Nature Reviews Immunology | Published online 23 November 2015; doi:10.1038/nri.2015.2

Journal club

IL-17 RECEPTOR COMPOSITION

It has now been a decade since the paradigm-shifting discovery of T helper 17 (T_H17) cells in 2005 forced everyone working on effector $CD4^+$ T cells to reinterpret their findings in the context of this interleukin-17 (IL-17)-producing T_H cell population. We now know that IL-17-induced signalling has a crucial role in immunity to extracellular microorganisms, particularly to fungal pathogens such as *Candida albicans*. Conversely, IL-17 mediates pathogenic inflammation in several autoimmune conditions. The study by Toy *et al.* in 2006 marked a major advance in our understanding of IL-17 signal transduction, showing that IL-17 receptor C (IL-17RC) is an obligate co-receptor with IL-17RA for signalling induced by IL-17A and IL-17F.

IL-17A (commonly known as IL-17) is the eponymous cytokine of T_H17 cells and the founding member of a structurally distinct subclass of cytokines. Both IL-17 and its closest homologue, IL-17F, had been previously shown to signal through IL-17RA, which was also unrelated to other known cytokine receptors (Yao *et al.*, 1995). However, it was unclear how IL-17RA operated at a molecular level.

> “IL-17RC … is an obligate co-receptor with IL-17RA for signalling induced by IL-17A and IL-17F”

Toy *et al.* approached this issue by reconstituting fibroblasts from *Il17ra*$^{-/-}$ mice with human IL-17RA. They observed that IL-17-induced signalling could only be restored in these fibroblasts upon co-expression of human IL-17RC with human IL-17RA, but not upon co-expression of other IL-17R family members. As the *Il17ra*$^{-/-}$ cells expressed endogenous mouse IL-17RC, this finding also revealed an unexpected species-dependent interaction between IL-17R subunits and their ligands, which was confirmed by co-immunoprecipitation of human IL-17RA with human IL-17RC. The authors then used this system to examine the structure–function requirements for IL-17RC; they found not only that IL-17RC is required for ligand binding but also that the IL-17RC cytoplasmic tail is essential for signalling in response to IL-17.

Since this ground-breaking study, IL-17RA has emerged as a common receptor subunit for multiple members of the IL-17 family, whereas IL-17RC seems to be specific for IL-17 and IL-17F. Nonetheless, there are few phenotypic differences between mice lacking IL-17RA or IL-17RC, and patients with null mutations in either subunit also have remarkably similar defects, with their major phenotype being chronic mucosal candidiasis (Puel *et al.*, 2011; Ling *et al.*, 2015). Thus, this important study by Toy *et al.* clarified the constituents of the IL-17 receptor complex, which set the stage for a deeper understanding of its biological activities.

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The author declares competing interests: see Web version for details.

ORIGINAL RESEARCH PAPER Toy, D. *et al.* Cutting edge: interleukin 17 signals through a heteromeric receptor complex. *J. Immunol.* **177**, 36–39 (2006)
FURTHER READING Yao, Z. *et al.* Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* **3**, 811–821 (1995) | Puel, A. *et al.* Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* **332**, 65–68 (2011) | Ling, Y. *et al.* Inherited IL-17RC deficiency in patients with chronic mucocutaneous candidiasis. *J. Exp. Med.* **212**, 619–631 (2015)