Re-Beat Whole Decellularized Mouse Heart with Human iPS Cell-Derive Cardiovascular Progenitors

Awardee: Lei Yang
Award: New Innovator Award
Awardee Institution: University of Pittsburg at Pittsburg

Introduction: Approximately one person dies in every 34 seconds as a consequence of heart diseases in the United States, and over 50% of patients with heart disease do not respond to regular medications. Thus heart disease therapy requires novel therapeutic strategies, such as personalized medicines, new resource of cells for replacement therapy, or donor hearts for transplantation. Heart tissue engineering holds a great potential for future heart disease therapy by building patient and disease-specific heart tissues for those applications.

Material and Methods: C57BL6/J mice were euthanized and the ascending aorta was cannulated with a blunted 20-gauge needle that was sutured to allow retrograde coronary perfusion, followed with a decellularization process with enzyme and detergent treatments [1]. In the meanwhile, human induced pluripotent stem (iPS) cells, which were maintained on mitotically inactivated MEFs in human ES cell medium, were induced for cardiovascular differentiation using our established protocol [2,3]. Approximately 1.0 $X10^7$ human iPS cell-derived multipotential cardiovascular progenitors (MCPs) [1,2], were delivered into one acellular mouse heart through the connected cannula. After 20 days culture, the engineered heart constructs showed contractions, followed with histological, electrophysiological and drug response analyses.

Results and Discussions: In this report, we engineered human heart tissues by repopulating whole decellularized mouse hearts with human iPS cell-derived MCPs. MCPs represent the earliest heart progenitors during human cardiogenesis. The seeded MCPs differentiated *in situ* into CMs, smooth muscle cells (SMCs) and endothelial cells (ECs) with high efficiency, which reconstructed the decellularized mouse hearts. The recellularized mouse hearts exhibited myocardium and vessel-like structures, contracted spontaneously with a rate of 40 to 50 beats/min, exhibited intracellular Ca^{2+} transients (CaiT) and responded as expected to various drug interventions. In addition, we found mouse heart ECM could promote proliferation, specific cell differentiation and myofilament formation of cardiomyocytes from the repopulated human MCPs.

Conclusion: This study at the first time utilized a novel patient-specific cell resource, which is the iPS cell-derived MCPs, for engineering patient-specific heart constructs that could be beneficial to study heart development, and future preclinical applications.

References:

1. Lu TY, Lin B, et al, and Yang L. Repopulation of Decellularized Mouse Heart with Human Induced Pluripotent Stem Cell Derived Cardiovascular Progenitor Cells. ***Nature Communications***. 2013. 4: 2307.
2. Yang L, et al. and Keller G. ***Nature***. 2008, 453: 524-528.
3. Lin B, et al., and Yang L. ***Cardiovascular Research***. 2012. 95:327-335.