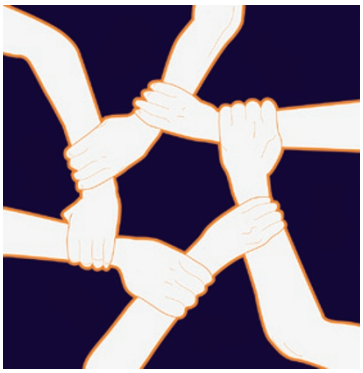
IMMUNE REGULATION

Linking integrins, TGFβ and autoimmunity

DOI:
10.1038/nri2162



> “…loss of TGFβ-activating $\alpha_V\beta_8$-integrin in dendritic cells (DCs) results in severe inflammatory bowel disease and autoimmunity…”

Transforming growth factor-β (TGFβ), partly through its induction of regulatory T cells, has a crucial role in maintaining immune homeostasis. However, TGFβ must be activated to exert its regulatory effects, and the exact mechanisms involved in its activation and function *in vivo* are controversial. Now, Travis and colleagues show that the loss of TGFβ-activating $\alpha_V\beta_8$-integrin in dendritic cells (DCs) results in severe inflammatory bowel disease and autoimmunity in mice, indicating an important role for $\alpha_V\beta_8$-integrin in the prevention of immune dysfunction.

Previous studies have shown that the complete loss of β_8-integrin (encoded by *Itgb8*) expression in mice is lethal, so the authors generated mice with a conditional deletion of *Itgb8* in leukocytes. By 10 months of age, all surviving mice developed severe colitis and had high levels of circulating autoantibodies. These mice also had higher numbers of peripheral activated or memory T cells that expressed interleukin-4 and interferon-γ, and increased serum IgE, IgA and IgG1 levels compared with control mice. The phenotype of these mice is almost identical to the phenotype of mice that lack key elements of the TGFβ signalling pathway, indicating that $\alpha_V\beta_8$-integrin has an important role in activating TGFβ *in vivo*.

To identify the exact subset of leukocytes involved, mice were generated that specifically lacked β_8-integrin expression in T cells or in DCs. Mice with a conditional loss of β_8-integrin expression in T cells were phenotypically indistinguishable from control mice, whereas mice with a conditional loss of β_8-integrin expression in DCs were identical to mice that lacked β_8-integrin expression in all leukocytes. Further *in vitro* analysis showed that although the lack of β_8-integrin expression did not affect the maturation of DCs, the ability of these DCs to convert $CD4^+$ T cells into regulatory T cells — as determined by their expression of forkhead box P3 (FOXP3) — was greatly reduced. However, the addition of active TGFβ to *in vitro* co-cultures restored the induction of regulatory T cells by β_8-integrin-deficient DCs. Interestingly, the percentage of $FOXP3^+$ regulatory T cells in the spleens of mice with β_8-integrin-deficient DCs was the same as that in control mice. However, there was a 50% reduction in the percentage of regulatory T cells in colonic lamina propria of these deficient mice relative to control mice.

Taken together, the data indicate an important role for $\alpha_V\beta_8$-integrin-mediated TGFβ activation and the subsequent induction of regulatory T cells in the maintenance of immune homeostasis in the colon, disruption of which results in autoimmunity and inflammatory bowel disease.

Olive Leavy

ORIGINAL RESEARCH PAPER
Travis, M. A. *et al.* Loss of integrin $\alpha_V\beta_8$ on dendritic cells causes autoimmunity and colitis in mice. *Nature* 12 August 2007 (doi:10.1038/nature06110)