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ASTHMA AND ALLERGY

TGFβ — too much of a good thing?

> excessive activation of the TGFβ signalling pathway may promote allergic disease by skewing T_{Reg} cell functions

Transforming growth factor-β (TGFβ) supports the expansion of regulatory T (T_{Reg}) cell populations, but a new report now suggests that excessive TGFβ receptor (TGFβR) signalling may lead to dysregulated T_{Reg} cell activity and may underlie a diverse range of allergic diseases in humans.

Most studies investigating TGFβ have relied on genetically engineered mouse models. However, patients with Loeys–Dietz syndrome (LDS) have naturally occurring mutations in the genes encoding the TGFβR and provide a unique opportunity to investigate the functions of TGFβ in humans. Frischmeyer-Guerrerio *et al.* characterized a group of 58 patients with LDS, who have heterozygous mutations that affect either *TGFBR1* or *TGFBR2*. They found that 31% of these patients had food allergies (compared with 2–6% of the general population) and that 45% had been diagnosed with asthma, 48% with allergic rhinitis and 38% with eczema. In addition, two thirds of the patients reported gastrointestinal complaints and 10% of patients had been diagnosed with eosinophilic gastrointestinal diseases, which have a prevalence of approximately 0.05% in the general population.


GETTY

Consistent with the allergic phenotypes seen in the patients with LDS, these patients had significantly increased eosinophil counts, elevated levels of IgE and higher levels of the T helper 2-type cytokines interleukin-5 (IL-5), IL-13 and CC-chemokine ligand 2. By contrast, their overall white blood cell counts and their serum levels of non-IgE antibody isotypes and 21 other cytokines were normal.

To assess whether these disease phenotypes arose from defects in immune tolerance, the authors examined T_{Reg} cells from the patients with LDS. Forkhead box P3 $(FOXP3)^+$ T_{Reg} cells from patients with LDS showed no functional defect in *in vitro* suppression assays. However, compared with non-allergic control individuals, patients with LDS had increased numbers of $FOXP3^+$ T_{Reg} cells in the peripheral blood and, surprisingly, these cells expressed IL-13. In response to culture with increasing doses of TGFβ, naive T cells from patients with LDS and from control individuals showed a similar upregulation of FOXP3 expression, but $FOXP3^+IL\text{-}13^+$ T cells only accumulated in the cultures of cells from patients with LDS.

The authors found that T cells from patients with LDS had increased phosphorylation of the signalling proteins SMAD2 and SMAD3 in response to TGFβ, which suggests that TGFβR signalling is enhanced, rather than repressed, in these individuals. Notably, patients with allergic diseases, but not with LDS, also showed increased frequencies of $IL\text{-}13^+$ T_{Reg} cells.

These findings suggest that, despite its role in supporting the expansion of T_{Reg} cell populations, excessive activation of the TGFβ signalling pathway may promote allergic disease by skewing T_{Reg} cell functions.

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ORIGINAL RESEARCH PAPER Frischmeyer-Guerrerio, P. A. *et al.* TGFβ receptor mutations impose a strong predisposition for human allergic disease. *Sci. Transl. Med.* **5**, 195ra94 (2013)