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Original Article

Enhanced Myocardial Vascularity and Contractility by Novel FGF-1 Transgene in a Porcine Model of Chronic Coronary Occlusion

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Abstract:

Background: *Angiogenesis gene therapy has long been sought as a novel alternative treatment for restoring the blood flow and improving the contractile function of the ischemic heart in selected clinical settings. Angiogenic fibroblast growth factor-1 (FGF-1) is a promising candidate for developing a promising gene therapy protocol due to its multipotent ability to stimulate endothelial cell (EC) growth, migration, and tube formation. Despite these advantages, however, FGF gene therapy has suffered setbacks mainly due to the inefficient delivery rate of the growth factor in vivo. Given the potent angiogenic effect of FGF-1, we reasoned that constitutively synthesized minute quantities of this polypeptide hormone, when empowered with the ability to escape the cellular constraint, could freely act in a paracrine/autocrine fashion on nearby existing capillary plexuses and lead to neovascularization and restoration of the blood flow to ischemic tissues for reparative purpose.*

Methods: *We report the direct gene transfer of a retroviral-based mammalian expression vector encoding a secreted form of FGF-1 (sp-FGF-1) for the purpose of therapeutic angiogenesis into the porcine myocardium subjected to the surgical placement of an ameroid occluder to induce the chronic coronary occlusion of the left circumflex coronary artery (LCx) and regional myocardial ischemia. Coronary angiography, performed 3 weeks after surgery, confirmed the interruption of the blood flow in the LCx distal to the site of ameroid placement.*

Results: *Immunohistochemical analysis using antibody specific to von Willebrand factor (vWF), an endothelial marker, showed a significant increase ($p<0.05$) in myocardial vascularity in the sp-FGF-1 hearts compared to the control (vector alone).*

Importantly, an assessment of the cardiac function by echocardiography, performed 3 weeks after surgery, demonstrated improved cardiac contractility due to increased left ventricular free wall contraction in the sp-FGF-1-treated animals only.

Conclusion: *These results suggest that the intramyocardial delivery of our chimeric secretory FGF-1 gene can enhance vascularity and improve cardiac contractility in a chronic ischemic heart. This protocol may serve useful for developing reparative angiogenesis strategies aimed at improving the pumping function of the ischemic hearts in human patients.*

Keywords:

Angiogenesis inducing agents ، Fibroblast growth factor 1 ، Ischemia ، Heart ، Gene therapy ، Transfection

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top ▲