

T-bet Targeted Mutation Mice

Targeted deletion of the T-bet gene creates a unique immune system phenotype useful for the study of asthma, Crohn's disease and colitis, inflammation and autoimmune disorders.

Applications of the T-bet Targeted Mutation Mouse Models

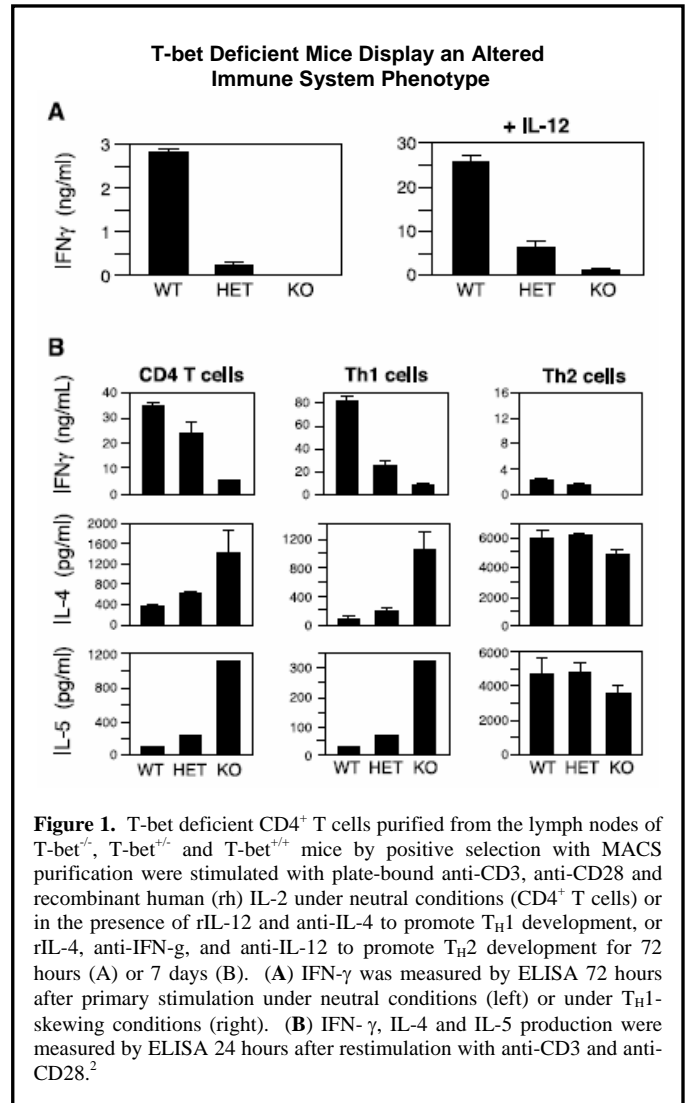
Taconic's T-bet Targeted Mutation Mice are homozygous for a targeted deletion of the *Tbx21* gene, a member of the T-box transcription factor family that controls expression of the cytokine IFN- γ .^{1,2} T-bet plays a critical role in the differentiation of CD4⁺ T helper precursor cells into T_H1 lymphocytes through the stimulation of IFN- γ . Disruption of T-bet results in altered cytokine production that shifts developing T helper precursor cells from a T_H1 lineage to a T_H2 lineage. There is also a decrease in NK cell function. This imbalance between the two T cell subsets results in the lack of functional T_H1 immune response, which protects against some autoimmune disorders such as inflammatory bowel disease. Conversely, the shift towards production of T_H2 cells predisposes the homozygous mutants to immune disorders in which T_H2 activity is implicated, such as spontaneous airway hyperreactivity and asthma. The T-bet Targeted Mutation Mice are thus good models for certain types of immune system hypersensitivity.

Applications include:

- Study of immune system development
- Characterization of the roles of T_H1 and T_H2 T cells in normal and disease processes
- Use as a model of human asthma and airway hyperresponsiveness
- Use in research involving Crohn's disease and colitis, cancer metastasis, inflammation and certain autoimmune disorders

Features of the T-bet Model

- Available on two backgrounds: model 003427-M is a homozygous knockout on a congenic C57BL/6 background. Model 03469-M is a homozygous knockout on a congenic BALB/c background.
- Homozygous mice lack T-bet RNA and protein, as measured in CD4 T cells.



