

 T CELL DEVELOPMENT

## Lead role for BCL-6 in T<sub>FH</sub> cell development

The requirement for T cell help for B cells has been known for many years, but it is only recently that specialized T cells — T follicular helper (T<sub>FH</sub>) cells — have been identified that express high levels of CXC-chemokine receptor 5 (CXCR5), which enables them to localize to B cell follicles during T cell-dependent immune responses. Although the phenotype of T<sub>FH</sub> cells has been well characterized, the factors governing their differentiation are poorly understood. Now, three studies show that the transcription factor B cell lymphoma 6 (BCL-6) is a master regulator of T<sub>FH</sub> cell differentiation.

As BCL-6 is selectively expressed by the T<sub>FH</sub> cells in the T cell lineage, Yu *et al.* investigated the role of BCL-6 in T<sub>FH</sub> cell lineage commitment. They generated mixed chimaeras by injecting BCL-6-deficient and

BCL-6-sufficient fetal liver cells into recipient mice, which were then immunized with sheep red blood cells 8 weeks later. BCL-6-deficient T cells were unable to differentiate into T<sub>FH</sub> cells, showing that BCL-6 is essential for the development of T<sub>FH</sub> cells. Further experiments showed that T cell-restricted deficiency of BCL-6 also prevented the formation of germinal centres. BCL-6 expression was not required for the development of T<sub>H</sub>1, T<sub>H</sub>17 or regulatory T cells — in fact, overexpression of BCL-6 repressed the production of the key T<sub>H</sub>1-type cytokine interferon- $\gamma$  (IFN $\gamma$ ) and the T<sub>H</sub>17-type cytokine interleukin-17 (IL-17). Nurieva *et al.* also reported that overexpression of BCL-6 in T cells induced T<sub>FH</sub> cell differentiation and inhibited the differentiation of T<sub>H</sub>1, T<sub>H</sub>2 and T<sub>H</sub>17 cells. BCL-6 expression was regulated by IL-6 and IL-21, and was required by both T and B cells for germinal centre interactions.

BCL-6 is a transcriptional repressor, so how does it specify T<sub>FH</sub> cell fate? In the Yu *et al.* study, chromatin immunoprecipitation assays using human tonsil T<sub>FH</sub> cells and B cells showed that BCL-6 bound to the promoters for the transcriptional regulators T-bet (also known as TBX21) and retinoic acid receptor-related orphan receptor- $\gamma$ t (ROR $\gamma$ t), which determine T<sub>H</sub>1 and T<sub>H</sub>17 cell fate, respectively, resulting in the repression of IFN $\gamma$  and IL-17 production. Furthermore, BCL-6 also suppressed the expression of microRNAs that are thought to repress T<sub>FH</sub> cell gene expression.

Johnston *et al.* showed that BCL-6 was upregulated and B lymphocyte-induced maturation protein 1 (BLIMP1; also known as PRDM1), which antagonizes BCL-6, was strongly downregulated in T<sub>FH</sub> cells compared with non-T<sub>FH</sub> CD4<sup>+</sup> T cells. Constitutive overexpression of BCL-6 resulted in almost all T cells becoming T<sub>FH</sub> cells and enhanced both germinal centre formation and antibody responses. Expression of BCL-6 and differentiation of T<sub>FH</sub> cells were shown to require cognate interaction with B cells. Further experiments showed that the absence of BCL-6 expression in CD4<sup>+</sup> T cells prevented the formation of germinal centres. Retroviral overexpression of BLIMP1 prevented BCL-6 expression in CD4<sup>+</sup> T cells and greatly reduced the differentiation of T<sub>FH</sub> cells. Conversely, BLIMP1-deficient CD4<sup>+</sup> T cells showed enhanced T<sub>FH</sub> cell differentiation.

Taken together, these results show that BCL-6 is both necessary and sufficient for T<sub>FH</sub> cell development and provide further evidence to support the idea that T<sub>FH</sub> cells are a separate lineage of T<sub>H</sub> cells.

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ORIGINAL RESEARCH PAPERS Yu, D. *et al.* The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* 23 Jul 2009 (doi:10.1016/j.immuni.2009.07.002) | Nurieva, R. I. *et al.* Bcl6 mediates the development of T follicular helper cells. *Science* 23 Jul 2009 (doi:10.1126/science.1176676) | Johnston, R. J. *et al.* Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. *Science* 16 Jul 2009 (doi:10.1126/science.1175870)