MUCOSAL IMMUNOLOGY

Another piece of the puzzle

Recently, there has been a growing effort to understand the pathogenesis of Crohn's disease and ulcerative colitis, and a complex picture integrating environmental, genetic and immunological factors is emerging. However, details of the molecular mechanisms involved are still lacking. Now, Neurath and colleagues describe another piece of this puzzle by identifying the transcription factor interferon-regulatory factor 4 (IRF4) as an important regulator of interleukin-6 (IL-6) production by mucosal T cells, which has a pathogenic role in T-cell-dependent colitis.

Here, the authors used three models of T-cell-dependent colitis in IRF4-deficient mice to examine the role of IRF4 in this disease. In the first two models the authors induced colitis in *Irf4*$^{-/-}$ mice (or wild-type controls) by administering the chemicals oxazolone or trinitrobenzene sulphonic acid. They found that, in contrast to wild-type mice, *Irf4*$^{-/-}$ mice were protected from chemically induced colitis and that colonic mucosal inflammation in *Irf4*$^{-/-}$ mice was absent.

But how does the loss of IRF4 expression protect against colitis? The authors found that the expression of IL-6 in the lamina propria was higher in wild-type mice than *Irf4*$^{-/-}$ mice following chemical treatment and that *Irf4*$^{-/-}$ mice became susceptible to chemically induced colitis following treatment with either IL-6 or a combination of IL-6 plus soluble IL-6 receptor. They identified that IRF4-dependent IL-6 was produced by T cells in the lamina propria.

The third model of colitis involved the transfer of either wild-type or *Irf4*$^{-/-}$ $CD4^{+}CD45RB^{hi}$ T cells into immunocompromised hosts. Using this model, the importance of the loss of T-cell-dependent IL-6 production in the protective effect of IRF4 deficiency was confirmed. The mice that received *Irf4*$^{-/-}$ T cells did not develop colitis and had reduced IL-6 expression compared with those that received wild-type T cells. Interestingly, the authors showed that patients with Crohn's disease or ulcerative colitis have higher *Irf4* mRNA levels in lamina propria T cells than control patients, and that *Il6* mRNA levels correlated closely with *Irf4* mRNA levels.

So, the data show that IRF4 has an important role in mediating T-cell-dependent experimental colitis through its regulation of IL-6 production by mucosal T cells. Therefore, IRF4 could be a potential therapeutic target for the treatment of inflammatory bowel diseases in humans.

Olive Leavy

ORIGINAL RESEARCH PAPER Mudter, J. *et al.* The transcription factor IFN regulatory factor-4 controls experimental colitis in mice via T cell-derived IL-6. *J. Clin. Invest.* 5 June 2008 (doi:10.1172/JCI133227)