REGULATORY T CELLS

CD8⁺ T_{Reg} cells join the fold

Most research to date on regulatory T (T_{Reg}) cells has focused on the CD4⁺FOXP3⁺ T_{Reg} cell population. Although a subset of CD8⁺ T cells has been shown to suppress CD4⁺ T cells, little is known about the exact function of CD8⁺ T_{Reg} cells. Reporting in *Nature*, Kim *et al.* show that CD8⁺ T_{Reg} cells suppress autoantibody formation and the development of systemic lupus erythematosus (SLE)-like disease through the inhibition of follicular helper T (T_{FH}) cells.

Previous studies have implicated the non-classical MHC class I molecule Qa-1 in CD8⁺ T_{Reg} cell-mediated suppression of autoreactive CD4⁺ T cells. So, the authors generated Qa-1-mutant mice in which CD8⁺ T cell receptor-mediated recognition of Qa-1 was disrupted but recognition of Qa-1 by natural killer group 2, member A (NKG2A) on CD8⁺ T cells and natural killer cells was intact. These Qa-1-mutant mice developed an autoantibody-dependent autoimmune disease that was similar to SLE at 4–6 months, suggesting a suppressive function for Qa-1-restricted CD8⁺ T cells.

T_{FH} cells, but not other CD4⁺ T helper cell subsets, were found to express high levels of Qa-1, suggesting that T_{FH} cells are the main targets of CD8⁺ T_{Reg} cells. Indeed, the number of T_{FH} cells, as well as the germinal-centre area and the number of isotype-switched B cells, was increased in Qa-1-mutant mice compared with control mice.

The suppressive CD8⁺ T cells seemed to belong to the CD44⁺ICOSL⁺ subpopulation:

when transferred to recombination-activating gene 2 (*Rag2*)^{-/-} mice that had been reconstituted with naive wild-type B cells and wild-type CD4⁺ T cells, these CD8⁺ T cells suppressed high-affinity antibody production by targeting Qa-1⁺ T_{FH} cells. However, suppression did not occur when *Rag2*^{-/-} mice were reconstituted with Qa-1-mutant CD4⁺ T cells. Further analysis showed that the suppression of T_{FH} cells by CD8⁺ T_{Reg} cells was dependent on perforin and interleukin-15.

Finally, Qa-1-mutant T_{FH} cells, but not wild-type T_{FH} cells, promoted robust antibody responses in syngeneic mice (which contained a full complement of CD4⁺ T_{Reg} cells), indicating that this immune response was controlled by the Qa-1-dependent suppression of donor T_{FH} cells by host CD8⁺ T_{Reg} cells.

So, inhibition of T_{FH} cells by CD8⁺ T_{Reg} cells is a fundamental mechanism for maintaining tolerance.

Olive Leavy

ORIGINAL RESEARCH PAPER Kim, H.-J., Verbinen, B., Tang, X., Lu, L. & Cantor, H. Inhibition of follicular T-helper cells by CD8⁺ regulatory T cells is essential for self tolerance. *Nature* 15 Sep 2010 (doi:10.1038/nature09370)