P30651: **Interactions of and within Orai proteins control Orai channel function**

The present project **"Interactions of and within Orai proteins control Orai channel function"** aims to enhance the knowledge about the Ca^{2+} release-activated Ca^{2+} (CRAC) channel, a prominent Ca^{2+} entry pore in living cells. Ca^{2+} ions are indispensable for a variety of signalling processes within mammalian cells, controlling processes such as their growth, gene expression and the function of the immune system. CRAC ion channels are fully reconstituted by the two molecular key players STIM1 and Orai. Defects in those proteins can cause diverse pathologies like immune dysfunction, highlighting the clinical relevance of CRAC channels.

The major goal of the presented research is to provide detailed, so far unknown, regulatory mechanisms on the assembly and activation of the Orai pore.

Orai channels are known to form hexameric complexes composed of six Orai subunits, however, how their assembly is established has remained elusive so far. We assume that individual neighbouring Orai subunits form interactions, stabilizing the functional hexameric Orai channel complex, which we aim to uncover here. Further, the mechanisms involved in activation of Orai channels have so far only been partially understood. Basically, STIM1 coupling to the Orai channel results in pore opening, however, how the activation signal of STIM1 binding propagates to the pore in detail has remained unclear. We assume that the Orai channel undergoes a global conformational change from the closed to the open state, involving break or formation of a series of interactions between adjacent and within single Orai subunits. Here, we aim to elucidate those interactions as well as their progression upon STIM1 coupling leading to an open Ca^{2+} pore. In order to identify essential interactions between and within Orai subunits, we will employ a combined approach of molecular biology, biochemistry and biophysics, which will be complemented by simulation and structural studies.

In aggregate, this project will provide fundamental insights into molecular mechanisms governing Orai channel assembly. Moreover, detailed conformational changes within the Orai channel upon its activation will be resolved. Gained knowledge within this project provides novel targets to interfere with the assembly or activation steps of the CRAC channel for therapeutic treatments of immune deficiency, autoimmune or allergic disorders.