Molecular components of store-operated Ca^{2+} entry in liver cells

G.Y. Rychkov, School of Molecular and Biomedical Science, University of Adelaide, Adelaide, SA 5005, Australia.

To maintain Ca^{2+} homeostasis and to deliver Ca^{2+} to the right place at the right time living cells use a complex array of Ca^{2+} pumps, transporters and ion channels. It has been generally accepted that in most animal cells replenishment of Ca^{2+} lost due to the activity of plasma membrane Ca^{2+}-ATPase is mediated through a store-operated Ca^{2+} entry (SOCE) mechanism. According to this theory, release of Ca^{2+} from the intracellular Ca^{2+} stores caused by hormone binding to G-protein- or tyrosine kinase- coupled receptors activates store-operated Ca^{2+} channels (SOCs) in the plasma membrane. Recent evidence suggests that the Ca^{2+} release activated Ca^{2+} channel expressed in hematopoietic cells, which is the best characterised SOC, is composed of Orai1 polypeptides that interact with STIM1 (Stromal interaction molecule 1), an EF hand containing, Ca^{2+}-binding polypeptide which senses the decrease in Ca^{2+} in the ER. Depletion of intracellular Ca^{2+} stores causes STIM1 to accumulate in areas of junctional ER located in close proximity to the plasma membrane, while Orai1 accumulates in the areas of plasma membrane apposed to STIM1 puncta. Utilizing siRNA mediated knockdown we have shown that STIM1 and Orai1 proteins are major components of SOCE in liver cells. However, there is evidence that several other proteins are also involved. Knockdown of PLC-γ1 in H4-IIE cells substantially decrease the amplitude of I_{SOC} initiated by either IP_3 or thapsigargin. No interaction between PLC-γ1 and STIM1 is detected in immunoprecipitation experiments. This suggests that PLC-γ1 is required to couple ER Ca^{2+} release to the activation of SOCs independently of any PLC-γ1-mediated generation of IP_3 and independently of a direct interaction between PLC-γ1 and STIM1. The likelihood that there are additional to STIM1 and Orai1 proteins that are involved in SOCE is supported by our recent results of the ectopic expression of STIM1 and Orai1 in liver cells. We have found that some biophysical properties of the Orai1/STIM1 current vary significantly between transfected cells and depend on the levels of expression of STIM1 and Orai1.