BIOMECHANICAL INVESTIGATION OF ENGINEERED MUSCLE TISSUE CONSTRUCTS FOR DISEASE MODELING AND BIOROBOTICS

By

Neerajha Nagarajan

ABSTRACT

Contractility of heart muscle cells, or cardiomyocytes (CM), is the major parameter for determining their maturity and functionality. Consequently, investigating the effect of mechanical microenvironment on CM function is vital for understanding the underlying mechanism of their behavior in healthy as well as in diseased state. In this work, we investigated contractile biomechanical properties of cardiomyocytes using two different approaches, for biomedical applications ranging from biorobotics to heart disease studies.

In the first section, a bionanoindentor was used to investigate the effect of substrate stiffness on the CM contractile force as well as force propagation through neighboring non-contractile cells (i.e. cardiac fibroblasts (CFs)). To this extent, an elastomeric polymer, polydimethylsiloxane (PDMS) was used to form in vitro patterned cocultures of CM and CF. By leveraging the tunable properties of the PDMS polymer, substrates of varying stiffness were fabricated to mimic the mechanical characteristics of normal and diseased myocardial tissue. It was observed that CMs on soft (14 kPa) substrate exhibited higher contractile force of 250 nN and larger propagation distance of mechanical signals (800 μm), as compared to those cultured on stiff (484 kPa) substrate, which was 100 nN and 200 μm, respectively. We also observed corresponding biochemical changes in cell adhesion and cell-cell interaction proteins. The outcome of this work has significant potential to advance our understanding of the effect of scar tissues, which are comparatively stiffer than healthy tissues, on cardiac function and help the development of novel therapies for cardiovascular diseases.

Since the indentation approach can be used to quantify only a single cell at a time, an alternate method, the thin-film bending technique was used to measure the contractile forces generated by a large group of CMs cultured as a cell sheet. CM cell sheets that are made to beat synchronously could be used as bioactuators for potential biorobotics applications. To this extent, in the second part of this work, a bioactuator was fabricated by combining a PDMS base with a thin PDMS film cantilever seeded with a confluent layer of CMs. Characterization of the cell sheet contractions revealed a gradual increase of the dynamic contraction force and the static cell traction force over time, which was accompanied by a linear increase in the expression levels of contractile and cytoskeletal proteins. The rhythmic contractions of the cantilever produced sufficient force, which was harnessed to drive a small biorobot. The biorobot was engineered by incorporating the bioactuator with a two composite PDMS base made of materials with different mass densities (i.e.

PDMS with microballoons and PDMS with Nickel powder). The difference in the densities of the materials enabled self-stabilization of the device which exhibited different swim propulsion modes depending on the resting angle of its “fin” (the cantilever). The technique described in this work to stabilize and propel the biorobot can pave the way for novel discoveries in biorobotics.