RESEARCH NEWS

The Tim Family: New Players in the Th1/Th2 Paradigm

A review of: Monney L, Sabatos CA, Gaglia JL *et al.* 2002 Th1-specific cell surface protein Tim-3 regulates macrophage activation and severity of an autoimmune disease. *Nature* 415:536–541

NAIVE T HELPER cells differentiate into one of two distinct subsets: T helper one (Th1) and T helper two (Th2) cells which are characterized both by cytokine profiles and their ability to contribute to either cell-mediated or humoral immune responses (1). In addition, Th1 and Th2 cells cross regulate each other's functions. For example, Th1 cells can suppress Th2 cells and vice versa. Current evidence suggests that an inappropriate balance in Th1 or Th2 development is involved in the pathogenesis of certain diseases. As an example, mice deficient in T-bet, a Th1 specific transcription factor that initiates Th1 differentiation, have a global increase in Th2 cells and spontaneously develop features of asthma (2). Significant data exists with regards to the molecular factors that mediate T cell differentiation. However, a recent paper by Monney *et al.* provides new information with respect to regulation of T cell differentiation and function (3).

Employing a simple and elegant strategy, monoclonal antibodies derived from mice immunized with Th1 cell lines or clones were screened for their ability to specifically recognize Th1 surface proteins. Using gene expression cloning, antibodies that were positive in the screening assay were subsequently utilized to identify a complementary DNA encoding a transmembrane protein called Tim-3 for T cell immunoglobulin- and mucin-domain- containing molecule. A human homologue of Tim-3 was also

NICOLA L. JONES

identified which resides on chromosome 5q33.2. Expression profiles showed Tim-3 was mainly restricted to Th1 and T cytotoxic 1 cells at a late stage of development suggesting a role in mediating effector functions but not in the polarization of lymphocytes. In addition, Tim-3 was expressed on CD4+ and CD8+ lymphocytes in brain tissue obtained from mice with experimental autoimmune encephalitis, which is thought to be a Th1-mediated disease. Furthermore, *in vivo* administration of anti-Tim-3 enhanced disease severity in this model. The more severe phenotype in anti-Tim-3 treated mice was associated with increased infiltration of activated macrophages at the site of injury.

Isolated splenocytes obtained from the anti-Tim-3 treated mice displayed an enhanced basal level of proliferation compared with splenocytes from control mice. The population of proliferating cells consisted of activated macrophages.

Recently, additional members of the Tim family have been identified, which currently includes Tim-1, Tim-2 and Tim-3 (4). Polymorphisms in Tim-1 and Tim-3 are associated with Th1 and Th2 cell differentiation and airway hyperactivity in a murine model. Thus, the Tim family is involved in modulating host immune responses likely by altering the Th1/Th2 balance. However, many questions remain regarding Tim-3 and the Tim

family. The ligand for Tim-3 is not known and the exact molecular mechanism by which Tim-3 engagement influences macrophages is not known. The importance of this gene family both in human health and disease such as during infection and in autoimmune conditions has yet to be elucidated. However, new insights into the molecular mechanisms by which Tim-3 and the Tim family modulate host immune responses should provide us with improved knowledge regarding the interactions between innate and acquired immune responses. In addition, future studies may demonstrate that the Tim family is a therapeutic target for the modulation of inflammatory diseases.

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Division of GI/ Nutrition
Infection, Immunity, Injury, Repair Program
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario M5G 1X8
Canada