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National Institutes of Health

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A Mouse Model for Systemic Inflammation in Glucocerebrosidase-Deficient Mice With Minimal Glucosylceramide Storage

Richard L. Proia (NIDDK). DHHS Reference No. E-256-2003/0—Research Tool. *Licensing Contact:* Susan Carson; (301) 435-5020; carsonsu@mail.nih.gov.

Gaucher disease, the most common lysosomal storage disease, is an inherited metabolic disorder in which harmful quantities of the lipid glucocerebroside accumulate in the spleen, liver, lungs, bone marrow and in rare cases in the brain, due to a deficiency of the enzyme glucocerebrosidase (Gba) that catalyses the first step in the biodegradation of

glucocerebroside. Type 1 Gaucher disease is the most common and is distinguished from the other forms of the disease, types 2 and 3, by the lack of neurologic involvement. The clinical features of Type 1 are heterogeneous, vary broadly in clinical severity and affect many organ systems. The major disease manifestations include enlarged spleen and liver, bone lesions, hematologic abnormalities and lung involvement. The disease has also been associated with a sustained inflammatory reaction. Gaucher disease is most prevalent in the Ashkenazi Jewish population with an incidence of approximately 1 in 450 persons while in the general public the incidence is 1 in 100,000. There are an estimated 30,000 Gaucher disease patients world-wide with approximately 3000 patients currently receiving enzyme replacement therapy which has been shown to be highly effective in treatment of the disease. The cost of therapy is approximately \$100,000-\$300,000 annually and is a life-long treatment, which makes the case for affordable new therapies urgent.

The etiology of the disease has been difficult to study due to the absence of viable mouse models for the disease, as a complete disruption of the glucocerebrosidase (Gba) gene results in rapid neonatal death. In an attempt to produce a viable model scientists at the NIDDK introduced a human Gaucher disease point mutation, L444P, into the mouse Gba gene in order to cause a partial enzyme deficiency (J. Clin. Invest. (2002) 109, 1215-1221; Proc. Natl. Acad. Sci. USA (1998) 95, 2503-2508).

The mice exhibit a partial glucocerebrosidase deficiency (15-20% of normal activity), without bulk accumulation of glucosylceramide or the presence of Gaucher cells. The mice demonstrate other clinical features of Gaucher disease, including multisystem inflammation, B cell hyperproliferation, skin abnormalities, anemia and lymphadenopathy. These mice provide a useful model for studying certain aspects of Gaucher disease pathology and in evaluating new therapeutic treatments.

Tec Kinase Deficient Mice

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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: 1183-1188). 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.