STIM calcium sensing and conformational change

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STIM1 and STIM2 are ER membrane proteins that sense decreases in ER-luminal free Ca^{2+} and— through a conformational change in the STIM cytoplasmic domain— control gating of the plasma membrane Ca^{2+} channel ORAI1.

To understand how STIM proteins monitor ER-luminal Ca^{2+} levels, we undertook a close examination of Ca^{2+} binding and the resulting conformational change, using soluble STIM1 constructs with geometric constraints resembling those on the luminal domain in native STIM1. We find that the STIM1 luminal domain has 5–6 previously undetected binding sites for Ca^{2+} at physiological concentrations, that occupancy of these sites acts as a latch to prevent Ca^{2+} dissociation from the EF-hand site, and that loss of Ca^{2+} from all the sites induces a switch from the known Ca^{2+}-bound structure to a second structured conformation. Altering Ca^{2+} binding at the novel sites by engineered mutations retunes STIM1 Ca^{2+} sensitivity in cells, confirming the physiological relevance of the latching mechanism.

To determine how STIM conveys a signal from the ER lumen to the cytoplasm, we studied the Ca^{2+}-dependent conformational change of engineered STIM1 proteins in isolated ER membranes and, in parallel, the physiological activation of the same engineered proteins in cells. We find that conserved ‘sentinel’ features of the CC1 region help to prevent STIM activation while Ca^{2+} is bound to the STIM ER-luminal domains. Reduced ER-luminal Ca^{2+} drives a concerted conformational change in which the paired luminal domains of a STIM dimer rearrange and the STIM transmembrane helices and initial parts of the CC1 regions pair in an extended coiled coil. This intradimer rearrangement overcomes the relatively weak CC1-SOAR/CAD interactions that hold STIM in an inactive conformation, releasing the SOAR/CAD domain to activate ORAI channels.

Our findings provide new insight into Ca^{2+} sensing by STIM proteins, in particular pointing to molecular mechanisms that govern the Ca^{2+} threshold for activation, that can explain the steep Ca^{2+} concentration dependence of activation, and that underlie the concerted conformational change from inactive to active STIM.