



S. Bradbrook/NPG

## T CELLS

# Seq-ing out the ‘bad’ guys

T helper 17 ( $T_H17$ ) cells can be good or bad: on the one hand, they provide defence against extracellular pathogens and tissue homeostasis and, on the other hand, they can induce autoimmunity. In two linked studies published in *Cell*, researchers used single-cell RNA sequencing to investigate this functional heterogeneity and identify molecules that regulate the pathogenicity of  $T_H17$  cells. One candidate molecule, known as CD5L, regulates  $T_H17$  cell pathogenicity by modulating cellular fatty acid composition and thus ligand availability for the  $T_H17$  cell master transcription factor, ROR $\gamma$ t.

Previous studies have shown that  $T_H17$  cells that are polarized *in vitro* with interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6 and IL-23 adopt a more pathogenic state (that is, they can cause severe autoimmune responses upon adoptive transfer into mice), whereas  $T_H17$  cells polarized with transforming growth factor- $\beta$  and IL-6 are non-pathogenic. The authors profiled the transcriptome of individual  $T_H17$  cells isolated from mice with experimental autoimmune encephalomyelitis (EAE) and compared them with the *in vitro*-differentiated  $T_H17$  cells. They found substantial heterogeneity in gene expression between individual cells raised in all conditions and, using a functional annotation approach, were able to assign cells

into a range of states according to regulatory or pro-inflammatory function and maturation status (effector versus memory). Importantly, they identified a group of potential pathogenicity regulators that co-vary with pro-inflammatory and regulatory expression modules in  $T_H17$  cells. Some of the most interesting genes proposed by the analysis were the glycosphingolipid receptor *Gpr65*, the cell surface regulatory molecule *Faim3* (FAS apoptotic inhibitory molecule 3; also known as *Toso*) and the transcriptional repressor *Plzp* (promyelocytic leukaemia zinc finger; also known as *Zbtb32*), which were all shown in functional studies to promote  $T_H17$  cell pathogenicity.

Another of the novel pathogenicity regulators identified in this study was *Cd5l*, which is described in the second paper (Wang *et al.*). CD5L expression was associated with non-pathogenic  $T_H17$  cells *in vitro* and *in vivo*. Consistent with a role for CD5L as a regulator of  $T_H17$  cell pathogenicity, *Cd5l*<sup>-/-</sup> mice developed more-severe EAE than wild-type mice. *In vitro* analysis showed that CD5L represses the effector functions but not the differentiation of  $T_H17$  cells: effector memory  $T_H17$  cells from *Cd5l*<sup>-/-</sup> mice make more IL-17 and less IL-10 per cell than wild-type control cells. Moreover, loss of

CD5L expression could convert non-pathogenic  $T_H17$  cells into pathogenic  $T_H17$  cells that induce autoimmunity.

CD5L has previously been shown to regulate lipid metabolism in adipocytes, so the authors profiled the lipidome of  $T_H17$  cells with or without CD5L expression. They found that CD5L expression alters the fatty acid composition in  $T_H17$  cells, resulting most markedly in an increase in polyunsaturated fatty acids and a decrease in cholesterol metabolites. As cholesterol metabolites, such as oxysterols, can function as ligands for ROR $\gamma$ t, the authors tested whether ROR $\gamma$ t ligand restriction influences  $T_H17$  cell pathogenicity. Indeed, chromatin immunoprecipitation of ROR $\gamma$ t showed higher binding to the *Il17* and *Il23r* loci and reduced binding to the *Il10* region in *Cd5l*<sup>-/-</sup>  $T_H17$  cells compared with wild-type cells. Moreover, addition of endogenous ROR $\gamma$ t ligand rescued the CD5L-induced suppression of *Il17* transcription, together suggesting that lipid metabolism is important in balancing immune protection versus disease induced by  $T_H17$  cells.

Lucy Bird

“... loss of CD5L expression could convert non-pathogenic  $T_H17$  cells into pathogenic  $T_H17$  cells...”

**ORIGINAL ARTICLES** Gaublotte, J. T. *et al.* Single-cell genomics unveils critical regulators of Th17 cell pathogenicity. *Cell* **163**, 1400–1412 (2015) | Wang, C. *et al.* CD5L/AIM regulates lipid biosynthesis and restrains Th17 cell pathogenicity. *Cell* **163**, 1413–1427 (2015)