IMMUNE REGULATION

New player in the generation of T_H17 cells

T helper 17 (T_H17) cells comprise a recently identified T_H -cell lineage that has a pro-inflammatory role in autoimmunity and tissue inflammation. Now, three groups report that the cytokine interleukin-21 (IL-21) is not only produced by T_H17 cells but is also a potent and necessary inducer of T_H17 -cell differentiation.

The differentiation of T_H17 cells is initiated by transforming growth factor- β (TGF β) and IL-6, and IL-23 is additionally required for T_H17 -cell differentiation *in vivo*. The transcription factors signal transduction and activator of transcription 3 (STAT3) and retinoic-acid-receptor-related orphan receptor- γ (ROR γ) mediate lineage commitment.

Using gene-expression analysis, Nurieva and colleagues compared T_H17 cells with the other known T_H -cell subsets (T_H1 and T_H2 cells) and found that expression of *Il21* mRNA was significantly higher in T_H17 cells

“...TGF β and IL-6 together [might] initiate the differentiation of T_H17 cells, which then produce IL-21 and this creates an amplification loop for further generation of T_H17 cells.”

compared with the other effector cells. They next investigated how IL-21 expression is regulated in T_H17 cells and found that it is upregulated in response to IL-6 but not to TGF β or IL-23. IL-21 expression was severely impaired in STAT3-deficient cells, but cells lacking ROR γ produced similar levels of IL-21 compared with wild-type T cells. So, IL-21 expression by T_H17 cells is dependent on STAT3, whereas IL-17 expression is dependent on both STAT3 and ROR γ . Similar results were also obtained by Zhou and colleagues.

In vitro stimulation experiments showed that IL-21-deficient T cells were defective in differentiating into T_H17 cells and this was associated with enhanced differentiation of cells expressing the transcription factor forkhead box P3 (FOXP3), which is associated with the generation of regulatory T cells (T_{Reg} cells). Further experiments suggested that IL-21 is acting in an autocrine manner, as does interferon- γ (IFN γ) for T_H1 cells and as does IL-4 for T_H2 cells. Finally, when the authors induced experimental autoimmune encephalomyelitis (EAE; a disease in which T_H17 cells are known to be pathogenic) in IL-21-deficient mice, they found that the lack of IL-21 impaired the generation of T_H17 cells and ameliorated the disease.

Previous work from Vijay Kuchroo's group had suggested a reciprocal relationship in the generation of T_H17 cells versus T_{Reg} cells, in which IL-6 is pivotal in controlling T_H17 -cell-lineage specification. In the present study, when Korn and colleagues crossed IL-6-deficient mice with green-fluorescent-protein-labelled FOXP3 knock-in mice and EAE was induced, T_H17 cells did not develop but the mice had higher numbers of CD4⁺CD25⁺FOXP3⁺ T_{Reg} cells, which was in line with their predictions. As it was possible that the IL-6-deficient environment led to the expansion of T_{Reg} cells at the expense of effector T cells, the authors deleted T_{Reg} cells

in IL-6-deficient mice and expected to observe induction of autoimmunity mediated by IFN γ -producing T_H1 cells but not T_H17 cells. As expected, these T_{Reg} -cell-depleted mice were susceptible to EAE. However, they unexpectedly found that IL-17 production was almost similar to wild-type levels, suggesting that T_H17 cells could be generated *in vivo* in the absence of IL-6. By testing a number of candidate cytokines that could suppress the TGF β -mediated induction of FOXP3 expression, the authors showed that IL-21 in combination with TGF β could suppress both FOXP3 expression and induce IL-17 production in naive T cells. However, the frequency of T_H17 cells induced by TGF β plus IL-21 was lower than that stimulated by TGF β plus IL-6. Further experiments led the authors to suggest that TGF β and IL-6 together initiate the differentiation of T_H17 cells, which then produce IL-21 and this creates an amplification loop for further generation of T_H17 cells.

The experiments conducted by Zhou and colleagues yielded similar data — they found that IL-6 induced STAT3-dependent but ROR γ -independent expression of IL-21. IL-21 then acts in a self-amplifying loop and cooperates with TGF β in a ROR γ -dependent pathway to induce IL-17 production. IL-21 production also induces expression of the IL-23 receptor, enabling the IL-23 that is produced by antigen-presenting cells to act together with TGF β to induce the expression of IL-17 and other cytokines.

Together these studies reveal a role for IL-21 in the generation of T_H17 cells and suggest that IL-21, together with IL-6 and IL-23, might be new targets for the therapy of inflammatory diseases.

Elaine Bell

ORIGINAL RESEARCH PAPERS Nurieva, R. et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 20 June 2007 (doi:10.1038/nature05969) | Zhou, L. et al. IL-6 programs T_H17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nature Immunol.* 20 June 2007 (doi:10.1038/ni1488) | Korn, T. et al. IL-21 initiates an alternative pathway to induce proinflammatory T_H17 cells. *Nature* 20 June 2007 (doi:10.1038/nature05970)

BANANASTOCK