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Letter to Editor Open Access

Engineering Of Thick Human Functional Myocardium via Static Stretching and Electrical Stimulation

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Letter to Editor

Human cardiac-muscle patches constructed from induced pluripotent stem cell derived cardiomyocytes can replicate the genetics of individual patients, and consequently be used for drug testing, disease modeling, and therapeutic applications. However, conventional hCMPs are relatively thin and contain iCMs with fetal cardiomyocyte structure and function [1]. Here, we used our layer-by-layer fabrication to construct thicker triple-layered hCMPs, and then evaluated iCM maturity after ten days of standard culture (Control), static stretching (Stretched), or stretching with electrical stimulation at 15 or 22 V (Stretched+15V or Stretched+22V). Assessments of stained hCMPs suggested that expression and alignment of contractile proteins was greater in Stretched+22V, whereas quantification of mRNA abundance and protein expression indicated the Stretched+22V enhanced bimolecular maturation [2]. Transmission electron microscope images indicated that stretching and electrical stimulation were associated with increases in development of Z-lines and gap junctions, and sarcomeres were significantly longer following any of the maturation protocols.

Disease modeling and drug testing have historically been conducted primarily in animal models. However, the development of techniques for generating tissues from human induced pluripotent stem cells has enabled researchers to conduct *in vitro* experiments on an entirely human platform Furthermore, because hiPSCs can be reprogrammed from each patient's own somatic cells, cardiomyocytes differentiated from hiPSCs fully reproduce all the genetic factors that may influence the etiology and progression of heart disease in an individual patient, as well as the patient's response to treatment . Nevertheless, conventional fabrication techniques typically produce human cardiac muscle patches that are relatively thin, and hiPSC-CMs are structurally and functionally more similar to CMs from fetal and neonatal hearts than from the hearts of adults, which has deterred both the investigational and therapeutic use of engineered hiPSC-derived cardiac tissues.

For example, during the continuous, normal pumping of the heart, an electrical signal is first propagated throughout the tissue because of the firing of special pacemaker cells, causing changes in ion concentrations inside and outside the cells. These differences in concentrations trigger an action potential in different areas of the heart as the signal travels to the various chambers, leading to contraction and stretching of the heart tissue. To recapitulate this process, we can develop an optimized, concerted balance between electrical and mechanical stimuli, aided by the extracellular matrix composition of the surrounding environment, which would in turn support physiologically relevant cell signaling cascades.

Despite continued refinement of the techniques and materials used to generate engineered myocardial tissues, few studies have been conducted with hCMPs of clinically relevant dimensions [4]. hCMPs with surface areas of 8 cm^2 have been investigated in a swine model of myocardial infarction, but even these relatively large patches were only ~1.25 mm thick. The hCMPs generated for this report exceeded 2.1 mm in thickness, and at least in principle, our lbl fabrication protocol could be used to produce even thicker hCMPs simply by depositing additional layers of hiPSC-CM–containing solution during manufacture.

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Conflict of Interest

The authors declare that they are no conflict of interest

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