Opposing regulation of cytokine and TCR sensitivity of naïve CD8 T cells by self-reactivity

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After CD8 single-positive thymocytes are positively selected with a weak affinity/avidity interaction of T cell antigen receptor (TCR) with a self-peptide bound major histocompatibility complex (MHC) molecules (self-pMHC), these cells leave thymus and constitute a dominant population of peripheral T cells as a naïve phenotype, which form a critical adaptive immune component protecting host from various pathogenic infections. In a steady state, these cells are long-lived in interphase with little or no cell division, for which naïve T cells require continuous TCR contacts with self-pMHC ligands, along with engagement of cytokine interleukin-7 (IL-7). Given prior notions that naïve T cells are heterogeneous in their TCR avidity for self-pMHC ligands – variable degree of mild self-reactivity – and previous observations that polyclonal naïve CD8 T cells of relatively high self-reactivity, namely $CD5^{hi}$ cells, better respond to cytokines than do those of low self-reactivity ($CD5^{lo}$ cells), we posit that there is a requirement for a compensatory mechanism by which restrains a subset bias toward dominating for $CD5^{hi}$ cells and accommodates fair and stable maintenance of peripheral naïve CD8 T cell pools with a broad range of self-reactivity. Indeed, for naïve CD8 T cells, we show here that in marked contrast to the responsiveness to cytokines, TCR responsiveness is far more sensitive for low self-reactive cells than for high self-reactive counterparts, which is surprising as prevailing notions support opposite cases. Here we will show a compelling evidence and plausible mechanism of how self-reactivity poses an opposing regulation for the responsiveness to essential homeostatic cues.