

Drak2, a negative regulator of lymphocyte signaling

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

¹Division of Biology, 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

Drak2 is a member of the DAP kinase family of serine/threonine kinases. Members of this family induce apoptosis in various cell types. Drak2, in particular, is highly expressed in T cells and B cells, and its expression in T cells is dramatically increased during the CD4⁺CD8⁺ stage of development in the thymus. To investigate the role of Drak2 in lymphocyte development and function, we generated Drak2 deficient mice. Surprisingly, Drak2 deficient mice had no defect in negative selection or antigen induced cell death. In fact, there was no defect in death initiated by a variety of apoptotic stimuli. However, there was an increase in development of CD4⁺ thymocytes, which was enhanced in the presence of a MHC class II-restricted TCR transgene. Even more surprising was the observation that Drak2 deficient T cells responded to CD3 stimulation in the absence of costimulation, and were hypersensitive to suboptimal stimuli. This hypersensitivity included an increase in calcium flux, CD25 expression, cytokine production, and proliferation. These data suggest that Drak2 functions as a negative regulator of T cell activation. Due to the fact that Drak2 deficient T cells respond to CD3 without costimulation, we hypothesized that the mice would have an increased propensity for autoimmune disease. However, much to our surprise, Drak2 deficient mice were remarkably resistant to antigen-induced experimental autoimmune encephalomyelitis (EAE).