Heart Disease on a Chip: Using Tissue Engineering to Model Cardiac Pathologies

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The heart is a complex and highly dynamic organ, relying on the rapid spread of electrical impulses to trigger synchronous organ-level contractions. Cardiac myocytes are the force-generating muscle cells in the heart and rely on a hierarchical spatial organization, spanning from the nanoscale to the macroscale, to effectively pump blood through the vasculature. Historically, investigating cardiac disease mechanisms has been relatively reductionist, focusing on the pathological effects of a single protein, such as an ion channel. We instead are taking a systems-level approach by quantifying the effects of the extracellular microenvironment, cell and tissue architecture, and intrinsic and extrinsic mechanical forces on the form, function, and pathological remodeling of engineered cardiac myocyte cells and tissues.

Here, I describe several cardiac disease models we have engineered to reveal novel disease mechanisms and serve as platforms for drug testing. In concentric hypertrophy, myocyte aspect ratio decreases, which could be an adaptive response to fibrotic stiffening of the extracellular matrix. To test this, we cultured neonatal rat ventricular myocytes on fibronectin-micropatterned polyacrylamide gels with tunable elasticity. Myocytes with lower aspect ratios had a functional advantage when the microenvironment became stiffer, which could underlie myocyte shape remodeling in concentric hypertrophy. To determine if microenvironmental elasticity also impacts tissue assembly, we cultured two-cell cardiac μtissues on the same flexible substrates and monitored cell-cell junction formation over time. As isolated myocytes transitioned to interconnected μtissues, focal adhesions disassembled and mechanical forces were transmitted almost completely through the cell-cell junction. However, μtissues on stiffer substrates retained focal adhesions near the cell-cell interface, suggesting that myocyte de-coupling in cardiac disease could be potentiated by stiffening of the microenvironment. Next, we developed a model of failing cardiac tissue by applying cyclic stretch to engineered anisotropic cardiac tissues, which altered intracellular calcium cycling similar to heart failure and decreased contractile stresses. This platform has applications as an *in vtiro* drug testing platform for heart failure. We are now extending our efforts in disease modeling by engineering cells and tissues with human iPS-derived cardiac myocytes from patients, which holds significant promise for the emerging field of personalized medicine.