# Peripheral tolerance of CD8 T lymphocytes

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Peripheral tolerance prevents autoimmune attack by self-reactive T cells that escape thymic deletion. Tolerance mechanisms intrinsic to the T cell include T cell inactivation (anergy), deletion and 'tuning' of TCR signal transduction. The distinguishing molecular features that determine the difference between deletion and anergy are not known. Using an *in vivo* tolerance model in which anergy and deletion of CD8 T lymphocytes is determined by antigen dose or strength of signal, we identified features unique to each mechanism. As compared with cells undergoing deletion, anergic cells exhibited increased levels of CD122 and demonstrated responsiveness to IL-15, suggesting its serves as the survival cytokine for anergic cells. Anergic CD8 T cells also exhibited increased expression of negative co-stimulatory molecules characteristic of expressed of exhausted CD8 T cells, including PD-1, Tim-3 and NKG2A. Cells undergoing deletion exhibited increased expression of the pro-apoptotic molecule BIM, and reduced levels of expression of numerous proteins involved in cholesterol metabolism. Recently we have also examined the role of the protein tyrosine phosphatase, PTPN22 in maintaining T cell tolerance by 'tuning' down TCR signaling. It appears to play a particularly important role in reducing the strength of TCR signal in mouse and human memory T cells so as to prevent T cell activation in response to self-antigens.