T CELLS

The T_{FH}-like transition of T_H1 cells

The extent to which T helper (T_H) cell subsets — including T follicular helper (T_{FH}) cells — are distinct cell lineages has been the subject of much debate in recent years. Now, new evidence suggests that early during their development T_H1 cells pass through a T_H1–T_{FH} cell stage, which involves a dynamic balance of signals mediated by the transcription factors signal transducer and activator of transcription 4 (STAT4), T-bet and B cell lymphoma 6 (BCL-6).

T_{FH} cells, which support germinal centre B cell responses, can be induced by interleukin-6 (IL-6) and IL-21 acting via STAT3, and these cells have been defined as a unique lineage based on the expression of BCL-6 and IL-21. By contrast, T_H1 cells are induced by IL-12 and interferon-γ (IFNγ) acting via STAT4 and STAT1, respectively, and they express T-bet and IFNγ.

In this study, the authors cultured naive T cells under T_H1 cell-polarizing conditions for 5 days. Approximately 25% of the cells in these cultures were shown to produce both IFNγ and IL-21 and to have phenotypic characteristics of both T_H1 and T_{FH} cells, including the expression of T-bet and BCL-6. IL-12-mediated activation of STAT4 was required for the expression by these cells of BCL-6 and IL-21, in addition to that of T-bet and IFNγ, and *Stat4*$^{-/-}$ mice had fewer T_{FH} cells and germinal centre B cells than wild-type mice early after immunization with ovalbumin. However, this T_H1–T_{FH} cell-like phenotype was transient (lasting up until day 5), and it was followed by a loss of IL-21 and BCL-6 expression but retention of IFNγ and T-bet expression.

So what is the molecular mechanism underlying this loss of the T_{FH} cell phenotype? IFNγ was shown to antagonize IL-21 expression at later time points, even though it was a positive regulator of IL-21 at early time points. IL-12-activated STAT4 induced the expression of *Il21, Bcl6* and *Tbx21* (which encodes T-bet), but T-bet repressed the expression of *Bcl6*. This suggests that, as differentiation progresses under T_H1 cell-polarizing conditions, T-bet suppresses the T_{FH} cell phenotype (possibly when a certain expression threshold is reached). Conversely, overexpression of BCL-6 suppressed both IFNγ and T-bet expression in T_H1 cells.

Finally, T_{FH}-like cells were rapidly generated in mice infected with *Toxoplasma gondii*, which induces a potent T_H1 cell response. However, most of the IL-21$^+$ T_{FH}-like cells that were isolated early after infection also expressed IFNγ and T-bet. Furthermore, loss of T-bet expression resulted in the generation of higher numbers of T_{FH} cells later during the infection, supporting the *in vitro* observations that T-bet is necessary to suppress the early T_{FH} cell-like characteristics of developing T_H1 cells.

So, these data suggest the existence of phenotypic heterogeneity between T_H1 and T_{FH} cells, whereby IL-12 signalling via STAT4 induces a transient T_H1–T_{FH} cell stage. The expression of T-bet, together with IFNγ, inhibits the T_{FH} cell-like phenotype, allowing full T_H1 cell differentiation.

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