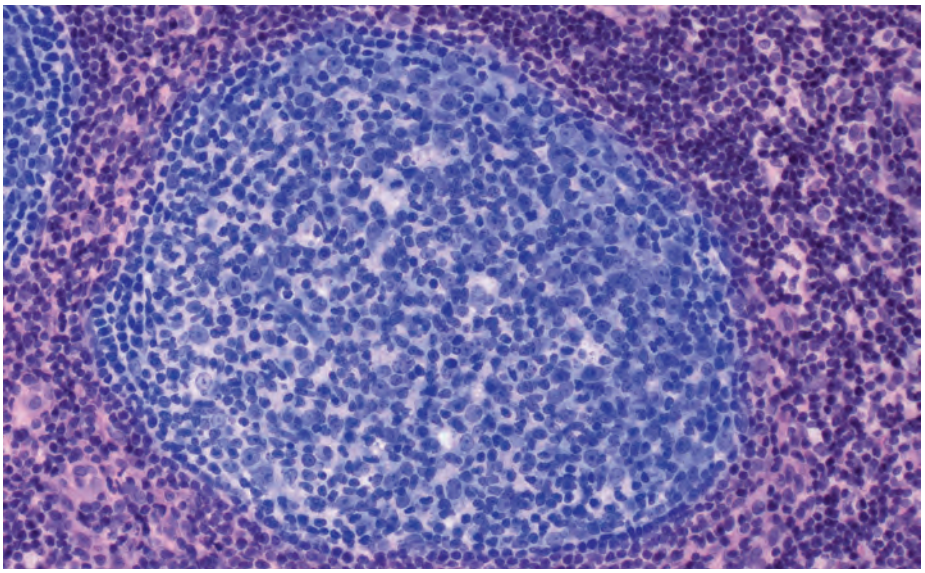
Milestone 19



T_{FH} cells: the mysterious B cell helpers

Pioneering studies in the late 1960s demonstrated a fundamental role for T cells in providing help to B cells but the T cell subset responsible for this function remained widely unrecognized for more than four decades. After the turn of the millennium, accumulating evidence for the existence of what we now call T follicular helper (T_{FH}) cells became too great to ignore.

In 1986, Timothy Mosmann and Robert Coffman introduced the concept that T_H cells consist of two subsets (T_H1 and T_H2 cells) with distinct and cross-regulating cytokine profiles (Milestone 11). In their model, T_H1 cells promote cell-mediated responses to intracellular pathogens, whereas T_H2 cells promote humoral responses to extracellular pathogens. Neatly explaining the apparent polarized nature of various inflammatory diseases, this idea became so ingrained in scientific doctrine that any idea that challenged it faced strong opposition.

The notion of a third subset of T_H cells emerged in 2000 with the identification of a specialized population of $CXCR5^+$ T cells that localized to the B cell follicles. Producing few cytokines, these cells did not fit into the standard T_H1–T_H2 classification and instead were strong inducers of antibody production. Apparent effector functions and the follicular location of these cells led to the proposal of a new type of T_H cell, termed 'follicular B helper T cells'.

"T cell-specific expression of BCL-6 is both necessary and sufficient for T_{FH} cell development"

Following the identification of additional T_H cell subsets — regulatory T cells (Milestone 15) and T_H17 cells (Milestone 18) — the binomial T_H1–T_H2 classification was on shaky ground. Emerging evidence of the importance of stable contact-dependent T cell–B cell interactions in germinal centres for antibody reactions gave additional credence to the idea of a T cell subset that is responsible for this function.

The final tipping point came in 2009 when four research groups, led by Shane Crotty, Joe Craft, Chen Dong and Carola Vinuesa, simultaneously identified BCL-6 as a lineage-defining transcription factor in T_{FH} cells. The four other known T cell subsets at that time already had their own unique master regulator that was central to the control of the differentiation and function of these cells. The identification of a T_{FH} cell master regulator solidified the concept of a fifth T cell subset, linking BCL-6 function, T_{FH} cell differentiation and T cell help to B cells in germinal centres.

Previous work in BCL-6-deficient mice had already shown an essential role for this transcription factor in antibody responses, but as germinal centre B cells also express BCL-6 this defect was attributed to a B cell-intrinsic effect. Gene expression profiling of the various T cell lineages revealed the selective expression of BCL-6 by T_{FH} cells. A combination of techniques were used to assess the effects of loss or gain-of-function of BCL-6 in T cells, both in vitro and in mice, including the use of adoptive transfer experiments and mixed chimera approaches. These experiments demonstrated that T cell-specific expression of BCL-6 is both necessary and sufficient for T_{FH} cell development and subsequent germinal centre reactions.

More specifically, microarray analysis revealed that BCL-6 promotes T_{FH} cell differentiation by repression of transcription factors that are involved in the differentiation of other T_H cell subsets (T_H1 and T_H17 cells). Johnston et al. further identified BLIMP1 as a reciprocal master repressor of T_{FH} cell differentiation, by antagonising the effects of BCL-6 and functioning to prevent T_{FH} cell gene expression in the other subsets.

The discovery of BCL-6 control of T_{FH} cells and subsequent demonstration of the central role of T_{FH} cells in B cell help ignited research in this area that continues to this day, including into the molecular and cellular mechanisms that regulate T_{FH} cell differentiation and function, and the function of these cells in protective antibody responses during infection or vaccination as well as during pathogenic antibody responses in autoimmunity, cancer and allergy.

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Nature Reviews Rheumatology

Milestone studies

Nurieva, R. I. et al. Bcl6 mediates the development of T follicular helper cells. *Science* **325**, 1001–1005 (2009) | Johnston, R. J. et al. Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. *Science* **325**, 1006–1010 (2009) | Yu, D. et al. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* **31**, 457–468 (2009)

Further reading

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