Heart Failure-iPS Cells Derived Cardiomyocytes Show Functional Integration with Preexisting Myocytes

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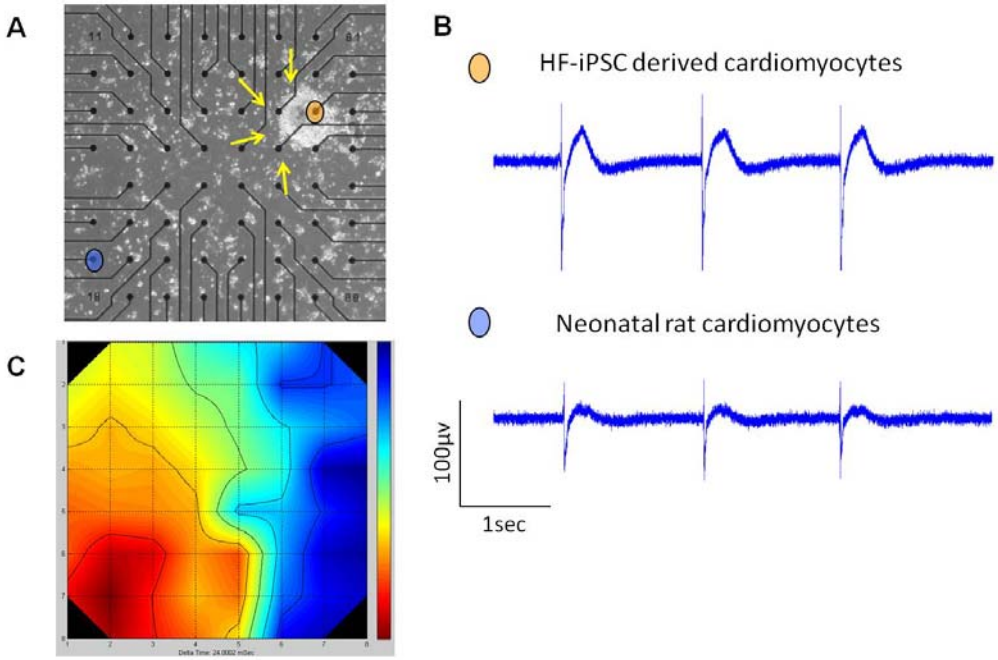
The ability to derive patient-specific human induced pluripotent stem cells (iPSC) by somatic cell reprogramming may provide useful platform for cell therapy in myocardial repair. In our study we generated iPSC from post-myocardial infarction heart failure (HF) patients, successfully differentiated them into cardiomyocytes (CMs), and assessed the hypothesis that functional syncytium can be formed between donor and recipient cells in vitro.

Dermal fibroblasts from two heart failure patients were efficiently reprogrammed by retroviral infection of the reprogramming factors: Oct4, Sox2, and Klf4. All the generated HF-iPSC lines expressed pluripotent markers as determined by immunocytochemistry and quantitative RT-PCR analysis, and generated teratomas in SCID mice. The HF-hiPSC were then coaxed to differentiate into the cardiac lineage. The HF-iPSC derived CMs were similar to healthy-iPSC derived CMs in cardiac gene expression pattern, and in their structural and electrophysiological properties.

We next assessed the ability of the HF-iPSC derived CMs to integrate with primary cultures of neonatal rat ventricular myocytes. A microelectrode array (MEA) imaging technique was used to map their electrical activity. By recording extracellular potentials simultaneously from 60 electrodes, we were able to generate high-resolution activation maps that characterize impulse initiation and conduction within the co-cultures. We showed that electrically active donor CMs derived from HF-iPSC can functionally integrate with primary cultures of neonatal rat ventricular myocytes, to induce rhythmic electrical and contractile activities. Immunofluorescent staining for connexin43 and human mitochondria demonstrated the presence of gap junctions between the two tissue types, the major sites for intercellular electrical and mechanical coupling respectively.

These results may pave the way for future use of these cells as a biological pacemaker and for cardiac regenerative medicine in general.



Functional integration in the co-cultures. [A] Co-culturing of the HF-hiPSCs-CMs (arrows) with neonatal rat ventricular cardiomyocytes (NRVCMs) on top of MEA plates. **[B]** Electrogram recordings from two electrodes underlying the HF-hiPSCs-CMs (orange) and NRVCMs (blue) showing synchronized activity. **[C]** Activation map showing the propagation of the electrical activity from the rat to human cardiomyocytes.