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.