Scientific Profiles of the T-bet Targeted Mutation Mouse Models

T-bet knockout mice have an altered immune system characterized by a decrease in production of the cytokine interferon- γ (IFN- γ) and a shift in T helper precursor cells toward the T_H2 subtype. CD4⁺ cells from T-bet^{-/-} mice produce very low levels of IFN- γ compared to wild type counterparts, which causes the failure of CD4⁺ T cells to

differentiate into the T_H1 subtype and the subsequent default of such cells to the T_H2 subtype. Production of IL-4 and IL-5 by these cells is elevated. NK cells isolated from T-bet^{-/-} mice produce much less IFN- γ and display diminished cytolytic function.² Under antigen-specific stimulation conditions, naive CD8⁺ cells of T-bet knockout mice do not differentiate properly into mature effector cells, display greatly reduced cytolytic activity and produce much less IFN- γ .²

Mice lacking T-bet spontaneously develop a phenotype similar to that of human acute and chronic asthma in the absence of allergen exposure. In humans, T-bet expression is lower in asthmatic lungs than controls. Without immunologic sensitization and challenge, both homozygous and heterozygous T-bet knockout mice exhibit airway hyperresponsiveness (AHR) in response to methacholine administration. Naïve T-bet deficient mice display airway remodeling as measured by increased collagen deposition beneath the basement membrane as well as increased numbers of bronchial myofibroblasts.⁴

T-bet knockout mice are more susceptible to T_H2-mediated colitis, whereas T-bet deficiency offers a protective effect in T_H1-mediated colitis models. Overexpression of T-bet has been found in humans with Crohn's disease compared to controls or patients with ulcerative colitis. Increased T-bet expression was also found in three animal models of T_H1-mediated chronic intestinal inflammation. In adoptive transfer experiments, T-bet deficiency had a protective effect against T_H1-mediated experimental colitis. However, mice homozygous for T-bet deletion are more susceptible to T_H2-mediated oxazolone-induced colitis than heterozygous or wild type mice.⁵

T-bet helps regulate cancer progression and primary tumor metastasis. T_H1 cells and IFN- γ play a role in antitumor responses to prostate cancer. In the transgenic adenocarcinoma mouse prostate (TRAMP) model, animals homozygous for T-bet deletion had a higher frequency of metastatic disease compared to T-bet^{+/+} animals. T-bet had no significant effect on primary tumor incidence.⁶

T-bet knockout mice are protected from the development of experimentally induced inflammatory arthritis. Compared to wild type controls, T-bet^{-/-} mice showed delayed onset of inflammation and decreased severity of disease.

Susceptibility to inflammatory arthritis was restored in homozygous T-bet knockout mice by adoptive transfer of wild type dendritic cells. T-bet deficient dendritic cells produced significantly lower levels of certain proinflammatory cytokines and displayed impaired ability to prime naïve T cells.⁷

T-bet deficient mice provide a unique model for the study of the regulation of humoral immune responses. The IgG2a Ig subclass has been implicated in the pathogenesis of autoimmune disease such as lupus. T-bet is required for class switch recombination to IgG2a in response to T cell-independent, but not T cell-dependent, stimuli. Specific IgG2a phenotypes show genetic background-dependent effects, with some T-bet knockouts of the BALB/c background showing low-titer IgG2a antibodies after immunization with a T cell-independent stimulus.⁸

Origins of the Models

The T-bet Targeted Mutation Mouse Models were developed by Dr. Laurie H. Glimcher and her colleagues at the Harvard School of Public Health and Harvard Medical School.^{2,4} TC-1 embryonic stem cells from 129S6/SvEvTac mice were gene targeted. Chimeric mice were mated to C57BL/6J females. Line 003427-M mice were mated to C57BL/6J females for nine generations. Line 003427-M mice were backcrossed to BALB/cJ mice for nine generations. Mice were received at Taconic in August of 2004 and embryo transfer derived by mating to C57BL/6JBom or BALB/cJBom mice, respectively. Mice are maintained at Taconic by inbreeding of homozygous mice.

Ready for Your Experiments

Taconic's T-bet Targeted Mutation Models are produced in Isolator Barrier Unit (IBUTM) facilities. Mice are shipped in Taconic Transport Cages (TTCTM) and come with an up-to-date health report documenting their Murine Pathogen Free (MPFTM) health status. Barrier housing conditions are recommended for maintenance of T-bet Targeted Mutation Mice.

Related Mouse Models from Taconic

Taconic provides a number of mouse models relevant to immunology. Call or fax for information about these additional models:

- **Stat1 Targeted Mutation Mouse (model 002045)** – carries a homozygous disruption of a gene involved in regulation of cellular signaling and transcription. The mice develop normally but do not respond at a cellular level to either induction by IFN- α or IFN- γ . Stat1 mice are very sensitive to infection by microbial pathogens and viruses. This model has applications in determining the role of a variety of cytokines in immune responses and in evaluation the role of STAT1 protein in mediating interferon-dependent responses and tumorigenesis.
- **Rag2 Targeted Mutation Mouse (models 000461, 000601, RAG2 and RAGN12)** – deficient in a gene responsible for development of the lymphocyte repertoire. Homozygous mutant mice show the total inability to initiate V(D)J rearrangement, resulting in the failure to generate mature T or B lymphocytes. This model can be used for vaccine development, transplantation studies and hematopoiesis research.

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