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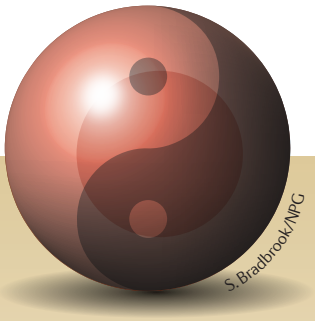

T CELLS

Role reversal

CD4$^+$ T helper (T_H) cells differentiate into different specialized subsets depending on their circumstances. Increasing evidence suggests that this process is more flexible than originally thought. This study shows that T_H17 cells transdifferentiate into T regulatory type 1 (T_R1) cells and contribute to the resolution of inflammation in mice.

The authors used reporter mice to track the fate of T_H17 cells *in vivo*: T cells that have expressed high levels of interleukin-17A (IL-17A) were permanently marked with yellow fluorescent protein and any subsequent expression of the regulatory T cell markers IL-10 and forkhead box P3 (FOXP3) was also tagged and could be measured directly *ex vivo*. In the steady state, approximately half of all mouse intestinal CD4$^+$ T cells that had expressed IL-17A no longer expressed this cytokine — the authors referred to these cells as ex-T_H17 cells. Some intestinal ex-T_H17 cells expressed IL-10 and some expressed FOXP3. Following a self-limiting inflammatory response induced by injection of CD3-specific monoclonal antibody, an expansion of the intestinal T_H17 cell population was followed by an increase in the number of ex-T_H17 cells expressing high levels of IL-10, with a few of these cells co-expressing IL-10 and FOXP3. The IL-10$^+$ ex-T_H17 cells more closely resembled T_R1 cells than T_H17 cells (that is, they were LAG3$^+$CCR6$^-$RORγt^{low}).

Using a modified version of the mouse model in which IL-17A expression was induced by tamoxifen, the authors showed that T_H17 cells also convert into T_R1 cells during an immune response. Comparison of the gene signatures of T_H17 cells and T_R1 cells confirmed that the conversion of T_H17 cells into T_R1 cells is associated with transcriptional reprogramming — a process known as transdifferentiation. In support of this, ex-T_H17 T_R1 cells were able to prevent T_H17 cell-mediated colitis.

The conversion of T_H17 cells into T_R1 cells seems to be a common phenomenon: transdifferentiation was observed during transient inflammation in the intestine, during secondary infection with the worm *Nippostrongylus brasiliensis* and during an acute infection with the bacterium *Staphylococcus aureus*. Interestingly, during the primary immune response to *N. brasiliensis*, T_H17 cells lost IL-17A expression and gained a T_H2-type phenotype. But when the mice were re-infected with *N. brasiliensis*, T_H17 cells converted into T_R1 cells, suggesting that this conversion is a physiological mechanism to limit potentially destructive immune responses.

Finally, the authors investigated the pathways that drive this transdifferentiation. They found that transforming growth factor-β1 (TGFβ1) promoted the conversion of T_H17 cells into T_R1 cells *in vitro*, with the downstream signalling molecule SMAD3 appearing to have an essential role. In addition, TGFβ1 induces the expression of aryl hydrocarbon receptor (AHR), which is known to promote *Il10* transactivation. Accordingly, the conversion of intestinal T_H17 cells into T_R1 cells was enhanced by the addition of AHR ligands to T cell cultures containing TGFβ1.

This study opens up potential new therapeutic opportunities for resolving inflammatory disease by forcing formerly pathogenic T_H17 cells to adopt an anti-inflammatory state.

Lucy Bird

> “ex-T_H17 T_R1 cells were able to prevent T_H17 cell-mediated colitis”

ORIGINAL RESEARCH PAPER Gagliani, N. *et al.* T_H17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature* http://dx.doi.org/10.1038/nature14452 (2015)