PATTERN CORRELATION REVEALS CHANGE OF SR/SL JUNCTION ARCHITECTURE IN FAILING HEART.

Tytus Bernas[1], Zachary Wilson[2], Gea-Ny Tseng[2]

[1] Department of Anatomy, and Neurobiology, Virginia Commonwealth University
[2] Department of Biophysics, Virginia Commonwealth University
1101 East Marshall Street, Richmond, VA 23298, USA

E-mail: Tytus.Bernas@vcuhealth.org

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Introduction Junctions between sarco/endoplasmic reticulum (SR/ER) and sarcolemma (SL), where Ca-induced Ca release (CICR) takes place, are important for myocardial contractility. Junctophilin-2 (JPH2) is the major SR/SL tether in cardiomyocytes.
Hypothesis JPH2 interacts with diverse proteins depending on its subcellular location. Furthermore, JPH2's distribution and relations with its interactors are subject to remodeling in diseased state.
Methods We studied spontaneously hypertensive rats (SHR): 2-3 months (SY, healthy) and ≥ 20 months (SO, in heart failure). We used immunoprecipitation (IP) and global unbiased search (proteomics) to identify JPH2's interactors in cardiomyocytes. We use 3D imaging (image scanning, SIM), followed by deconvolution and 2D localization microscopy to probe cellular distribution of JPH2 and its interactors at multiple scales. The JPH interactions are then quantified with object-based segmentation, nearest-neighbor distance distribution and signal density correlation.
Results Based on proteomics JPH2's interactors are involved in: SR/ER function, sub-sarcolemma scaffold, ion transporters/channels and intercalated disc (ICD) organization. We quantified spatial relationships between JPH2 and 4 interactors representing distinct subcellular compartments: RyR2 (junctional SR), Cav1.2 (t-tubules), dystrophin (peripheral SL) and connexin-43 (ICD). In SY myocytes, JPH2 is well organized along the z-lines and peripheral SL, consistent with close and reciprocal association in JPH2/RyR2 and JPH2/dystrophin. In SO myocytes, JPH2 is dispersed from z-lines but stays close to peripheral SL and clusters to ICD. Consequently, the proximity between JPH2 and Cav1.2 or RyR2 is reduced, but JPH2 comes into closer contact with connexin-43. These interactions are manifested at different spatial scales in SY and SO myocytes.
Conclusions In failing heart, a portion of JPH2 shifts from t-tubule/SR junctions (where CICR occurs) to ICDs (where store-operated Ca entry 'SOCE' occurs), likely contributing to dysregulation of intracellular Ca handling.