Repairing the Infarcted Heart with Engineered Human Myocardium

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Cardiomyocytes derived from human embryonic stem cells (hESCs) attenuate heart failure when transplanted into experimental infarcts. Grafts typically average <1% of left ventricular mass, suggesting non-contractile mechanisms cause the benefit. We have created scaffold-free patches (~3 mm x 400 um) of human myocardium by self-aggregating hESC-derived cardiomyocytes. Unfortunately, when these patches were implanted into skeletal muscle, survival was poor, likely due to ischemic injury. We then devised a technique to "pre-vascularize" the patches, co-seeding human endothelium and marrow stromal cells (MSCs). Under the influence of MSCs, endothelium formed plexus-like branching networks. When implanted into athymic rat hindlimbs, the tri-cell patches survived >10-fold better than cardio-only patches. Importantly, the human endothelium formed definitive microvessels that contained rat erythrocytes, demonstrating anastomosis with the host circulation. When pre-vascularized patches were implanted onto the epicardium of infarcted athymic rat hearts, large grafts of human myocardium formed. Graft thickness equal to infarcted wall thickness was seen, and human vessels anastomosed to the rat's coronary circulation. Thus, tissue engineering can offer substantial advantages in cardiac repair compared to transplantation of dispersed cells. Pre-vascularizing the constructs with endothelium and MSCs markedly enhanced survival of the engineered tissue, indicating important synergies in replacing both the cardiomyocyte and stromal-vascular compartments of the heart.