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Distinct T cell clones are deleted during the two waves of thymic negative selection

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Abstract

T cells are the central mediators of adaptive immunity and provide diverse receptors to recognize pathogens. While this diversity protects the host from a wide variety of pathogens, it comes with the potential for harmful autoreactivity. To circumvent autoimmune disease, thymocytes bearing T cell receptors (TCRs) that bind with high affinity to self-peptide/MHC are removed in a process called negative selection, while cells with a low degree of affinity mature into conventional T cells. Recently, it has been shown that the process of negative selection occurs in two stages during thymocyte development, corresponding to medullary or cortical localization in the thymus. Little is known about the self-antigens that are presented and selected against in these locations, and thereby the corresponding T cell repertoires. We examined the T cell repertoires of these two deletion stages by sequencing thymocyte TCRs from mice with impaired negative selection (Bim−/−). These mice were crossed with transgenic Nur77GFP mice, in which GFP expression correlates with TCR signaling strength. Therefore, the rescued autoreactive clones can be identified in Bim deficient mice based on high GFP expression. The two pools of autoreactive clones – CD4+CD8+ double positive thymocytes (largely cortical and CCR7−) and CD4+ single positive thymocytes (predominantly medullary and CCR7+) – had only partially overlapping TCR sequences. As deletion selectively pruned clones, these observations indicate that thymocytes encounter different self-peptide/MHC molecules in the thymic cortex and thymic medulla. To further test if negative selection is TCR intrinsic, we are creating ‘retrogenic’ mice with auto-reactive TCRs identified from each wave.

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