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Structural elements of stromal interaction molecule mediated store operated calcium entry regulation

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Abstract:

Calcium (Ca2+) is a universal signaling entity in eukaryotic cells mediating diverse processes such as the immune response, hypertrophy, apoptosis, platelet aggregation and memory, to name a few. These processes require a sustained elevation of cytosolic Ca2+ levels which is facilitated by store operated Ca2+ entry (SOCE). SOCE is the process whereby endoplasmic reticulum (ER) luminal Ca2+ depletion signals the opening of ion channels on the plasma membrane (PM) which facilitate the movement of Ca2+ down the concentration gradient from the extracellular space into the cytosol. Th e principal molecules that mediate SOCE include the ER resident stromal interaction molecule-1 (STIM1) and PM ORAI1 protein subunits which assemble into a channel pore. Upon ER luminal Ca2+ depletion, STIM1 undergoes a destabilization coupled oligomerization which leads to translocation of this Ca2+ sensor to ER-PM junctions where it couples to ORAI1 subunits and opens these PM Ca2+ channels. Since the identification of STIM1 and ORAI1 as the principal molecules driving SOCE, considerable progress has been made elucidating their high-resolution structural mechanisms of action. Author will present available structural data on the STIM1 Ca2+ sensing mechanism and how this regulator may complex to ORAI1 subunits. Th e coupling mechanism revealed using soluble human STIM1 and ORAI1 fragments are congruent with the hexameric assembly elucidated in the D. melanogaster crystal structure. Finally, author will present unpublished work showing how post translational modifications within the luminal domain of STIM1 aff ects the structural mechanisms of Ca2+ sensing. Ultimately, the post-translation modifi cation driven STIM1 structural and biophysical changes have implications in the agonist induced hypertrophic response and pinpoint a new therapeutic target for heart disease.

Biography:

Peter B Stathopulos applies structural biology approaches to reveal molecular mechanisms driving calcium signaling processes in health and diseased states including heart disease, cancer and immunodefi ciency. He integrates nuclear magnetic resonance spectroscopy and x-ray crystallography with a host of biophysical, chemical biology and live cell methodologies to understand the relationship between structure and function of critical calcium signaling proteins. Ultimately, this structure-function data is used for the rational identifi cation of new drug binding targets with the potential to modulate these pathways to maintain health or treat disease.

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