

Interplay of T cell receptor- and IL-7 receptor-mediated signals for survival and homeostatic proliferation of naïve T cells

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The peripheral T cell pool is homeostatically regulated — integrating cell input from the thymus, cell proliferation, and cell death to maintain a remarkably constant total number of cells. T cells require input from both the TCR and IL-7-receptor for continued survival as quiescent naïve cells awaiting antigen stimulation. When the peripheral compartment is depleted of T cells, these survival signals become stimuli for antigen-independent proliferation, known as homeostatic proliferation. To better understand how these signals are integrated to promote T cell homeostasis, we have taken two approaches.

First, we have investigated the gene expression profiles of T cells along the continuum of peripheral maturation. T cells undergoing homeostatic proliferation acquire a surface phenotype and functional status similar to that of memory T cells. When gene expression profiles of naïve, activated, memory and homeostatically dividing CD8⁺ T cells were compared, we found that the profile of genes upregulated during homeostatic proliferation was for the most part a dampened version of that (over the naïve) of activated and memory populations. However, a minor set of genes was upregulated only in this population and distinguished CD8⁺ T cells proliferating in a lymphopenic environment from activated and memory populations, perhaps giving clues to the differential outcome of TCR- and IL-7-receptor-mediated signals by naïve versus homeostatically dividing T cells.

Second, the relationship between TCR- and IL-7-receptor-mediated survival signals is under exploration at both the cellular and molecular levels using mice that allow the T cell-specific, tetracycline-regulatable expression of both of these receptors. The kinetics of death and gene expression changes by T cells when either TCR- or IL-7-receptor-mediated signals, or both, are extinguished is being studied.

Relevant Publications:

- 1) Labrecque N, Whitfield LS, Obst R, Waltzinger C, Benoist C, Mathis D. How much TCR does a T cell need? *Immunity*. 2001 Jul;15(1):71-82.
- 2) Vivien L, Benoist C, Mathis D. T lymphocytes need IL-7 but not IL-4 or IL-6 to survive in vivo. *Int Immunol*. 2001 Jun;13(6):763-8.
- 3) Witherden D, van Oers N, Waltzinger C, Weiss A, Benoist C, Mathis D. Tetracycline-controllable selection of CD4(+) T cells: half-life and survival signals in the absence of major histocompatibility complex class II molecules. *J Exp Med*. 2000 Jan 17;191(2):355-64.
- 4) Goldrath, AW and MJ Bevan. Low-affinity ligands for the TCR drive proliferation of mature CD8⁺ T cells in lymphopenic hosts. *Immunity*. 1999 Aug;11(2):183-90.