Peripheral Tolerance Through T cell Receptor Revision

Pamela J. Fink; Department of Immunology; University of Washington, Seattle, WA 98195

Our model system for studying peripheral T cell tolerance consists of TCR Vα5 transgenic (Tg) C57BL/6 mice whose Tg α chain pairs with a diverse set of endogenous TCR β chains. As expected, greater than 98% of both $CD4^+$ and $CD8^+$ T cells express the transgene in young mice. While the $CD8^+$ peripheral T cell compartment remains uniformly $V\alpha5^+$, a weak peripheral tolerogen encoded by Mtv-8 drives the chronic selection against $V\alpha5^+CD4^+$ T cells. $CD4^+$ T cells undergo an age-dependent deletion, resulting in the inversion of the peripheral CD4:CD8 ratio that is correlated with the loss of transgene expression in the surviving cells. These $V\alpha5^-CD4^+$ cells exhibit a memory cell surface antigen phenotype, express diverse endogenous Vβ elements ($V\beta^{endo+}$), and can comprise up to 50% of the peripheral $CD4^+$ T cell compartment in middle aged Vα5 Tg mice. $V\beta^{endo+}$ $CD4^+$ T cells are self tolerant, and unlike their anergic $V\alpha5^+$ counterparts, proliferate strongly upon TCR crosslinking.

Tolerogen-driven TCR revision is likely the mechanism for the appearance of $V\beta^{endo+}CD4^+$ cells because the lymphocyte-specific components of the antigen receptor recombination machinery (RAG1, RAG2, and TdT) have all been detected in $V\alpha5^{low}$ and $V\alpha5^-$ $CD4^+$ peripheral T cells by RT-PCR. The appearance of recombination intermediates in these cells indicates both that the recombinase is functional and the TCR loci are accessible.

Recent work suggests the targets of this novel tolerance pathway are mature peripheral T cells, rather than thymocytes, transitional T cells, or recent thymic emigrants. The appearance of $V\alpha5^-CD4^+$ cells is restricted to the lymphoid periphery, and occurs with similar kinetics in normal and thymectomized mice. The undersized N regions in revised TCR genes distinguish these sequences from those generated in the adult thymus. Furthermore, the mature, memory cell phenotype of $V\beta^{endo+}$ $CD4^+$ T cells and their B cell- and CD28-dependence all point to their extrathymic origin. Recent experiments using Vα5 Tg reporter mice in which the expression of green fluorescent protein is driven by the RAG2 promoter demonstrate that spleen cells stimulated through the TCR can be induced to reexpress RAG genes, even in mice thymectomized several weeks previously. Our results demonstrate that tolerogen-driven receptor revision can target mature peripheral T cells and can expand the TCR repertoire extrathymically, contributing to the flexibility of the immune repertoire.

Relevant references:

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