

In vivo reprogramming of murine cardiac fibroblasts into induced cardiomyocytes.

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Public Summary:

The reprogramming of adult cells into pluripotent cells or directly into alternative adult cell types holds great promise for regenerative medicine. We reported previously that structural cells in the heart called cardiac fibroblasts, which represent 50% of the cells in the mammalian heart, can be directly reprogrammed to beating heart muscle-like cells in petri dishes. This work builds on our previous findings by using mice that had experienced a heart attack. We delivered three genes that normally guide embryonic development (abbreviated as GMT) directly into the damaged region of the mouse heart. Within a month, non-beating cells that normally form scar tissue transformed into beating heart cells. Within three months, the hearts were beating even stronger and pumping more blood. When this experiment was performed with GMT and the additional delivery of a protein called thymosin beta 4, which encourages blood vessel growth, the improvements in scar area and cardiac function were even more pronounced. These findings demonstrate that cardiac scar tissue can be transformed into heart muscle-like cells in their native environment for potential regenerative purposes.

Scientific Abstract:

The reprogramming of adult cells into pluripotent cells or directly into alternative adult cell types holds great promise for regenerative medicine. We reported previously that cardiac fibroblasts, which represent 50% of the cells in the mammalian heart, can be directly reprogrammed to adult cardiomyocyte-like cells in vitro by the addition of Gata4, Mef2c and Tbx5 (GMT). Here we use genetic lineage tracing to show that resident non-myocytes in the murine heart can be reprogrammed into cardiomyocyte-like cells in vivo by local delivery of GMT after coronary ligation. Induced cardiomyocytes became binucleate, assembled sarcomeres and had cardiomyocyte-like gene expression. Analysis of single cells revealed ventricular cardiomyocyte-like action potentials, beating upon electrical stimulation, and evidence of electrical coupling. In vivo delivery of GMT decreased infarct size and modestly attenuated cardiac dysfunction up to 3 months after coronary ligation. Delivery of the pro-angiogenic and fibroblast-activating peptide, thymosin beta4, along with GMT, resulted in further improvements in scar area and cardiac function. These findings demonstrate that cardiac fibroblasts can be reprogrammed into cardiomyocyte-like cells in their native environment for potential regenerative purposes.

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