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Calcium signals in lymphocyte activation and disease

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Calcium ions function as universal second messengers in virtually all eukaryotic cells including cells of the immune system where they are crucial for the function of T and B cells, mast cells and dendritic cells. The predominant mechanism regulating intracellular Ca^{2+} levels in cells of the adaptive immune system is store-operated Ca^{2+} influx through so-called Ca^{2+}-release activated Ca^{2+} (CRAC) channels. We identified ORAI1 (also named CRACM1) as a pore subunit of the CRAC channel essential for the function of T cells and mast cells. ORAI1/CRAC channels are activated when intracellular Ca^{2+} stores are depleted. The resulting decrease in the ER Ca^{2+} concentration is sensed by stromal interaction molecule 1 (STIM1) that is required for activation of ORAI1/CRAC channels. We showed that murine T cells lacking STIM1 exhibit severely impaired store-operated Ca^{2+} influx. T cells from mice lacking STIM1 or its paralogue STIM2 both showed significantly reduced cytokine production in vitro and a defect in regulatory T cell development as well as lympho- and myeloproliferation *in vivo*. Mutation of ORAI1 in humans is associated with severe combined immunodeficiency (SCID), increased susceptibility to infections and a failure to thrive. A similar defect is found in mice transgenic for the equivalent R93W mutation in murine ORAI1, which all but abrogates CRAC channel function and T cell activation. Taken together STIM1, STIM2 and ORAI1 are essential regulators of store-operated Ca^{2+} entry in cells of the immune system and other tissues.