A molecular mechanism for Orai1 channel activation by STIM1

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Store operated calcium entry (SOCE) represents a key mechanism by which cells generate Ca^{2+} signals and maintain Ca^{2+} homeostasis by replacing Ca^{2+} lost from endoplasmic reticulum (ER) with Ca^{2+} that enters the cytoplasm through plasma membrane channels. SOCE was characterized biophysically over a 20-year period and the field exploded recently with the identification of the genes that encode its essential proteins. The primary components are STIM1, the Ca^{2+} sensor of the ER, which is activated when the ER is depleted of Ca^{2+} and then activates the plasma membrane Ca^{2+} release activated Ca^{2+} (CRAC) channel, and Orai1, the CRAC channel pore forming subunit. Abnormal SOCE due to aberrant expression or function of STIM1 and Orai1 is implicated as a leading cause of several diseases including chronic inflammation, muscle weakness, and a severe combined immunodeficiency syndrome. Yet, although the process of Orai1 channel activation by STIM1 has been intensely investigated the molecular and structural basis of how STIM1 regulates the opening of the Orai1 channel pore remains poorly understood. Here, I will discuss recent work in our laboratory that seeks to understand how coupling with STIM1 leads to molecular rearrangements in the Orai1 channel protein underlying the opening of the channels pore.