CDB SEMINAR

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Three-dimensional heart tissues generated from human iPS cells for regenerative therapy and disease modeling

Summary

Three-dimensional bioengineered constructs recapitulating heart tissue would be promising for cardiac repair and disease modeling. Utilizing cardiovascular populations (cardiomyocytes [CMs]/ endothelial cells [ECs]/ vascular mural cells [MCs]) from mouse ES cells (mESCs), we generated mESC-derived cardiac tissue sheets (CTSs). The transplantation of the CTSs onto a rat myocardial infarction (MI) model exhibited a functional recovery mainly mediated by neovascularization which was diminished in a transplantation of sheets lacking CMs (EC/MC sheets), indicating that CMs play a central role (*Stem Cells*, 2012). To extend the strategy toward human iPS cells (hiPSCs), we simultaneously induced multiple cardiovascular populations by sequential supplementation of cytokines, and generated self-pulsating hiPSC-CTSs which exhibited myocardial regeneration *in vivo* (*Sci Rep*, 2014). To further promote tissue regeneration, we engineered thicker CTSs from mESCs using gelatin hydrogel microspheres leading to facilitated myocardial regeneration supported by functional capillary network *in vivo* (*Sci Rep*, 2015). We further generated thicker hiPSC-CTSs (hiPSC-derived cardiac tissue; HiCT) and confirmed an excellent functional recovery in rat and porcine MI models, and in a δ-sarcoglycan-deficient dilated cardiomyopathy hamster model. We recently developed cylindrical engineered cardiac tissues (ECTs) using hiPSC-derived cardiovascular cells and biomaterials. Incorporation of multiple cardiovascular populations enhanced electromechanical function and facilitated ECT maturation (*Sci Rep*, 2016). The ECTs were advantageous for functional recovery *in vivo*, and can be prepared as a larger mesh-like format suitable for large animal pre-clinical and clinical studies (*Sci Rep*, in press). These hiPSC-derived heart tissues may also contribute to disease modeling such as an *in vitro* drug-induced Torsade de Pointes (polymorphic lethal arrhythmia) model (*Nat Commun*, in revision) or disease-specific iPSC-derived ECTs which can be used for drug development and safety tests. Here we demonstrated that hiPSC-derived three-dimensional heart tissues hold novel properties relevant for clinical translation.

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