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T CELL DEVELOPMENT

# Seeing self in a positive light

Weak interactions between T cell receptors (TCRs) and self-peptide–MHC complexes induce positive selection of double-positive thymocytes in the thymus. Naturally occurring self peptides involved in positive selection have been identified only for $CD8^+$ T cells. Now, two papers published in *Nature Immunology* have identified endogenous self peptides that can positively select MHC class II-restricted $CD4^+$ T cells and provide a link between positive selection and peripheral T cell activation and survival.

Both studies tested a panel of more than 90 self peptides for their ability to select an MHC class II-restricted TCR *in vitro*. Lo *et al.* identified a self peptide from the endocytic receptor protein gp250 (termed gp250 peptide) presented by the MHC class II molecule I-$E^k$ that positively selected AND TCR-transgenic thymocytes. Ebert *et al.* identified several endogenous peptides that positively selected I-$E^k$-restricted 5C.C7 TCR-transgenic thymocytes, the most potent of which was a peptide derived from the group-associated antigen–protease–polymerase (Gag–Pro–Pol) polypeptide (termed GP peptide). Interestingly, AND and 5C.C7 T cells recognize the same agonist peptide, a fragment of moth cytochrome *c* (MCC), in the context of I-$E^k$. Therefore, the fact that these two MCC–I-$E^k$-specific TCRs are positively selected by two distinct self peptides suggests that the process of positive selection involves a high degree of peptide specificity. Indeed, gp250 peptides with single-amino-acid substitutions at the predicted TCR contact residues did not induce positive selection of AND T cells.

Further analysis by both groups showed that the positively selecting gp250 and GP peptides, but not the non-selecting peptides examined, could also act as co-agonists and thereby enhance MCC–I-$E^k$-induced peripheral T cell activation (as determined by T cell proliferation and cytokine production). Lo *et al.* showed that the self peptide gp250 also enhanced the survival of AND T cells undergoing homeostatic proliferation, with a degree of specificity similar to that for positive selection. Together, the data indicate that positively selecting self peptides also influence the activation and homeostasis of peripheral MHC class II-restricted T cells.

The microRNA miR-181a enhances TCR sensitivity in thymocytes relative to mature T cells, so Ebert *et al.* examined the role of miR-181a in thymic selection. They found that inhibition of miR-181a in thymic cultures resulted in the development of self-reactive T cells specific for self peptides of moderate affinity that normally would induce negative selection. Double-positive 5C.C7 thymocytes were shown to downregulate miR-181a expression in response to acute stimulation with GP–I-$E^k$, indicating that positively selecting signals provide feedback to lower the TCR sensitivity threshold through the regulation of miR-181a expression, perhaps to avoid negative selection of these cells.

The data show that positive selection of MHC class II-restricted T cells is extremely specific for self peptides. This peptide specificity might be important for the selection of TCRs that can interact with those positively selecting self-peptide–MHC complexes that also contribute to the activation and maintenance of peripheral T cells. In addition, miR-181a facilitates negative selection of T cells that respond to moderate-affinity self-peptide–MHC complexes through the modulation of the TCR signalling threshold.

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**ORIGINAL RESEARCH PAPERS** Lo, W.-L. *et al.* An endogenous peptide positively selects and augments the activation and survival of peripheral $CD4^+$ T cells. *Nature Immunol.* 4 Oct 2009 (doi:10.1038/ni.1796) | Ebert, P. J. R. *et al.* An endogenous positively selecting peptide enhances mature T cell responses and becomes an autoantigen in the absence of microRNA miR-181a. *Nature Immunol.* 4 Oct 2009 (doi:10.1038/ni.1797)