CYTOKINES

An antagonistic family member

> IL-17B dampens IL-25-dependent signalling through IL-17RB by competition for receptor binding

Family relationships can often be confrontational and it seems that the interleukin-17 (IL-17) family is no exception. New research in *Immunity* indicates that IL-17B has an antagonistic relationship with IL-17E (commonly known as IL-25) in terms of regulating mucosal inflammation.

IL-17 family cytokines have largely been defined by the pro-inflammatory activities of the two most well-studied members, IL-17A and IL-17F. Of the other four family members, IL-25 has the least in common with IL-17A and IL-17F (in terms of amino acid sequence), and it has unique functions in inducing T helper 2 (T_H2) cell responses. IL-17B, IL-17C and IL-17D are less well-known members of the family.

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IL-17B and IL-25 are expressed at basal levels in the colon under steady-state conditions, and there was a marked increase in the expression of both cytokines after the induction of acute colitis in mice by dextran sodium sulfate (DSS) administration. Most of this cytokine expression occurred in colonic epithelial cells (CECs), and *in vitro* stimulation of CECs with Toll-like receptor or nucleotide-binding oligomerization domain 2 (NOD2) agonists resulted in increased IL-17B and IL-25 expression.

In the DSS-induced colitis model, *Il25*$^{-/-}$ mice had decreased colonic inflammation compared with wild-type animals, which resulted in marked protection from weight loss. The resistance to DSS-induced colitis was maintained in mice with an epithelial cell-specific deletion of *Il25*, and this correlated with decreased production of pro-inflammatory cytokines and chemokines, including IL-6. Conversely, IL-17B-deficient mice had increased colonic inflammation, including higher levels of IL-6 production, and greater weight loss than wild-type counterparts after DSS administration. So, IL-25 has a pathogenic role in DSS-induced colitis, whereas IL-17B has a protective role.

IL-25 and IL-17B both bind the IL-17 receptor subunit IL-17RB, although IL-25 has the greater affinity. Mice with a deficiency of IL-17RB in the non-haematopoietic compartment were protected from DSS-induced colitis, which suggests an important role for CECs in this model in both producing and responding to pathogenic IL-25. Treating CECs with IL-25 *in vitro* led to the dose-dependent induction of IL-6, which could be inhibited by simultaneous treatment with increasing concentrations of IL-17B. In support of a model in which IL-17B dampens IL-25-dependent signalling through IL-17RB by competition for receptor binding, high doses of IL-17B markedly inhibited binding of IL-25 to a cell line expressing IL-17RB. Also, double-deficient mice lacking IL-25 and IL-17B were protected from the colonic inflammation, IL-6 production and weight loss that is associated with DSS-induced colitis in IL-17B-deficient animals, which indicates the antagonism between the two pathways.

The opposing roles of IL-25 and IL-17B in inflammation were also demonstrated in an oral infection model with *Citrobacter rodentium* and in an allergic asthma model. This work defines the first major biological function for IL-17B as an antagonistic member of the IL-17 family.

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ORIGINAL RESEARCH PAPER
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