as subcutaneous adipose tissue–derived ECs, would be explored.

References


Printing a Tissue: A New Engineering Strategy for Cardiovascular Regeneration
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