

TCR down-regulation plays an important role in T cell homeostasis

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Signaling through the TCR and interleukin-7 receptor is crucial for the complex homeostatic mechanisms that maintain relatively stable numbers of T cells throughout life. However, a reduction in naïve T cell numbers and accumulation of memory T cells are typically observed in old individuals despite of the homeostatic mechanisms. The decline in naïve T cells leads to reduced TCR diversity and holes in the T cell repertoire. We have previously shown the di-leucine-based (diL) motif found in the CD3 γ chain of the TCR is required for normal TCR down-regulation and trafficking. Recently, we found that the CD3 γ diL motif plays a central role in fine-tuning TCR expression and TCR signaling, and that the motif is required for efficient expansion of virus-specific CD8⁺ T cells. The role of the CD3 γ diL motif in T homeostasis is unknown. In this study, we show that the numbers of naïve CD4⁺ and CD8⁺ T cells are reduced in mice with a mutated CD3 γ diL motif. The age-associated decline in naïve T cells and accumulation of memory T cells were accelerated in CD3 γ LLAA mice. This resulted in a complete dominance of memory T cells with very few naïve T cells in old CD3 γ LLAA mice. The accelerated decline in naïve T cells in CD3 γ LLAA mice was not caused by increased apoptosis but most probably by the combination of reduced thymic output of mature T cells and increased transition of naïve T cells to memory T cells. These results identify an important role of CD3 γ -mediated TCR down-regulation in T cell homeostasis.