T CELLS

Colonial competition

“this model may explain how T cell numbers are regulated without a loss of diversity to the T cell repertoire”

In a recent study, Singh *et al.* propose a new mechanism to explain how expanded CD4⁺ T cell clones contract following the resolution of an immune response. They report that rare ‘deletor’ T cells are present in the peripheral T cell compartment and regulate the frequencies of specific neighbouring T cell clones by outcompeting them for an endogenous non-stimulatory T cell receptor (TCR) ligand. Importantly, this model may explain how T cell numbers are regulated without a loss of diversity to the T cell repertoire.

In an earlier study, the authors found that endogenous T cells regulate potentially autoreactive T cells in a model of lymphopenia-induced autoimmunity. When 5C.C7 cells (which are TCR-transgenic CD4⁺ T cells specific for the model antigen pigeon cytochrome *c* (PCC)) are transferred into mice that express PCC as an endogenous antigen, autoimmune disease ensues if the

recipients are lymphopenic, but not if endogenous T cells are present. Indeed, when polyclonal T cells are co-transferred with 5C.C7 cells into lymphopenic recipients, the 5C.C7 cells are slowly removed from the peripheral circulation and the mice do not develop disease. Using this system, the authors explored how polyclonal T cells are able to regulate the 5C.C7 cells. They found that 5C.C7 cells were not deleted if they were co-transferred into lymphopenic mice with other monoclonal T cell populations, even when the other population was also specific for PCC. This suggests that polyclonal T cells do not regulate 5C.C7 cells by competing for generic survival factors or for specific TCR agonists.

The authors next transferred 5C.C7 cells to PCC-expressing mice with a less diverse (although still polyclonal) T cell repertoire (their CD4⁺ T cells expressed a fixed TCR β chain but could generate a random TCR α chain). From these mice, they identified particular ‘centipools’ (populations expressing no more than 100 unique TCRs) that could regulate the 5C.C7 cells. Interestingly, the deletor centipools were not enriched for FOXP3⁺ T cells, and they could not regulate other T cell clones besides the 5C.C7 cells. By cloning and sequencing individual TCR α chains from the deletor centipools, the authors identified a monoclonal population of V α 2⁺ T cells that could recapitulate the deletor activity shown by the entire polyclonal CD4⁺ T cell population against the 5C.C7 cells. Notably, the V α 2⁺ T cells did not respond to PCC. Instead, the V α 2⁺ T cells and, to a lesser extent, the 5C.C7 cells weakly

responded *in vivo* to high doses of GP, a peptide generated from an endogenous retrovirus. Importantly, the V α 2⁺ T cells could prevent 5C.C7 cells from responding to GP *in vivo*. However, neither population responded to GP in conventional antigen-presenting assays. This suggests that GP is a non-stimulatory, subthreshold TCR ligand that may promote the survival of both populations, and that V α 2⁺ T cells regulate 5C.C7 cells by outcompeting them for GP.

Finally, the authors examined another model of lymphopenia-induced autoimmunity, in which disease is induced by a distinct population of monoclonal T cells. They found that polyclonal T cells also restrained the pathological monoclonal T cells in this system, but the V α 2⁺ T cell population did not. Thus, different CD4⁺ T cell clones seem to be controlled by unique populations of deletor T cells. The authors propose that the peripheral T cell repertoire comprises numerous small colonies, each of which operates as a homeostatic unit. T cells in any individual unit compete for survival signals that are delivered following the recognition of a subthreshold TCR ligand. Limiting competition for survival to such microcolonies of T cells may ensure that peripheral T cell numbers can be regulated without a loss in the overall diversity of the TCR repertoire.

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ORIGINAL RESEARCH PAPER Singh, N. J., Bando, J. K. & Schwartz, R. H. Subsets of nonclonal neighboring CD4⁺ T cells specifically regulate the frequency of individual antigen-reactive T cells. *Immunity* 27 Sep 2012 (doi:10.1016/j.immuni.2012.08.008)