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A transcription factor compelling Th1 differentiation

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Keywords

T box proteins, T cell differentiation, Th1/Th2 cells

Context

Upon activation, Thp cells differentiate into at least two distinct subsets. Th1 cells bias the immune response towards cell-mediated immunity and activate macrophages. Th2 cells mediate humoral immune responses, activate B cells and downregulate macrophage activation. The hallmark of Th1 and Th2 dichotomy is the distinct pattern of cytokines that drive the effector functions associated with the respective subsets. Th1 cells produce TNF-?, IL-2 and IFN-?, whereas Th2 cells secrete IL-4, IL-5, and IL-9. Much interest has focused on genes that are involved in directing the differentiation of uncommitted Thp cells towards Th1 or Th2 effectors. Some progress has been made in elucidating the genetic control of Th2 development, and TFs specific for Th2 cells have been described, eg c-Maf and GATA-3. However, little is known about the genetic factors driving Th1 development. To find Th1-restricted TFs that control Th1-specific cytokine gene transcription, and to study the influence of TF expression in developing Th2 cells.

Significant findings

A Th1-restricted TF was isolated with a 69% sequence homology to the T box motif of the T box TF family. It was therefore named 'T-bet'. T-bet expression was restricted to activated Th1 clones. The 62 kDa T-bet protein was expressed in antigen-activated Thp cells only under Th1-inducing conditions. As T-bet bound to, but did not transactivate, the IL-2 promoter, the authors reasoned that T-bet might regulate IFN-?, because both its promoter and intron III carry potential T-box binding sites. Co-transfected EL-4 mouse thymoma cells revealed a more than 20-fold transactivation of the IFN-? gene. Since T-bet activated IFN-?, the influence of T-bet expression on $CD4^+$ T cell development in Th1- and Th2-polarizing conditions was studied. T-bet expression increased IFN-? production at the early stage of both mitogen-activated and antigen-activated Thp cells. When mitogen-activated $CD4^+$ T cells were grown in Th2-inducing conditions, T-bet expression increased IFN-? expression and simultaneously decreased IL-4 and IL-5 production in developing and effector Th2 cells and in partially and fully polarized Th2 cells. Similar results were obtained in $CD8^+$ cytotoxic T lymphocytes, where polarized

Tc2 cells could be phenotypically converted to a Tc1 cytokine secretion profile. In developing Th2 cells, T-bet also induced the expression of Th1 surface markers such as PSGL-1 and CCR5. IL-4 and IL-5 repression in Th2 cells was not an indirect effect of IFN-? secretion, as T-bet exhibited similar alterations in cytokine secretion profiles in $CD4^+$T cells genetically deficient in the IFN-? receptor.

Comments

Expression of T-bet (T-box expressed in T cells) not only drives naive primary $CD4^+$T helper lymphocytes (Thp), but also converts developing, and even fully polarized, Th2 cells into the Th1 lineage. It is notable that, in addition to repressing IL-4 and IL-5 production, transfection of stable Th2 clones with T-bet could not elicit IFN-? expression, possibly due to loss of T-bet access to the IFN-? gene late in Th2 cell development. On the other hand, heterotopic expression of GATA-3 was previously shown to be sufficient to induce the expression of Th2 cytokines in fibroblasts. Thus, the precise role of T-bet in concert with other recently identified transcription factors (TFs) that mediate Th2 differentiation is still not clear and warrants future elucidation. Regulation of T-bet expression might be applied as an immunotherapeutical principle, since altered Th1/Th2 cytokine balances are involved in the pathogenesis of autoimmune diseases, allergy and HIV infection.

Methods

The yeast one-hybrid system, in which the IL-2 promoter was linked to the HIS3 reporter gene, was employed for cloning of genes encoding Th1-specific TFs. After stable integration of this construct, the yeast was transformed with a Th1-specific cDNA library. Growing yeast cells were screened for the expression of Th1-restricted proteins by hybridization with radiolabeled probes generated from mRNA from Th1 and Th2 clones via RDA (representational difference analysis). Northern blots of RNA from Th1 and Th2 clones and western blots of nuclear extracts were analyzed. EL-4 mouse thymoma cells were transfected with the T-bet expression plasmid and cytokine-luciferase reporter gene constructs (IFN-?.luc, IL-2.luc and IL-4.luc). Effects of T-bet expression on Th2 lineage development were studied by retroviral gene transfection of the T-bet gene into several developmental stages of Th2 cells under optimal Th2-inducing conditions.

Additional information

Two reviews of the T-box family of TFs, whose founding member was the brachyury gene, are reviewed by Smith J, *Trends Genet* 1999, **15:**154-158 and by Papaioannou VE *et al Bioessays* 1998, **20:**9-19 (Abstract) .

References

1. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH: A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000, 100: 655-669.