REGULATORY T CELLS

Pursuing a germinal centre career

Antigen-primed B cells form germinal centres, where, helped by follicular helper T (T_{FH}) cells, they develop into high-affinity plasma and memory B cells. This process is under stringent control to avoid uncontrolled B cell proliferation and production of autoantibodies. Now, two studies published in *Nature Medicine* report that germinal centre reactions are controlled by regulatory T (T_{Reg}) cells with a T_{FH} cell-like phenotype.

The two studies identified forkhead box P3 (FOXP3)$^+$ T_{Reg} cells expressing the T_{FH} cell-associated factors CXC-chemokine receptor 5 (CXCR5) and B cell lymphoma 6 (BCL-6) in the germinal centres of immunized mice. These follicular T_{Reg} cells expressed both T_{FH} cell-associated and T_{Reg} cell-associated genes and were suppressive *in vitro*.

So, do follicular T_{Reg} cells develop from T_{FH} or T_{Reg} cells? Adoptive transfer experiments indicated that follicular T_{Reg} cells originate from T_{Reg} cells. Moreover, Linterman *et al.* showed that thymus-derived but not induced T_{Reg} cells are the follicular T_{Reg} cell progenitors. In addition, they observed that, similarly to T_{FH} cells, follicular T_{Reg} cells require signalling through CD28 and SLAM-associated protein (SAP) for their generation, and both studies demonstrated that BCL-6 expression is essential for their differentiation. Thus, BCL-6 expression and SAP-mediated signalling lead to the development of follicular T_{Reg} cells from natural T_{Reg} cells.

But what is the function of follicular T_{Reg} cells? To address this, Linterman *et al.* generated chimeric mice that contained SAP-deficient T cells (which cannot differentiate into T_{FH} or follicular T_{Reg} cells), as well as T cells expressing the diphtheria toxin receptor under the control of the *Foxp3* promoter. Selective depletion of follicular T_{Reg} cells with diphtheria toxin resulted in increased numbers of T_{FH} cells and germinal centre B cells in response to immunization. Intriguingly, the numbers of non-antigen-specific B cells were increased, whereas the percentages of antigen-specific plasma cells and memory B cells were reduced in chimeric mice lacking follicular T_{Reg} cells, compared with the numbers in control chimaeras. Thus, the authors suggest that follicular T_{Reg} cells limit T_{FH} cell numbers, and possibly select against those that are self-reactive, thereby providing a competitive advantage to high-affinity antigen-specific B cells.

By contrast, Chung *et al.* observed no increase in T_{FH} cell numbers in response to immunization when they transferred naive CD4$^+$ T cells together with BCL-6- or CXCR5-deficient T_{Reg} cells (which cannot differentiate into follicular T_{Reg} cells) into T cell-deficient recipients. In their model, the absence of follicular T_{Reg} cells resulted in increased numbers of germinal centre B cells but also in elevated levels of antigen-specific B cells and high-affinity immunoglobulins.

Taken together, the two studies describe the BCL-6-dependent differentiation of natural T_{Reg} cells into follicular T_{Reg} cells, which negatively regulate germinal centre B cell numbers. The seemingly opposing conclusions on the effect of follicular T_{Reg} cells on antigen-specific B cell responses may rely on the experimental approaches used, and further research will clarify the contribution of follicular T_{Reg} cells to the regulation of germinal centre reactions.

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ORIGINAL RESEARCH PAPERS Linterman, M. A. *et al.* Foxp3$^+$ follicular regulatory T cells control the germinal center response. *Nature Med.* **17**, 975–982 (2011) | Chung, Y. *et al.* Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nature Med.* **17**, 983–988 (2011)

FURTHER READING Campbell, D. J. & Koch, M. A. T_{reg} cells: patrolling a dangerous neighborhood. *Nature Med.* **17**, 929–930 (2011) | Campbell, D. J. & Koch, M. A. Phenotypical and functional specialization of FOXP3$^+$ regulatory T cells. *Nature Rev. Immunol.* **11**, 119–130 (2011)