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

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Calcium (Ca^{2+}) 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 Ca^{2+} levels which is facilitated by store operated Ca^{2+} entry (SOCE). SOCE is the process whereby endoplasmic reticulum (ER) luminal Ca^{2+} depletion signals the opening of ion channels on the plasma membrane (PM) which facilitate the movement of Ca^{2+} down the concentration gradient from the extracellular space into the cytosol. The 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 Ca^{2+} depletion, STIM1 undergoes a destabilization coupled oligomerization which leads to translocation of this Ca^{2+} sensor to ER-PM junctions where it couples to ORAI1 subunits and opens these PM Ca^{2+} 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 Ca^{2+} sensing mechanism and how this regulator may complex to ORAI1 subunits. The 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 Finally, author will present unpublished work showing how post translational modifications within the luminal domain of STIM1 affects the structural mechanisms of Ca^{2+} sensing. Ultimately, the post-translation modification driven STIM1 structural and biophysical changes have implications in the agonist induced hypertrophic response and pinpoint a new therapeutic target for heart disease.

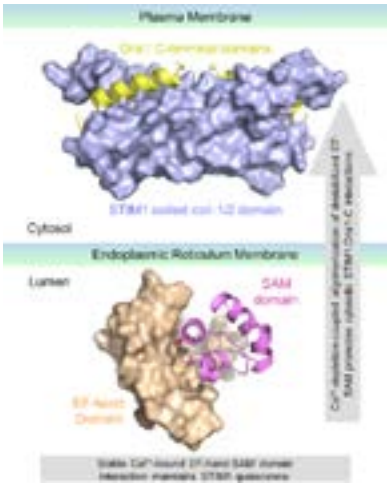

Figure 1: Solution NMR structures of the Ca2+-loaded STIM1 EF-SAM domain and the STIM1 coiled-coils in complex with two Orai1 C-terminal domains. Under Ca2+ replete conditions, EF-SAM adopts a compact conformation, mediated by intimate interactions between the EF-hand (beige) and SAM (violet) domains. Upon ER-luminal Ca2+ depletion, EF-SAM is destabilized and self-associates, promoting a conformational change in the STIM1 cytosolic domains (blue) which culminates in binding with the Orai1 C-terminal helices (yellow).

Recent Publications

1. Zhu J, Feng Q and Stathopulos P B (2017) The STIM-Orai pathway: STIM-Orai structures: isolated and in complex. Advances in Experimental Medicine and Biology 993:15-38.
2. Choi Y J, Zhu J, Chung S, Siddiqui N, Feng Q and Stathopulos P B (2017) Targeting cysteine thiols for *in vitro* site-specific glycosylation of recombinant proteins. Journal of Visualized Experiments DOI: 10.3791/56302.
3. Stathopulos P B and Ikura M (2017) Store operated calcium entry: From concept to structural mechanisms. Cell Calcium 63:3-7.
4. Choi Y J, Zhao Y, Bhattacharya M and Stathopulos P B (2017) Structural perturbations induced by Asn131 and Asn171 glycosylation converge within the EFSAM core and enhance stromal interaction molecule-1 mediated store operated calcium entry. Biochimica et Biophysica Acta 1864(6):1054-1063.
5. Lee S K, Shanmughapriya S, Mok M C Y, Dong Z, Tomar D, Carvalho E, Rajan S, Junop M S, Madesh M and Stathopulos P B (2016) Structural insights into mitochondrial calcium uniporter regulation by divalent cations. Chemistry & Biology 23(9):1157-1169.

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 immunodeficiency. 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 identification of new drug binding targets with the potential to modulate these pathways to maintain health or treat disease.

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