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GERMINAL CENTRES

An ephrin B1-based guidance system

Precise control over the migration of T cells and B cells to and from germinal centres (GCs) is crucial for effective humoral immunity. In particular, appropriate GC recruitment, retention and provision of help by T follicular helper (T_{FH}) cells are required to support GC B cell proliferation and differentiation. A recent study in *Science* shows that ephrin B1 (EFNB1) limits the retention of T_{FH} cells in GCs and yet promotes the production of IL-21 to support GC maintenance and plasma cell formation.

First, the authors noted that EFNB1 — which is best known for its role in guiding cell migration during development — is expressed at much higher levels on GC B cells than on naive B cells. However, wild-type mice reconstituted with B cells lacking EFNB1 did not show any impairment in GC formation or T_{FH} cell development in the draining lymph nodes 5 days after antigenic stimulation. However, at 7 days after stimulation, there were marked differences in the follicular and GC distribution of T_{FH} cells in the absence of B cell-expressed EFNB1 — in particular, more T_{FH} cells were found in GCs containing EFNB1-deficient B cells. Close tracking of T_{FH} cells in the two groups of mice using intravital microscopy revealed that T_{FH} cells entered the EFNB1-deficient GCs with a slightly increased frequency and left with a markedly reduced frequency, leading to an accumulation of T_{FH} cells in the absence of EFNB1.

Next, the authors tested whether EFNB1 might limit the retention of T_{FH} cells in GCs by disrupting antigen-specific T cell–B cell adhesion. Indeed, pre-activated T cells were less efficient in adhering to antigen-presenting B cells that expressed a high level of EFNB1 than to control B cells. Conversely, in a competitive GC reaction, EFNB1-deficient B cells more efficiently interacted with T_{FH} cells. To better understand the mechanism of EFNB1-mediated repulsion of GC T_{FH} cells, the authors used short hairpin RNA (shRNA) to knock down the expression of the T cell-expressed EFNB1 receptors EPHB4 and EPHB6. EPHB6 knockdown, but not EPHB4 knockdown, led to an accumulation of T_{FH} cells in the GCs, which suggests that EPHB6 mediates EFNB1-dependent repulsion of T_{FH} cells.

Contrary to expectation, the prolonged GC residence of T_{FH} cells occurring in the absence of the EFNB1–EPHB6 axis did not result in improved GC responses. Instead, the abundance of plasma cells in the spleen and bone marrow was reduced, which was accompanied by a decrease in serum antibody affinity for antigen. These defects were shown to be due to reduced levels of the T_{FH} cell-derived cytokine IL-21, which drives plasma cell development; T_{FH} cells from EFNB1-deficient GCs produced less IL-21 than those from control GCs. Knockdown of EFNB1 receptor expression indicated that EPHB4 is the receptor that transmits EFNB1 signals to stimulate IL-21 production by T_{FH} cells in the GC.

The combination of negative regulation of GC residence and positive regulation of effector functions of T_{FH} cells by EFNB1 seems counterintuitive, but the authors suggest that it may be a mechanism to ensure that the potentially dangerous GC reaction is productive but self-limiting.

Lucy Bird

> “more T_{FH} cells were found in GCs containing EFNB1-deficient B cells”

ORIGINAL ARTICLE Lu, P., Shih, C. & Qi, H. Ephrin B1-mediated repulsion and signaling control germinal center T cell territoriality and function. *Science* http://dx.doi.org/10.1126/science.aai9264 (2017)
FURTHER READING Qi, H. T follicular helper cells in space-time. *Nat. Rev. Immunol.* **16**, 612–625 (2016)