LEADING ARTICLE

T-bet and mucosal Th1 responses in the gastrointestinal tract

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T cells play an essential role in regulating mucosal immune responses in the gastrointestinal tract. Recent observations on T helper cell differentiation and activation by regulatory transcription factors—especially T-bet—in chronic inflammatory diseases have provided new perspectives for understanding mucosal immunity. Here we summarise recent advances in the field of transcription factors and discuss the implications of these findings for future therapeutic approaches in inflammatory bowel diseases. In particular, we have focused on the role of T-bet in controlling mucosal Th1 responses in the gastrointestinal tract.

On antigen presentation, naïve T helper cells can differentiate into one of two T cell subsets that can be distinguished by their cytokine production and functions.^{1,2} Whereas Th1 cells produce interferon γ (IFN- γ), and are important in macrophage activation as well as inflammatory and autoimmune reactions, Th2 cells produce cytokines such as interleukin (IL)-4, IL-5, IL-9, IL-10, and IL-13, and are mainly involved in controlling humoral and allergic immune responses.^{1–7}

T cells appear to play an important role in Crohn's disease and ulcerative colitis, two major forms of inflammatory bowel diseases (IBD) in humans. Although the aetiology of these diseases is unknown, it has been suggested that activation of the mucosal immune system in response to bacterial antigens with consecutive pathological cytokine production plays a key pathogenic role.^{5,6} In particular, cytokines produced by T lymphocytes appear to initiate and perpetuate chronic intestinal inflammation in IBD. Cytokine production by anti-CD2 plus anti-CD28 stimulated lamina propria CD4⁺ T lymphocytes differs between Crohn's disease and ulcerative colitis. Whereas Crohn's disease is associated with increased production of Th1-like cytokines such as IFN- γ and tumour necrosis factor (TNF), the cytokine profile in ulcerative colitis is characterised by increased production of the Th2 cytokine IL-5.⁸ Interestingly, both Th1 and Th2-type cytokines have been shown to play an important pathogenic role in various animal models of IBD suggesting that both Th1 and Th2 cells can induce chronic intestinal inflammation *in vivo*. The pathogenic function of Th1 and Th2 cells can be counteracted by immunosuppressive cytokines, such as IL-10 and transforming growth factor β (TGF- β), produced by regulatory T cells or Th3 cells.

T-BET REGULATES THE DIFFERENTIATION AND FUNCTION OF LYMPHOCYTES

Recent studies have focused on molecular mechanisms of Th1 and Th2 cell development. Transcription factors such as c-maf, STAT-6, GATA-3, JunB, and NFATc1 have been shown to induce or augment Th2 cytokine production. In contrast, transcription factors such as STAT-1, STAT-4, and the recently cloned T-bet protein are associated with IFN- γ and IL-12/IL-23 signalling, respectively, and play a key role in Th1 specific cytokine production.^{9–24} T-bet, a novel member of the T-box family, was cloned by Szabo *et al* in 2000 and was found to be expressed by IFN- γ -producing Th1 but not Th2 cells.⁹ Mechanistic studies showed that overexpression of T-bet by retroviral gene transduction in primary T cell was sufficient to induce IFN- γ production by chromatin remodelling at the IFN- γ gene locus and direct transactivation of the IFN- γ gene promoter in an IL-12 independent fashion.^{9–11} The homeoprotein Hlx has been recently identified as a target of T-bet and seems to contribute to the capacity of T-bet to induce IFN- γ production.²³ T-bet thus plays a key^{9–11} role in Th1 cell differentiation even before IL-12 dependent selection. In addition, T-bet was shown to upregulate IL-12 receptor β 2 chain expression on T cells thereby making T cells more susceptible to the IL-12/STAT-4 signalling pathway that plays an important role in Th1 T cell differentiation (fig 1). Finally, in T lymphocytes T-bet was found to be activated by IFN- γ signalling via the transcription factor STAT-1 suggesting an autocrine pathway by which T-bet induced IFN- γ production causes T-bet activation.^{11,19,21}

"T-bet plays a key role in controlling Th cell differentiation and effector functions *in vivo*"

T-bet deficient mice showed normal lymphoid development but exhibited profound defects in mounting Th1 mediated immune responses in response to IL-12.¹² CD4⁺ T cells and natural killer T cells of T-bet deficient mice produced reduced amounts of IFN- γ whereas cytotoxic CD8⁺ T cells showed unaltered IFN- γ production indicating a key role for T-bet in controlling IFN- γ production by CD4⁺ but not CD8⁺ T cells. Furthermore, T-bet deficient Black6 mice failed to cure *Leishmania* major infections and their susceptibility to infection was similar to that of the

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Abbreviations: IBD, inflammatory bowel disease; IFN- γ , interferon γ ; IL, interleukin; TNF, tumour necrosis factor; TGF- β , transforming growth factor β .

