CYTOKINES

IL-17C joins the family firm

IL-17C has a crucial role in promoting protective antibacterial immune responses at epithelial surfaces but may also have pathological functions

Much interest has focused on the interleukin-17 (IL-17) family of cytokines, mainly stemming from the pro-inflammatory roles that have been described for IL-17A and IL-17F. The biological functions of another family member, IL-17C, have been unclear. Now, three independent studies suggest that IL-17C signals through a receptor complex containing IL-17 receptor A (IL-17RA) and IL-17RE to promote innate defence at epithelial surfaces and potentiate T helper 17 (T_H17) cell responses.

Members of the IL-17 family (IL-17A to IL-17F) signal through heterodimers and homodimers of the IL-17R family (IL-17RA to IL-17RE). The ligand-binding capacity and functions of IL-17RE were unknown, but in expression analyses Song *et al.* found that *Il17re* mRNA is abundant in the intestine, particularly in colonic

epithelial cells. To explore the role of IL-17RE at this site, the authors orally infected IL-17RE-deficient mice with the bacterial pathogen *Citrobacter rodentium*. Unlike wild-type controls, which did not lose weight and survived the infection, IL-17RE-deficient mice experienced severe weight loss and died as a result of infection. Closer examination revealed that IL-17RE-deficient mice had higher bacterial counts in the spleen, colon and faeces and showed increased disruption of the colonic epithelium. Furthermore, the expression of several antibacterial peptides and cytokines was decreased in the colons of infected IL-17RE-deficient mice. These data suggested that IL-17RE signalling promotes innate antibacterial responses at the intestinal epithelium.

But what ligand was triggering the IL-17RE-mediated response? The authors found that IL-17A, IL-17C and IL-17F were all upregulated during *C. rodentium* infection. However, IL-17A and IL-17F were still able to drive antibacterial responses in IL-17RE-deficient colonic epithelial cells. On the contrary, IL-17C was found to induce an antibacterial response in wild-type, but not IL-17RE-deficient, colonic epithelial cells. IL-17C was shown to signal through an IL-17RA–IL17RE complex to activate nuclear factor- κ B and mitogen-activated protein kinase signalling pathways in colonic epithelial cells. Interestingly, as well as expressing IL-17RE, colonic epithelial cells were identified as the main cellular source of IL-17C in the intestine.

Similarly to Song *et al.*, Ramirez-Carrozzi *et al.* found that IL-17C signals through an IL-17RA–IL-17RE complex and protects the intestine from bacterium-driven pathology in a model of colitis. In addition to identifying colonic epithelial cells as a major source of IL-17C, they showed that tracheal epithelial cells and

keratinocytes also upregulate IL-17C in response to bacteria. Notably, Ramirez-Carrozzi *et al.* found that IL-17C drives disease pathology in a non-infectious model of skin inflammation. They propose that IL-17C has a crucial role in promoting protective antibacterial immune responses at epithelial surfaces but may also have pathological functions in diseases such as psoriasis, in which the epithelial barrier is dysfunctional.

The final study, by Chang *et al.*, also identified IL-17RE as a receptor for IL-17C and found that IL-17C was upregulated in the central nervous system (CNS) of mice with experimental autoimmune encephalomyelitis (EAE). The authors generated IL-17C-deficient mice and showed that these animals were less susceptible to EAE than wild-type controls, suggesting a pathological role for IL-17C in this disease. IL-17RE was shown to be upregulated on differentiating T_H17 cells, and IL-17C signalling through IL-17RA–IL-17RE promoted T_H17 cell-mediated production of IL-17A and IL-17F. This was mediated via the recruitment of the adaptor protein ACT1 (also known as CIKS) and the induction of the transcription factor I κ B ζ .

These three studies suggest that IL-17C has much in common with its 'brothers' IL-17A and IL-17F — it potentiates protective antibacterial responses at the intestinal epithelium but can have pathological roles in the skin and CNS.

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ORIGINAL RESEARCH PAPERS Song, X. *et al.* IL-17RE is the functional receptor for IL-17C and mediates mucosal immunity to infection with intestinal pathogens. *Nature Immunol.* 12 Oct 2011 (doi:10.1038/ni.2155) | Ramirez-Carrozzi, V. *et al.* IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. *Nature Immunol.* 12 Oct 2011 (doi:10.1038/ni.2156) | Chang, S. H. *et al.* Interleukin-17C promotes Th17 cell responses and autoimmune disease via interleukin-17 receptor E. *Immunity* 35, 611–621 (2011)