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Strong TCR/calcium signaling specifically controls the development of regulatory T cell subsets

Masatsugu Oh-hora[1, 3,-5], **Noriko Komatsu**[3, 4], **Stefan Feske**[6], **Shohei Hori**[7], **Anjana Rao**[1, 8], **Hiroshi Takayanagi**[2-4, 9, 10]

[1]Department of Pathology, Immune Disease Institute and Program in Cellular and Molecular Medicine, Children's Hospital, Harvard Medical School, Boston, MA, USA, [2]Department of Immunology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Japan, [3]Department of Cell Signaling, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [4]Global Center of Excellence (GCOE) Program, International Research Center for Molecular Science in Tooth and Bone Diseases,, Japan, [5]Japan Science and Technology Agency (JST), Precursory Research for Embryonic Science and Technology (PRESTO) program, Tokyo, Japan, [6]Department of Pathology, New York University, School of Medicine, New York, USA, [7]Research Unit for Immune Homeostasis, RIKEN Research Center for Allergy and Immunology, Kanagawa, Japan, [8]Present address: Division of Signaling and Gene Expression, La Jolla Institute for Allergy & Immunology, La Jolla, CA, USA, [9]Japan Science and Technology Agency (JST), Explorative Research for Advanced Technology (ERATO) program, Takayanagi Osteonetwork Project, Tokyo, 113-8549, Japan, [10]Centre for Orthopaedic Research, School of Surgery, The University of Western Australia, Nedlands, WA, Australia.

Abstract

T-cell receptor (TCR) signaling determines T cell fate in thymic development. Previous studies suggested that the magnitude and duration of calcium influx in thymocytes is determined by the affinity of TCR-peptide/MHC interactions, however, it is unknown how TCR-mediated calcium influx contributes to the lineage choice of T cells during thymic selection *in vivo*. In addition, although it has been widely assumed that store-operated calcium entry is essential for T cell development in the thymus, there is no direct evidence for this assumption. To address these questions, we have analyzed mice lacking STIM1 and STIM2, the two key mediators of

store-operated calcium entry, the primary mechanism for calcium influx in diverse non-excitable cell types including T cells.

We show here that surprisingly, lack of store-operated Ca^{2+} entry (SOCE) has no effect on conventional TCR$\alpha\beta^{+}$ T cell development including positive and negative selection, but SOCE specifically controls the development of self-reactive agonist-selected T cells including regulatory T cells, invariant natural killer T cells and TCR$\alpha\beta^{+}$ CD8$\alpha\alpha^{+}$ intestinal intraepithelial lymphocytes. Agonist selection of all T-lineage cells is achieved normally in the absence of STIM1 and STIM2, but there is a severe impairment of the post-selection proliferation and functional maturation of agonist-selected T cells. We have traced this to diminished expression of cytokine receptors and effector molecules due to inefficient expression of NFAT target genes. Consistent with this finding, double deletion of *Nfat1* and *Nfat2* in T cells with *LckCre* led to partial but specific reduction of agonist-selected T cells. These findings indicate that strong TCR/calcium signaling, leading to efficient NFAT activation, is critical for the development of agonist-selected T cells.