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# Molecular key determinants controlling the communication of STIM1 and Orai


**Abstract**

Calcium ($Ca^{2+}$) ions are essential in the control of many steps throughout the cell's life and ensure for example the immune response or muscle contraction. Altered $Ca^{2+}$ ion concentrations in the cell can lead to diseases such as immune deficiency or the development of cancer. $Ca^{2+}$ enters the cell via specific ion pores in the plasma membrane, the so-called ion channels. One prominent $Ca^{2+}$ ion channel represents the $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channel. Its unique features among the huge variety of $Ca^{2+}$ ion channels represent its hexameric stoichiometry and its composition of two components. It is fully reconstituted by the two proteins STIM1 and Orai. STIM1 is located in the $Ca^{2+}$ stores within the cell and functions there as a $Ca^{2+}$ sensor. Orai represents a highly $Ca^{2+}$ selective ion channel in the plasma membrane. Depletion of the $Ca^{2+}$ stores in the cell leads to the activation of the STIM1 and Orai proteins. A direct coupling of these two components initiates the transport of $Ca^{2+}$ across the Orai ion channel into the cell. Here, I will provide an overview on the key structures that establish and ensure an intact communication and typical biophysical properties of the STIM1 and Orai proteins [1-6]. Detailed insight will be given into the modulation of this $Ca^{2+}$ transport system by the lipid cholesterol [7]. Moreover, I will delineate potential mechanisms for the opening of the Orai ion channel pore. A detailed understanding of this $Ca^{2+}$ signaling mechanism provides novel targets for therapeutic approaches[8] against diseases such as allergies or cancer.



1. Fahrner, M. *et al.* Communication between N terminus and loop2 tunes Orai activation. *J Biol Chem* **293**, 1271-1285 (2018).
2. Derler, I. *et al.* Authentic CRAC channel activity requires STIM1 and the conserved portion of the Orai N terminus. *J Biol Chem* **293**, 1259-1270 (2018).
3. Derler, I., Jardin, I. & Romanin, C. Molecular mechanisms of STIM/Orai communication. *Am J Physiol Cell Physiol* **310**, C643-662 (2016).
4. Derler, I. *et al.* The extended transmembrane Orai1 N-terminal (ETON) region combines binding interface and gate for Orai1 activation by STIM1. *J Biol Chem* **288**, 29025-29034 (2013).
5. Muik, M. *et al.* Dynamic coupling of the putative coiled-coil domain of ORAI1 with STIM1 mediates ORAI1 channel activation. *J Biol Chem* **283**, 8014-8022 (2008).
6. Derler, I. *et al.* Increased hydrophobicity at the N terminus/membrane interface impairs gating of the severe combined immunodeficiency-related ORAI1 mutant. *J Biol Chem* **284**, 15903-15915 (2009).
7. Derler, I. *et al.* Cholesterol modulates Orai1 channel function. *Sci Signal* **9**, ra10 (2016).
8. Derler, I. *et al.* The action of selective CRAC channel blockers is affected by the Orai pore geometry. *Cell Calcium* **53**, 139-151 (2013).


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