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Generation of electrophysiologically functional cardiomyocytes from mouse induced pluripotent stem cells

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Induced pluripotent stem (iPS) cells can efficiently differentiate into the three germ layers similar to those formed by differentiated embryonic stem (ES) cells. This provides a new source of cells in which preclinical allogeneic transplantation models can be established. Our iPS cells were generated from mouse embryonic fibroblasts (MEFs) transfected with the Yamanaka factors, the four transcription factors (Oct4, Sox2, Klf4 and c-Myc), without antibiotic selection or MEF feeders. After formation of embryoid bodies (EB), iPS cells spontaneously differentiated into Flk1-positive cardiac progenitors and cardiomyocytes expressing cardiac-specific markers such as alpha sarcomeric actinin (α-actinin), cardiac alpha myosin heavy chain (α-MHC), cardiac troponin T (cTnT), and connexin 43 (CX43), as well as cardiac transcription factors Nk2 homebox 5 (Nkx2.5) and gata binding protein 4 (gata4). The electrophysiological activity of iPS cell-derived cardiomyocytes (iPS-CMs) was detected in beating cell clusters with optical mapping and RH237, a voltage-sensitive dye, and in single contracting cells with patch-clamp technology. Incompletely differentiated iPS cells formed teratomas when transplanted into a severe combined immunodeficient (SCID) mouse model of myocardial infarction. Our results show that somatic cells can be reprogrammed into pluripotent stem cells, which in turn spontaneously differentiate into electrophysiologically functional mature cardiomyocytes expressing cardiac-specific makers, and that these cells can potentially be used to repair myocardial infarction (MI) in the future.

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