A CRITICAL ROLE OF TRPC1-ORA1-STIM1 MEDIATED STORE OPERATED CALCIUM ENTRY IN CARDIAC HYPERTROPHY

Poster Contributions
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Authors: Senthil Selvaraj, Brij Singh, Christian Bollensdorff, Jassim Al Suwaidi, Magdi Yacoub, Qatar Cardiovascular Research Center, Doha, ND, Qatar

Background: The increase in intracellular Ca2+ ([Ca2+]i) plays an important role in the development of hypertrophy. It is generally thought that store operated calcium channels (SOC's) are responsible for [Ca2+]i elevation and provide a unique source of Ca2+ to activate cardiac hypertrophy through calcineurin mediated-nuclear factor of activated T-cells (NFAT) signaling. However, the exact molecular components constituting this process in cardiomyocytes and possible role in hypertrophic signaling remain elusive.

Methods and Results: H9C2 cardiomyocytes were exposed to vehicle or hypertrophic stimuli agents, angiotensin II or endothelin 1 for 24h. Angiotensin II or endothelin 1 treatment significantly induced SOCE subsequent NFAT nuclear translocation compared with vehicle treatment. The level of TRPC1 and Orai1 expression were increased (~2 fold) in HC. Silencing either TRPC1 or Orai1 by respective siRNA's attenuates SOCE and NFAT activation in HC suggest that SOC's signaling complex composed of TRPC1 and Orai1. Co-immunoprecipitation of STIM1, a Ca2+ sensor in the sarcoplasmic reticulum (SR), showed that the functional interaction between STIM1 with TRPC1 or Orai1 was also increased in HC than control cells. Membrane localization studies revealed that TRPC1 co-localize to Orai1 within LRD. TRPC1 and Orai1 predominantly present in the non-raft domain (NRD) in control cells whereas hypertrophic stimuli activated the movement of TRPC1 and Orai1 from NRD to LRD where these proteins interact and form the functional SOC channel. Cholesterol depletion by simvastatin markedly reduced the TRPC1-Orai1 mediated Ca2+ entry in hypertrophic cardiomyocytes by abolishing the STIM1 interaction with TRPC1-Orai1.

Conclusion: This study indicates that calcium influx through TRPC1-Orai1-STIM1 ternary complex is critical for Ca2+ dependent control of cardiac hypertrophy. The LRD is important for the formation of TRPC1, Orai1 and STIM1 ternary complex and subsequent activation of SOCE in hypertrophic cardiomyocytes. Simvastatin treatment affects the LRD and thereby dissociates the dynamic assembly of TRPC1-Orai1-STIM1 and revert the hypertrophic response.