Indian Institute of Science
Centre for BioSystems Science and Engineering

BSSE Colloquium

6th August 2020, 4:30 PM, Virtual

Engineering Disease Models for Cardiac and Skeletal Muscle Tissues

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ABSTRACT

Biomedical research aims to gain deeper insights into the mechanisms of human pathophysiology to develop improved therapies and diagnostics. Despite significant advances made in understanding and treatment of human diseases, many bottlenecks persist in successful clinical translation. Conventional culture techniques and animal models suffer from various limitations that fail to recapitulate human physiology and impede clinical translation of therapies. More recently, the focus has shifted to engineering experimental platforms that offer physiologically-relevant in vitro disease models. Among various human diseases, cardiovascular diseases account for the highest number of deaths worldwide. Similarly, skeletal muscle disorders are the leading contributor to disability across the globe. Given the enormous health burden associated with ailments of cardiac and skeletal muscles, the broad goal of this work was to engineer tissue-mimetic templates for these tissues that can serve as reliable in vitro disease models.

Toward this goal, simplified methods were standardized to obtain functionally superior primary cardiomyocytes and skeletal myotubes as a robust source of cells for these models. Alongside this, an unconventional and cost-effective surface coating derived from human hair was reported to be effective in supporting primary cardiomyocyte culture. Thereafter, microscale and nanoscale surfaces were designed and utilized for gaining unique insights into the cardiac and skeletal myocytes function in normal as well as diseased state. Specifically, UV lithography and etching techniques were used to create micro-ridges as an organotypic platform to study cardiac hypertrophy and live calcium currents in cardiomyocytes. This approach was further extended to develop a potential antioxidant and anti-hypertrophic cardiac patch using nanofibers decorated with therapeutic nanoparticles. Screening for a variety of engineered substrates was done to retain skeletal myotubes in culture, which often detached on smooth surfaces. A nanofibrous platform was thus optimized and investigated as a disease model for muscle degeneration. Overall, the study revealed altogether different aspects of culturing skeletal myotubes in comparison to cardiomyocytes. This work highlighted the cell-dependent response to topography even among structurally similar cell types. The developed platforms integrating primary cells and anisotropic substrates allowed to achieve precise cellular architecture and study their function in specific pathophysiological conditions. An improved understanding of alterations in cell function in response topography may lead to the development of laboratory models that better recapitulate the in vivo milieu than conventional culture and thereby improve translation of devised therapies from bench to bedside.