CDB SEMINAR

Masatsugu Oh-hora

Pediatrics Department, Harvard Medical School

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15:00~16:00 A7F CDB Conference Room

Roles of the Store-operated Ca^{2+} entry in T cell development and function

Summary

Store-operated Ca^{2+} entry via the Ca^{2+} release-activated calcium (CRAC) channel is the predominant mechanism of intracellular Ca^{2+} increase in stimulated immune cells. CRAC channels open after endoplasmic reticulum (ER) Ca^{2+} stores are depleted by inositol trisphosphate (IP3) binding to IP3 receptors. Sustained Ca^{2+} influx drives diverse functions of immune cells including T cell differentiation and cytokine expression. Recently, we and others used genome-wide RNAi screens in *Drosophila* to identify two key molecules controlling CRAC channel activity, the ER Ca^{2+} sensor Stim and a pore subunit of the CRAC channel, Orai. We also found that cells from patients with hireditary severe combined immune deficiency syndrome have a single missense mutation in *Orai1*. *Drosophila* Stim and its mammalian homologues, Stim1 and Stim2, are single-pass transmembrane proteins thought to sense ER Ca^{2+} levels through Ca^{2+}-binding EF hands located in the ER lumen. Stim1 is an established positive regulator of store-operated Ca^{2+} entry, but the function of Stim2 is controversial. To investigate the physiological roles of Stim1 and Stim2, we generated mice with conditional deletion of the *Stim1* and *Stim2* genes. We show that Stim1 is a predominant effector of store-operated Ca^{2+} entry in naïve T cells and mouse embryonic fibroblasts (MEFs), and its deficiency severely impairs T cell cytokine expression. In contrast, Stim2 has little effect on store-operated Ca^{2+} entry in naïve T cells, but contributes significantly to store-operated Ca^{2+} entry in MEFs and to cytokine expression by differentiated T cells, in part by sustaining the late phase of NFAT nuclear localisation. Thus Stim1 and Stim2 are both positive regulators of Ca^{2+}-dependent cytokine expression in differentiated T cells; the more abundant Stim1 is essential for response initiation but modest amounts of Stim2 have a crucial role in bolstering the function of Stim1. We also discuss some *in vivo* phenotypes of Stim1 and Stim2 double knockout mice.

Host:
Shinichi Nishikawa
Stem Cell Biology, CDB
nishikawa@cdb.riken.jp
Tel:078-306-1893
(ext : 5301)