Regulation of Calcium Entry via Plasmalemmal Calcium Channels by Intracellular Calcium Release Channels in Human Lymphocytes

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Calcium ions (Ca^{2+}) play a critical role in T-lymphocyte activation. Plasmalemmal Ca^{2+} channels activated upon Ca^{2+} store depletion serve as the major mechanism for extracellular Ca^{2+} entry, which is necessary for T cell activation. Due to limited capacity of intracellular Ca^{2+} store, the main role of the intracellular Ca^{2+} release channels located in the internal membranes (inositol trisphosphate receptors (IP_3R) and ryanodine receptors (RyR)) is believed to be limited to store depletion with consequent activation of Ca^{2+} entry via plasmalemmal channels. Because both IP_3R and RyR have multiple Ca^{2+} binding sites, we hypothesized that they can be modulated by Ca^{2+} that entered the cell via plasmalemmal channels and can affect intracellular Ca^{2+} dynamics during T-cell activation.

We developed experimental approach that allowed a simultaneous evaluation of store-operated Ca^{2+} influx and Ca^{2+} content within the store by monitoring changes in cytosolic Ca^{2+} concentration ($[\text{Ca}^{2+}]_i$). Using this approach we discovered that the elevation in $[\text{Ca}^{2+}]_i$ caused by Ca^{2+} entry inversely correlated with Ca^{2+} content within the store. In addition, in cells pre-

incubated with IP_3R and RyR blockers, the $[\text{Ca}^{2+}]_i$ elevation following the Ca^{2+} entry via store-operated Ca^{2+} channels was significantly reduced, whereas Ca^{2+} release induced by inhibitors of sarco-endoplasmic reticulum Ca-ATPase increased significantly. We conclude that in T-cells intracellular Ca^{2+} release channels control Ca^{2+} entry via plasmalemmal Ca^{2+} channels by regulating Ca^{2+} accumulation within the store following activation of Ca^{2+} entry.

Furthermore, the importance of the intracellular Ca^{2+} release channels in normal immune response was underscored by our findings that IP_3R and RyR inhibitors significantly suppressed secretion of interleukin 2 and proliferative activity of activated T-cells. Taken together, our data indicate that IP_3R and/or RyR can be used as molecular targets for suppression of functions of activated T-cells in treatment of autoimmune disorders.

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