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CELL-SHEET THERAPY WITH OMENTOPEXY PROMOTES ARTERIOGENESIS AND IMPROVES CORONARY CIRCULATION PHYSIOLOGY IN FAILING HEART

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Objectives: Cell sheet implantation induces angiogenesis for chronic myocardial infarction (MI), though insufficient capillary maturation and paucity of arteriogenesis may limit its therapeutic effects. The omentum, as a source of angiogenesis factors, has been used clinically to promote revascularization and healing of ischemic tissues by modulating growth of vasculature. We hypothesized that cell-sheet transplantation covered with an omentum-flap would effectively establish mature blood vessels and improve coronary microcirculation physiology, leading to enhanced functional capacity.

Methods & Results: Two weeks after left coronary artery ligation, MI rats were divided into four treatment groups; skeletal myoblast cell-sheet plus omentum-flap (combined), cell-sheet only, omentum-flap only, and sham operation (n>10 for each). At four weeks after the treatment, the combined group showed attenuated cardiac hypertrophy and fibrosis, and a greater amount of functionally (CD31+/lectin+) and structurally (CD31+/α-SMA+) mature blood vessels in the ischemic myocardium, along with myocardial upregulation of relevant genes. Synchrotron-based microangiography revealed that the combined procedure increased vascularization in resistance arterial vessels (3rd and 4th branching orders) with better dilatory response to endothelium-dependent agent, acetylcholine (treatment effect p=0.014). Serial 13N-ammonia PET showed a higher ratio of post- to pre-treatment global coronary flow reserve in the combined group, which was mainly caused by significant improvement in the basal left ventricle (ANOVA p=0.012). Consequently, the combined group had sustained improvements in cardiac function parameters and better functional capacity. Also, robust vascular communication between the omentum and native coronary arteries was revealed by in vivo angiography in the combined, but not omentum-flap only group. In vitro migration assay indicated that formation of collateral vessels between native the coronary arteries and omentum was accelerated by the interposed cell-sheets.

Conclusions: Cell-sheet transplantation with an omentum-flap better promoted arteriogenesis and improved coronary microcirculation physiology in ischemic myocardium, leading to potent functional recovery in failing heart.

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