Strategies for immunomodulation in cell-based cardiac regenerative therapy

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Abstract

Human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (hiPSC-CMs) can remuscularize infarcted hearts and restore post-infarct cardiac function. However, post-transplant rejection resulting from human leukocyte antigen (HLA) mismatching is an enormous obstacle of allogeneic cell therapy. Therefore, it is crucial to identify hypoimmunogenic hiPSCs for allogeneic cell therapy. Recently, we demonstrated low immunogenicity of HLA-E^{high}/HLA-G^{high}/HLA-II^{low} hiPSC-CMs *in vitro* and *in vivo*. Furthermore, under the treatment of very low dose cyclosporine A (CsA), HLA-E^{high}/HLA-G^{high}/HLA-II^{low} hiPSC-CMs survived *in vivo*, remuscularized the rats' infarcted myocardium with infarct size reduction and improved post-infarct cardiac function. HLA-E^{high}/HLA-G^{high}/HLA-II^{low} hiPSC-CMs evaded attack by natural killer (NK) cells and cytotoxic T cells because these hiPSC-CMs activated the SHP-1 signaling pathway of NK cells and cytotoxic T. Herein, we demonstrated that using clinically relevant CsA dose, HLA-E^{high}/HLA-G^{high}/HLA-II^{low} hiPSC-CMs repaired the infarcted myocardium and restored the post-infarct heart function. The hypoimmunogenic hiPSCs may serve as an universal cell source for regeneration medicine.