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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, RORγt.

Previous studies have shown that T_H17 cells that are polarized *in vitro* with interleukin-1β (IL-1β), 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-β 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.

> "... loss of CD5L expression could convert non-pathogenic T_H17 cells into pathogenic T_H17 cells..."

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, $Cd5l^{-/-}$ 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 $Cd5l^{-/-}$ 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 RORγt, the authors tested whether RORγt ligand restriction influences T_H17 cell pathogenicity. Indeed, chromatin immunoprecipitation of RORγt showed higher binding to the *Il17* and *Il23r* loci and reduced binding to the *Il10* region in $Cd5l^{-/-}$ T_H17 cells compared with wild-type cells. Moreover, addition of endogenous RORγt 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.

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ORIGINAL ARTICLES Gaublomme, 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 biosythesis and restrains Th17 cell pathogenicity. *Cell* **163**, 1413–1427 (2015)