Figure 1 Transcriptional control of T cell differentiation.^{6,9,13,32} The cytokines interleukin (IL)-4 and IL-12 direct the development of Th2 and Th1 cells from naïve CD4⁺ T cells. Antigen presenting cells (APCs), such as dendritic cells and macrophages, produce cytokines such as IL-6, tumour necrosis factor (TNF), interferon γ (IFN- γ), IL-12, and IL-18 after activation. IL-12, IFN- γ , and IL-18 bind to their specific receptors on the surface of the differentiating Th1 cell. Signalling via the IL-12 receptor induces activation of the transcription factor STAT-4 whereas IFN- γ signalling leads to activation of STAT-1 and the transcription factor T-bet. T-bet induces IFN- γ production and expression of the high affinity IL-12 receptor on T cells. IL-18 alone cannot induce Th1 cell differentiation but augments IL-12 induced Th1 cell development. TNF and IL-6 have costimulatory effects on Th1 cells. In Th2 T cell differentiation, the IL-4 inducible transcription factor STAT-6 activates GATA-3 leading to production of IL-4, IL-5, and IL-13. Furthermore, the transcription factor c-maf induces IL-4 gene expression.

naturally susceptible BALB/c wild-type strain.¹² Furthermore, T-bet deficient mice developed airway hyperresponsiveness, airway inflammation, and airway remodelling, which are characteristic features of asthma.²⁰ These results demonstrate that T-bet plays a key role in controlling Th cell differentiation and effector functions in vivo.

Furthermore, a role for T-bet in the regulation of IgG class switching, especially to IgG2a, has recently been shown.¹⁴ In fact, T-bet deficient B lymphocytes demonstrated impaired production of IgG2a, IgG2b, and IgG3, and were unable to generate germline or postswitch IgG2a transcripts in response to IFN- γ . In a murine model of lupus, absence of T-bet led to a reduction in autoantibody production, hypergammaglobulinaemia, immune complex mediated renal disease, and IgG2a production. Therefore, T-bet plays a role in controlling B cell mediated autoimmunity.

T-BET IN THE GASTROINTESTINAL TRACT

Recent studies suggested alterations of T-bet levels in patients with certain inflammatory diseases of the gastrointestinal tract. For instance, T-bet mRNA transcripts were increased in the inflamed gut of patients with coeliac disease (a disease associated with high levels of IFN- γ in the mucosa) compared with control patients. In addition, T-bet mRNA and protein levels were upregulated in the inflamed mucosa of patients

with Crohn's disease.^{15,16} These data suggested a potential regulatory role of T-bet in Th1 associated diseases of the gastrointestinal tract.

"Overexpression of T-bet is essential and sufficient to promote Th1 mediated colitis in vivo"

Recently, the function of T-bet in mucosal T cells in animal models of chronic intestinal inflammation was tested.¹⁶ Retroviral transduction of T-bet in CD62L⁺CD4⁺ T cells exacerbated colitis in reconstituted SCID mice compared with mice reconstituted with control transduced T cells. Conversely, T-bet deficient T cells failed to induce colitis in a Th1 mediated adoptive transfer model. This suggests that overexpression of T-bet is essential and sufficient to promote Th1 mediated colitis in vivo. T-bet deficient CD62L⁺CD4⁺ memory T cells showed enhanced protective functions in Th1 mediated colitis and exhibited increased Smad-3 signalling. A T-bet driven pathway of T cell activation therefore appears to control the intestinal cytokine balance. In addition, TGF- β was found to be a potent suppressor of T-bet expression in mucosal T cells suggesting that TGF- β mediated suppression of Th1 development may be due to TGF induced suppression of T-bet expression.^{16,24} Taken together, these data suggest an important regulatory function of T-bet in T cell mediated colitis in vivo.

PERSPECTIVES

A wide range of drugs has been investigated in the clinical management of IBD, including biological agents, antibodies, recombinant cytokines, or low molecular weight inhibitors. Some strategies have attempted to block the interaction between antigen presenting cell and T cells whereas others have targeted cytokines, cytokine signalling, and adhesion molecules. For instance, neutralising antibodies to TNF have been widely used for the treatment of chronic active Crohn's disease¹⁷ and further antibodies are currently being tested in clinical trials such as anti-CD40L, anti-IL6R, and anti-IL-12 antibodies.

"Targeted modulation of JAK/STAT and T-bet signalling in T cells might be helpful in interfering selectively with the clinical course of disease of IBD patients"

Recent data suggest however that targeted modulation of JAK/STAT and T-bet signalling in T cells might be helpful in interfering selectively with the clinical course of disease of IBD patients. At least in animal models, blockade of the IL-12/STAT4 pathway in the CD45RB^{hi} adoptive transfer model ameliorated experimental colitis and T-bet deficiency prevented Th1 mediated chronic intestinal inflammation.^{16,18} The potential advantage of targeting cytokine signalling compared with cytokines is that the former approach may affect various proinflammatory cytokines at the same time rather than one single cytokine. Therefore, it will be interesting to develop specific inhibitors of cytokine signalling and to determine whether such inhibitors may be useful in future therapeutic approaches in patients with IBD.

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