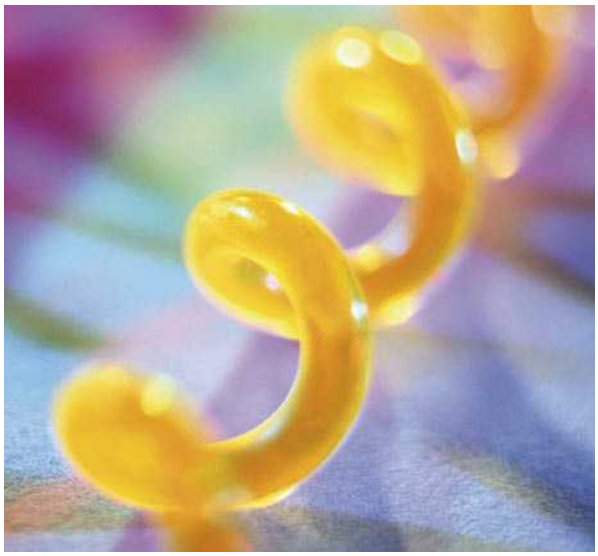
T CELLS

T_H1 cells do the twist

T helper 1 (T_H1) cells and the cytokines they produce are known to contribute to chronic inflammation. In a recent study, Radbruch and colleagues show that a transcription factor known as TWIST1 is an important negative regulator of this T_H-cell subset, and that its expression limits the pathology that is associated with chronic inflammatory states.

The authors first showed that the expression of TWIST1 was upregulated in T_H1 cells, but not T_H2 or T_H17 cells, following T-cell-receptor activation. Interleukin-12 (IL-12) signalling through STAT4 (signal transducer and activator of transcription 4) was necessary for the induction of TWIST1 expression, whereas other factors that are associated with T_H1-cell differentiation, such as interferon-γ (IFNγ) and T-bet, were not involved. In addition to identifying a binding site for STAT4, the authors also mapped conserved binding sites for nuclear factor-κB (NF-κB) and nuclear factor of activated T cells (NFAT) in the *TWIST1* promoter; the concerted action of these three transcription factors was important for the upregulation of TWIST1 expression in T_H1 cells.



Interestingly, repeated *in vitro* stimulation through the TCR 'imprinted' T_H1 cells for increased expression of TWIST1. In addition, analysis of both mouse and human T cells *ex vivo* showed that T_H1 cells with an effector memory phenotype expressed higher levels of TWIST1 compared with other T_H-cell subsets. Furthermore, T cells that were isolated from the inflamed tissues of patients with rheumatoid arthritis, Crohn's disease or ulcerative colitis had markedly increased levels of *TWIST1* mRNA compared with T cells from non-inflamed tissues from the same patients, or with T cells from healthy individuals. Therefore, high expression levels of TWIST1 are characteristic of effector memory T_H1 cells.

So, increased TWIST1 expression is associated with chronic inflammatory states, but what is its function in effector memory T_H1 cells? Overexpression of TWIST1 in effector memory T_H1 cells altered the expression of a large number of genes, 13 of which are related to cytokine or chemokine production in T_H1 cells. Although its expression was found to correlate with chronic inflammatory states, overexpression of TWIST1 was found to inhibit the production of IL-2, IFNγ and tumour-necrosis factor by up to 50% in effector memory T_H1 cells. Molecular analyses showed that TWIST1 interferes with NF-κB-dependent activation of specific genes, thereby repressing their transcription. These data indicate that TWIST1 acts as an autoregulator of T_H1-cell function, in part by inhibiting the transcription of specific cytokine genes.

To investigate how TWIST1 influences T-cell-mediated immunopathology *in vivo*, the authors manipulated its expression in two different mouse models of inflammation. In a model of antigen-specific delayed-type hypersensitivity, the adoptive transfer of T_H1 cells that were overexpressing TWIST1 led to significantly less immunopathology compared with that mediated by the transfer of control T_H1 cells. By contrast, the adoptive transfer of T_H1 cells in which TWIST1 expression was inhibited resulted in more severe tissue damage in an antigen-induced model of arthritis. So, TWIST1 expression is a biomarker of the T_H1 cells that are involved in chronic inflammation, in which it serves to limit the extent of tissue damage.

Together, these data indicate that TWIST1 is an important regulator of T_H1-cell function, and that targeting T_H1 cells that express TWIST1 might be a promising way to treat chronic inflammatory states in which effector memory T_H1 cells have a pathogenic role.

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ORIGINAL RESEARCH PAPER Niesner, U. *et al.* Autoregulation of Th1-mediated inflammation by *twist1*. *J. Exp. Med.* 28 July 2008 (doi:10.1084/jem.20072468)