Coupling of Transgene-Free Heart Failure-Induced Pluripotent Stem Cells with Host Cardiomyocytes

Zwi-Dantsis, Limor; Huber, Irit; Habib, Manhal; Winterstern, Aaron; Gepstein, Amira; Arbel, Gil; Gepstein, Lior
Technion - Israel Institute of Technology, Physiology, Haifa, Israel

Myocardial cell replacement therapies are hampered by the paucity of sources for human cardiomyocytes and by the expected immune rejection of allogeneic cell-grafts. Induced pluripotent stem cells (iPSCs) derived from somatic cells of patients represent a powerful tool for biomedical research and may provide a solution to these challenges.
In the current study, we aimed to derive transgene-free human iPSCs (hiPSC) from patients with advanced heart failure (HF), to induce their cardiomyocyte differentiation, and to evaluate their ability to integrate with pre-existing cardiac tissue both in-vitro and in-vivo.
Dermal fibroblasts from HF patient were reprogrammed into hiPSCs with a unique excisable single polycistronic lentiviral vector that contained four reprogramming factors (Oct4, Sox2, Klf4 and c-Myc). Subsequently, the vector was excised by the transient introduction of Cre-recombinase and eGFP, followed by a FACS sorting. The generated factor-free HF-hiPSCs were then coaxed to differentiate into cardiomyocytes. Gene expression and immunostainings confirmed their pluripotency and cardiomyocyte phenotype. Next, functional integration and synchronized electrical activities were demonstrated between HF-hiPSC derived cardiomyocytes and neonatal rat cardiomyocytes in co-culture studies. Finally, in-vivo transplantation studies in the rat heart revealed the ability of the HF-hiPSCs derived cardiomyocytes to engraft, survive, and structurally integrate with host cardiomyocytes.
In conclusion, our study demonstrates efficient reprogramming of human cells while avoiding the permanent presence of reprogramming transgenes. This represents a critical step toward the use of HF-hiPSCs for clinical purposes. Moreover, the capability of HF-hiPSC derived cardiomyocytes to couple with host cardiomyocytes both in-vitro and in-vivo is crucial for future use of these cells not only for the treatment of heart failure but also for conduction system repair (biological pacemaker approach).