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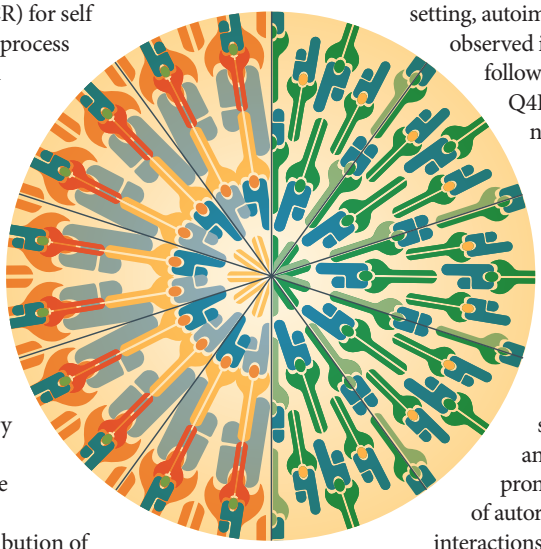
T CELLS

TCR affinity goes asymmetric

Most autoreactive T cells are deleted in the thymus, and the affinity of the T cell receptor (TCR) for self antigens regulates this process (negative selection). In addition, peripheral tolerance mechanisms control potentially autoreactive T cells that have escaped the thymus. Here, King *et al*. report that, similarly to what happens in the thymus, the affinity of antigen–TCR interactions in the periphery determines the fate of potentially autoreactive T cells.



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To assess the contribution of antigen–TCR affinity in peripheral tolerance, the authors transferred small numbers of ovalbumin (OVA)-specific $CD8^+$ T cells (OT-I cells) into transgenic mice expressing OVA as a self antigen in the pancreas (RIP–OVA mice). Antigenic stimulation of OT-I cells is required for the development of autoimmune diabetes in this mouse model. So, OVA peptide variants that are recognized by the OT-I TCR with affinities either above the threshold that leads to negative selection in the thymus (suprathreshold antigens) or below it (subthreshold antigens) were tested for their efficacy in disease induction.

Diabetes developed in RIP–OVA mice immunized with the suprathreshold antigen Q4 or Q4R7 but not in mice immunized with the subthreshold antigen V4 or Q4H7. Similarly, in a more physiological setting, autoimmune pathology was observed in RIP–OVA mice following infection with Q4R7-expressing, but not Q4H7-expressing, *Listeria monocytogenes*. These findings are striking given that the affinity of the OT-I TCR for Q4H7 compared with Q4R7 differs by only 1.5 fold.

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So, how do suprathreshold antigen–TCR interactions promote the pathogenicity of autoreactive T cells? These interactions induced higher expression levels of CD8 and the activation markers CD25 and CD69 as well as stronger activation of the adhesion molecule LFA1 on T cells than did subthreshold interactions. Moreover, Q4R7-stimulated OT-I cells proliferated more than Q4H7-stimulated OT-I cells. Q4R7-stimulated OT-I cells that had undergone many divisions also had high-level expression of the adhesion molecule VLA4, which was required for infiltration of the pancreas. Finally, suprathreshold-stimulated OT-I cells differentiated more readily into $IL\text{-}7R^{low}KLRG1^{hi}$ short-lived effectors cells than did subthreshold-stimulated OT-I cells.

Notably, antigen–TCR affinity controls T cell differentiation by dictating the type of cell division. Suprathreshold antigen–TCR interactions prolonged the contact of autoreactive T cells with antigen-presenting cells (APCs), partially as a result of increased LFA1 activation. These prolonged T cell–APC contacts correlated with the polarization of mitotic T cells and the subsequent asymmetric division of these cells. As a result of this asymmetric division, one daughter T cell (the proximal daughter) acquires more CD8 and LFA1 molecules than the other (the distal daughter). By contrast, subthreshold-stimulated OT-I T cells failed to establish prolonged contacts with APCs and proliferated through symmetric divisions.

Finally, the authors observed that, compared with distal $CD8^{low}$ daughter cells, proximal $CD8^{hi}$ daughter cells proliferate more (especially under limiting conditions, such as those present in the late phase of the immune response) and differentiate more efficiently into short-lived effectors cells. As a result, proximal daughter cells exhibited high pathogenicity even when transferred into RIP–OVA mice in very small numbers (10^4 T cells). Together, these findings indicate that an antigen–TCR affinity threshold determines the pathogenic potential of autoimmune T cells, by controlling the symmetry of T cell division and effector T cell differentiation.

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ORIGINAL RESEARCH PAPER King, C. G. *et al.* T cell affinity regulates asymmetric division, effector cell differentiation, and tissue pathology. *Immunity* **37**, 709–720 (2012)