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Tim-3: a novel TH1 defining surface antigen

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Keywords

EAE, TH1

Context

Antigen-activated naive T cells differentiate into TH1 or TH2 subsets depending upon various factors including cytokine signals they receive during initial antigen stimulation. However, although much is known about the biology and effector function of the T-helper cell subsets, there are few cell surface molecules that unambiguously distinguish between them. This paper describes a novel cell surface protein that is expressed on TH1 but not TH2 cells. *In vivo* data support an important role for this molecule in regulating the pathology of experimental autoimmune encephalomyelitis (EAE), a TH1 dependent autoimmune disease in mice.

Significant findings

To identify novel TH1-specific cell surface proteins, rats were immunised with TH1 T-cell lines and clones. By screening a large number of monoclonal antibodies (mAbs) the authors identified two mAbs that selectively stained TH1 cells. By gene-expression cloning they identified the target protein as Tim-3, a 281aa type 1 membrane protein with an extracellular domain consisting of an immunoglobulin variable region-like domain. Tim-3 is one of three family members (Kim-1, Tim-2 and Tim-3) and is located on chromosome 11 in the mouse. Cell surface expression of Tim-3 was also observed on $CD8^+$ Tc1 T cells and $CD11b^+$ cells, but not naive T cells, B cells, macrophages, or dendritic cells. Studies of Tim-3 expression in mice immunised with proteolipid protein 139-151 peptide demonstrated that Tim-3 mRNA expression in lymph nodes peaked just before the onset of EAE. To explore the role of Tim-3 in demyelinating disease, mice were treated with the anti-Tim-3 or control mAbs. Anti-Tim-3 treated mice developed a hyperacute and atypical EAE, characterized by an increased number of inflammatory foci and demyelinating lesions populated with an increased number of activated macrophages when compared to the control-immunoglobulin treated mice. Analysis of spleen cells showed that even in the

absence of specific antigen, basal cell proliferation was increased by 6-10-fold in anti-Tim-3 treated mice, with a twofold to threefold increase in the $CD11b^+$ cell population. BrdU labelling suggested that the high basal proliferation rate was due to activated $CD11b^+$ cells. Finally, experiments indicated that a cognate interaction between non-T cells and Tim-3 expressing TH1 cells is required to influence the expression of the disease phenotype.

Comments

This work documents a novel cell surface protein that may play important roles in macrophage activation in both health and disease. Previous studies have identified surface markers preferentially expressed on functionally distinct T-cell subsets including IL-12R, CCR5, IL-18Ra on TH1 cells and ST2 on TH2 cells. A major point not adequately addressed in this study is the precise mechanism by which anti-Tim-3 is exerting its effects *in vivo*. One possibility is that Tim-3 delivers a negative signal to a macrophage subset, and that inhibition of this signal by anti-Tim-3 mAb leads to enhanced macrophage activation. An alternative scenario is that anti-Tim-3 is an agonist mAb which activates T cells in such as way as to promote macrophage activation. The authors also postulate that mAb treatment may directly promote T-cell trafficking to the brain. Either way the outcome of anti-Tim-3 therapy is to promote TH1 activation and effector responses. This family of genes may be important for TH1 and TH2 mediated diseases based on the recent finding of a strong linkage between this loci and Balb/c congenic mice resistant to TH2 mediated airways hyperreactivity (see Additional information).

Methods

Flow cytometry, immunohistochemistry, quantitative RT-PCR, gene-expression cloning, peptide-induced EAE, cell proliferation assays, adoptive T-cell transfer, TH1 antibody generation

Additional information

McIntire JJ, Umetsu SE, Akbari O, Potter M, Kuchroo VK, Barsh GS, Freeman GJ, Umetsu DT, DeKruyff RH: **Identification of Tapr (an airway hyperreactivity regulatory locus) and the linked Tim gene family.** *Nat Immunol* 2001, **12**:1095-1116.

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