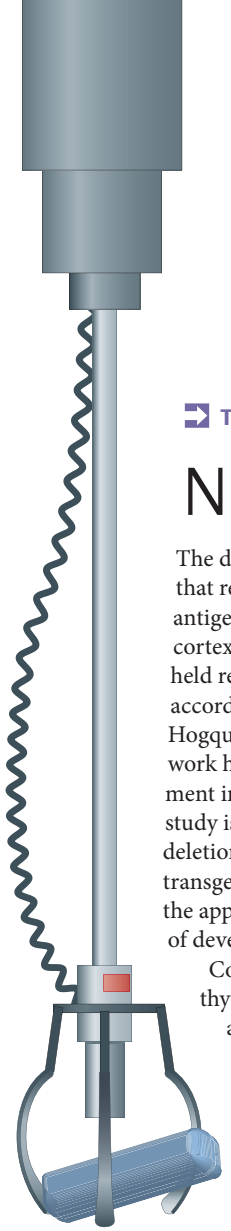


THYMOCYTE DEVELOPMENT

Negative selection in the cortex

The deletion of thymocytes that recognize a ubiquitous self antigen can occur in the thymic cortex without the traditionally held requirement of the medulla, according to new research by Hogquist and colleagues. Previous work has hinted at cortical involvement in negative selection, but this study is the first to show cortical deletion of thymocytes expressing a transgenic T-cell receptor (TCR) at the appropriate physiological stage of development.

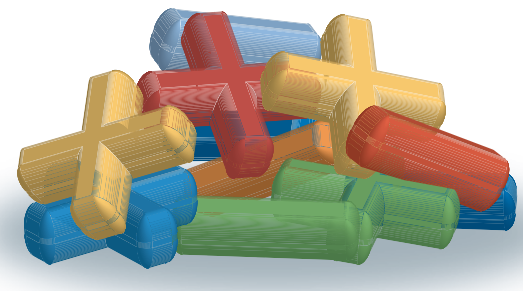
Conventional TCR-transgenic thymocytes express the TCR at the early double negative (DN) stage, and negative selection of these cells therefore occurs prematurely compared with wild-type thymocytes, which do not express surface TCR until the double positive (DP) stage. In the HY^{cd4} mice that were used in this study, expression of the TCR α-chain is delayed until the DN to DP transition, so that only DP thymocytes express the male antigen (HY)-specific transgenic TCR and are deleted in male mice, more closely reflecting the timing of deletion in wild-type mice.

To examine where this clonal deletion occurred, the authors used a mixed bone-marrow chimera strategy; this has the advantage of decreasing the frequency of TCR-transgenic cells and correcting the defects in thymic architecture that occur in conventional TCR-transgenic animals. Reconstitution of wild-type recipients with wild-type bone marrow mixed with bone marrow from HY^{cd4} mice that were deficient for CC-chemokine receptor 7 or its ligands — which are required for thymocyte migration to the medulla — did not result in a defect in the clonal deletion of HY^{cd4} thymocytes. This shows that the medulla is not involved in deletion in this case, which was supported by the fact that apoptotic HY^{cd4} thymocytes were found throughout the cortex, but not in the medulla, in male mice.

Female K14-HYp mice express the HY antigen specifically in cortical thymic epithelial cells (cTECs); transfer of mixed chimeras containing HY^{cd4} H2-D^{b}-deficient bone marrow into irradiated K14-HYp recipients, such that only the radioresistant cTECs of the recipient mice could present the HY antigen, resulted in the accumulation of a large population of activated DN HY^{cd4} thymocytes. So, cTECs can deliver a high-affinity signal to HY^{cd4} thymocytes that prevents further differentiation, but they are inefficient at inducing apoptosis. Further studies showed that apoptotic HY^{cd4} thymocytes are commonly found immediately adjacent to $CD11c^{+}$ cells in the cortex and that the conditional ablation of $CD11c^{+}$ dendritic cells in the thymus significantly decreased the percentage of apoptotic HY^{cd4} thymocytes.

These results, together with the observed kinetics of apoptosis, indicate that deletion can occur in the cortex *in vivo* but it is asynchronous; thymocytes that receive a high-affinity TCR signal from cTECs must interact with a second cell type, such as cortical $CD11c^{+}$ dendritic cells, for the efficient induction of apoptosis.

Kirsty Minton



ORIGINAL RESEARCH PAPER McCaughtry, T. M. *et al.* Clonal deletion of thymocytes can occur in the cortex with no involvement of the medulla. *J. Exp. Med.* 20 Oct 2008 (doi:10.1084/jem.20080866)