N-Cadherin mediated mechanosensitivity and its role in myocyte cytoskeleton remodeling:

Background: Myocardial mechanical integrity

1. Cell-matrix and cell-cell adhesions are crucial in maintaining the structural integrity and contractile function of cardiac myocytes.

Changes or disruptions to these adhesions can have adverse effects on myocyte shape and cytoskeletal architecture, resulting in loss of mechanical and electrical syncytium seen in heart failure.

Hypothesis:

N-Cadherin mediated mechanosensitivity and its role in myocardial mechanical integrity.

Myocardial scar is considerably stiffer than normal tissue; myocytes at its border zone experience a significantly stiffer environment which results in altered structure/morphology of these cells.

Cell-cell adhesion model system

1. Cell-cell interactions create a mechanical continuum, transmitting forces across the cell network.

2. Cardiac myocytes express N-Cadherins within the intercalated discs, connected to the cytoplasmic machinery.

Cardiomyocytes on ECM-coated substrates of varying stiffness:

1. Cardiomyocytes on ECM-coated substrates display significantly different morphology compared to that of aggregates.

N-Cadherins on ECM-coated substrates of varying stiffness display differential morphology, indicating that cells generate varying forces via integrin-mediated adhesion.

Cardiomyocytes on N-Cad-coated substrates of varying stiffness:

1. Cardiomyocytes on N-Cad-coated substrates display differential morphology, indicating that cells generate varying forces via N-Cad-mediated adhesion.

N-Cadherin Average Area

N-Cadherin Average Aspect Ratio

Cardiomyocytes on N-Cad-coated substrates of varying stiffness:

1. Cardiomyocytes on N-Cad-coated substrates of varying stiffness display differential morphology, indicating that cells generate varying forces via N-Cad-mediated adhesion.

N-Cadherin Average Area

N-Cadherin Average Aspect Ratio

Conclusion:

1. Changes in cellular structural and functional properties (spread area, aspect ratio, stiffness modulus as measured by AFM) in response to imposed substrate stiffness show that cell-cell mediated adhesions are capable at a macro-level to mechanically alter myocyte behavior.

2. These studies show, for the first time, that N-Cad-mediated structural response to the mechanical microenvironment can alter the cytoskeletal organization in a manner similar to integrins.

3. These results have broad implications in understanding remodeling associated with heart failure and therapies such as mechanical ventricular assistance.

Cell stiffness measurement by AFM on N-Cad-coated gels:

1. Atomic Force Microscopy measurements indicate that cell stiffen in response to the imposed stiffness of the adhesion surface.

Acknowledgements:

This work was supported by NIH grants HL099806 and HL123413, and by grants from the American Heart Association, Philadelphia Affiliate.