T-CELL DEVELOPMENT

Stimulating company

New research published in *Nature Immunology* shows that the co-stimulatory molecule ICOS (inducible T-cell co-stimulator) participates in amplifying responses of two $CD4^+$ T-cell subsets — T helper 17 (T_H17) cells and follicular T helper (T_{FH}) cells — by inducing the expression of the transcription factor MAF and regulating the production of interleukin-21 (IL-21).

ICOS has been linked to the development of T_{FH} cells and T_H17 cells, but it was previously unclear in which stage of their developmental pathways ICOS might act. To explore this issue, Kuchroo and colleagues used *Icos*$^{-/-}$ mice. Consistent with earlier reports that ICOS is required for T_{FH}-cell development, preliminary *in vitro* experiments revealed that only a few T_{FH} cells developed in *Icos*$^{-/-}$ mice. By contrast, the authors observed that there was no difference in the ability of naive $CD4^+$ T cells from wild-type and *Icos*$^{-/-}$ mice to differentiate into T_H17 cells in the presence of IL-6 and transforming growth factor-β (TGFβ). T_H17-cell development could also be efficiently induced *in vivo* in *Icos*$^{-/-}$ mice. However, further analysis indicated that *Icos*$^{-/-}$ $CD4^+$ T-cell populations that were expanded *in vitro* in the presence of IL-23 produced less IL-17 than wild-type T cells. This defect in IL-17 production was observed even when *Icos*$^{-/-}$ T cells were cultured with IL-6 and TGFβ prior to the addition of IL-23, which suggests that ICOS was required for the expansion of T_H17-cell populations in response to IL-23. Indeed, this unresponsiveness to IL-23 was found to be due to reduced expression of the IL-23 receptor (IL-23R) by *Icos*$^{-/-}$ T cells.

The previous finding that both T_H17 cells and T_{FH} cells produce IL-21, which is thought to amplify T_H17-cell responses by upregulating the expression of IL-17 and IL-23R, led the authors to investigate the functional relationship between these two T-cell subsets. Unexpectedly, they observed that, similarly to T_H17 cells, many T_{FH} cells also produced IL-17 and expressed IL-23R. Moreover, the ability of T_{FH} cells to produce IL-17 was increased in the presence of IL-23. Analysis of the few T_{FH} cells that developed in *Icos*$^{-/-}$ mice showed that they were significantly impaired in their ability to produce IL-17 and IL-21, even in the presence of IL-23.

To explore the mechanism by which ICOS regulates cytokine production, the authors carried out microarray analysis on T_H17 and T_{FH} cells. The transcription factor MAF, which is known to be downstream of ICOS, was found to be expressed at high levels in both T-cell subsets, and its expression was further increased when the cells were exposed to IL-23. *Icos*$^{-/-}$ T_H17 cells failed to upregulate the expression of MAF following activation in the presence of TGFβ and IL-6. Importantly, similarly to *Icos*$^{-/-}$ T cells, *in vitro* differentiation of *Maf*$^{-/-}$ T cells yielded fewer IL-17-producing cells and less IL-21 production than the differentiation of wild-type cells, confirming a role for MAF in ICOS-induced production of IL-21 and IL-17. Finally, a role for MAF-mediated IL-21 production in the development of T_{FH} cells was confirmed by the observation that fewer T_{FH} cells were generated in *Maf*$^{-/-}$ mice following antigen immunization.

Together, these data suggest that ICOS-mediated MAF expression induces IL-21 production that, in turn, promotes the proliferation of IL-17-producing T_H17 and T_{FH} cells.

Lucy Bird

ORIGINAL RESEARCH PAPER Bauquet, A. T. *et al.* The costimulatory molecule ICOS regulates the expression of c-Maf and IL-21 in the development of follicular T helper cells and T_H-17 cells. *Nature Immunol.* 21 Dec 2008 (doi:10.1038/ni.1690)