Tec Kinase Deficient Mice

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Technology description

Summary

Stimulation of T lymphocytes through the T Cell Receptor (TCR) elicits broad responses required for proper immune function, including cell proliferation, cytokine production and apoptosis. Activation of distinct families of tyrosine kinases (Zap-70, Src) are important in TCR signalling, while the role of other tyrosine kinases, such as the Tec Kinases Rlk and Itk is less clear. However, evidence suggests that these kinases play a role in CD4+ T helper (Th) cell differentiation. Responses to infection are regulated in part by two distinct types of T helper cells, type 1 (Th1) and Th2 subclasses which produce different cytokines and have discrete effector functions. Th1 cells produce interferon-gamma (IFN-gamma), which is a key mediator of cellular immunity. In contrast Th2 cells produce interleukin 4 (IL-4), Il-5, Il-10, and Il-13 which assist humoral immunity and dominate immune responses to both helminths and allergens. Regulation of these subclasses is important not only for normal immune response, but also for abnormal disease processes, including autoimmunity and hypersensitivity. Generation of type 1 and type 2 Th cells is influenced by multiple factors including cytokines, costimulation and TCR-based signals. Understanding the mechanisms and signals important in T cell signalling is important for identifying new therapeutics that target Th1 and Th2-mediated pathologies (for example autoimmune disorders and asthma, respectively).

The Tec family of tyrosine kinases have been implicated as important mediators of polarized cytokine production and Th2 cell differentiation. Rlk is preferentially expressed in Th1 cells and Itk is important in Th2 response. Numerous studies have implicated alterations in the strength of TCR-mediated signals as playing important roles in Th cell differentiation. Researchers at the NIH have developed transgenic mouse models in order to address these issues. Rlk-deficient mice and Rlk/Itk double-deficient mice were generated and have been shown to have defects in TCR responses including proliferation, cytokine production and apoptosis in vitro and adaptive immune response to infectious agents in vivo (Science (1999) 284, 638-641; Nature Immunol. (2001) 2: 1183-188). Molecular analyses of cells from these mice indicate that these kinases are critical for proper regulation of phospholipase C, calcium mobilisation and ERK activation as well as activation of downstream transcription factors in response to T cell receptor stimulation. Defects are minor in Rlk-deficient animals and most severe in Rlk/Itk double-deficient mice. These mice provide a useful mechanistic model for dissecting out the complex

interactions of TCR signalling. Additionally, the mice are useful for evaluation of therapeutics directed at specific classes of diseases (Th1 or Th2) and the utility of potential global Tec kinase inhibitors.

Institution

NIH - National Institutes of Health