Store operated Ca^{2+} channels and microdomains of Ca^{2+} in liver cells

G.J. Barritt,[1] T.L. Litjens,[2] J. Castro,[1] E. Aromataris[2] and G.Y. Rychkov,[2] [1]Department of Medical Biochemistry, School of Medicine, Flinders University, P.O.Box 2100, Adelaide, SA 5001, Australia and [2]Department of Physiology, School of Molecular and Biomedical Science, University of Adelaide, Adelaide, SA 5005, Australia.

Oscillatory increases in the cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_{cyt}$) play essential roles in the hormonal regulation of animal cells. Increases in $[Ca^{2+}]_{cyt}$ require the release of Ca^{2+} from the endoplasmic reticulum (ER) and Ca^{2+} entry across the plasma membrane. Store-operated Ca^{2+} channels (SOCs), activated by a decrease in Ca^{2+} in the lumen of the ER, are responsible for maintaining adequate ER Ca^{2+}. We are studying the nature and mechanism of activation of SOCs in liver cells. Patch clamp recording and fura-2 experiments indicate there is only one type of SOC in hepatocytes. These SOCs have a high selectivity for Ca^{2+} and properties essentially indistinguishable from those of Ca^{2+} release-activated Ca^{2+} (CRAC) channels. Orai1, a CRAC channel pore protein, and Stim1, a CRAC channel Ca^{2+} sensor, are components of liver cell SOCs. Recent studies in this laboratory have been directed to an investigation of the role of a sub-region of the ER in liver cell SOC activation (shown schematically in the figure). Experiments employing ectopically expressed TRPV1, localised in intracellular membranes, as an alternative method to deplete ER Ca^{2+}, have provided evidence that only a small component of the ER is required for the activation of SOCs. Consistent with this conclusion are the results obtained with choleretic bile acids, which activate SOCs without detectable Ca^{2+} release from the ER. Three aspects of Ca^{2+} microdomains appear to be important in SOC action. (i) The activation process probably requires a decrease in Ca^{2+} near the SOC channels at the cytoplasmic side of the plasma membrane. (ii) There is strong feedback of Ca^{2+} entry through Ca^{2+} localised at the mouth of the channel. (iii) A number of experiments indicate that Ca^{2+} in microdomains near the SOC channel has specific regulatory functions such as regulation of adenylate cyclase. Current experiments are directed to further elucidation of these microdomains of Ca^{2+}.