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TRANSDIFFERENTIATION OF CARDIAC FIBROBLASTS TO MYOFIBROBLAST PHENOTYPE AND ITS REGULATION BY EXTRACELLULAR MATRIX COMPOSITION AND MECHANICS

Poster Contributions
Hall C
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Session Title: Regulation of Cardiac Fibrosis in Heart Failure
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Background: The myocardium is a complex composite in which cardiomyocytes make up the bulk of the volume and fibroblasts are the most abundant cell type. Fibroblasts are known to transdifferentiate into the myofibroblast phenotype associated with cardiac fibrosis/remodeling, and are involved in disease entities such as atherosclerosis, diabetes, and cardiac fibrosis. These pro-fibrotic cells propagate via mechanical cues such as matrix stiffening, and biochemical cues. We hypothesize that selectively altering the ECM composition (hyaluronan-HA hydrogels) and substrate stiffness will reprogram myofibroblast towards normal phenotype.

Methods: Cardiac fibroblasts were isolated from neonatal rat hearts and differentiated into myofibroblasts by plating them on tissue culture plastic (TCP), and re-plated on varying stiffness (30kPa, 10kPa, 300Pa HA) matrices of polyacrylamide (PAA) and HA gels. The matrices mimicked fibrotic stiffness on 30kPa PAA, physiological stiffness on 10kPa PAA along with softer substrates. Cells were fixed and stained at 48 hours for alpha-smooth muscle actin, a definitive marker of myofibroblasts, nuclei and F-actin.

Results: Myofibroblast phenotype was characterized by the amount of α-SMA expressed by cells on each substrate. Fibroblasts on TCP demonstrated 100% α-SMA expression. Myofibroblasts on the 30kPa PAA gel exhibited an increased spread area, actin stress fiber assembly, and elevated expression of α-SMA at 67% ± 3.23. Myofibroblasts on 10kPa substrates showed reduced α -SMA expression of 41% ± 3.42 with a relatively lower spread area. In contrast cells on the softer gels were notably smaller with less stress fiber formation. The soft 300Pa PAA substrate showed minimal α-SMA expression 12% ± 2.91. Strikingly, cells grown on 300Pa HA retained their myofibroblast phenotype with prominent α-SMA expression 54% ± 5.65.

Conclusion: These results indicate that ECM elasticity and composition play an important role in fibroblast transdifferention. By selectively altering mechanical and biochemical milieu using tissue engineering strategy, it may be possible to induce dedifferentiation (reverse-remodeling) of the myofibroblast phenotype.