

A deficiency in Drak2 results in a T cell hypersensitivity

Maureen A. McGargill¹, Ben G. Wen², Craig M. Walsh³, and Stephen M. Hedrick¹

¹Division of Biology & UCSD Cancer Center, University of California, San Diego, La Jolla, CA 92093-0687; ²Department of Immunology, Genomics Institute of the Novartis Research Foundation, San Diego, CA 92121. ³Department of Molecular Biology and Biochemistry University of California, Irvine, Irvine, CA 92697-3900

The DAP kinase family is a subfamily of serine/threonine kinases which are capable of inducing apoptosis in a variety of cells. One member of this family, DRAK2 (DAP kinase-related apoptosis-inducing protein kinase), is expressed highly in the thymus, spleen, and lymph nodes. To investigate the role of this kinase in T cell development and function, we created DRAK2 deficient mice. Interestingly, there was no defect in apoptosis induced by various agents in either thymocytes or peripheral T cells. In addition, negative selection was unaffected in two *in vivo* models. However, to our surprise, DRAK2 deficient T cells fluxed increased levels of calcium, produced more IL-2, and proliferated to a greater extent in response to antigen than wildtype T cells. Furthermore, in the absence of DRAK2, T cells required less co-stimulation for antigen-induced proliferation than wildtype T cells. These data imply that DRAK2 negatively regulates TCR-induced signals. We are currently investigating the biochemical mechanism in which DRAK2 suppresses signals originating from the TCR. Preliminary data suggest that following antigenic stimulation, DRAK2 deficient T cells have decreased levels of activated NFATc2 in the nucleus compared to wildtype T cells. Interestingly, NFATc2 deficient T cells are hyperproliferative to antigen stimulation, similar to DRAK2 deficient T cells. Thus, DRAK2 may somehow affect the NFAT pathway of activation.