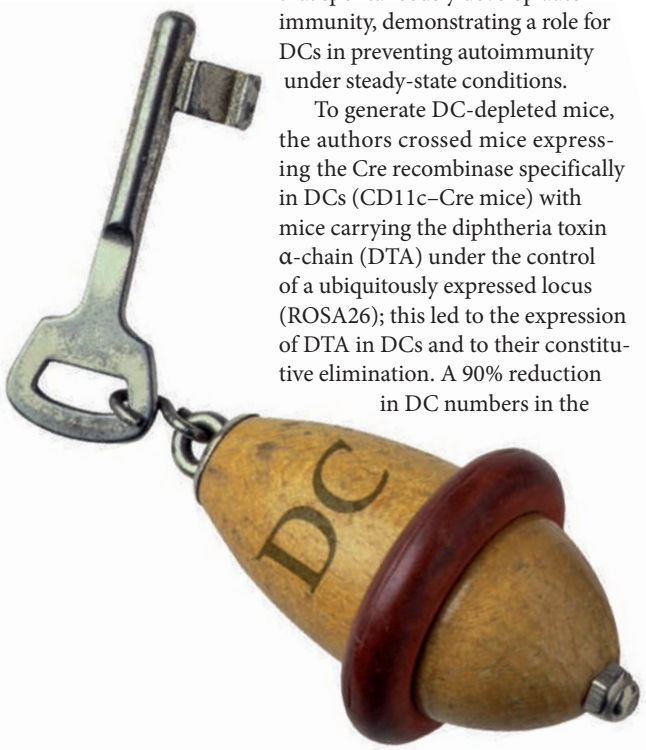
TOLERANCE

Key role for DCs in preventing autoimmunity

Immunological tolerance ensures that the body does not respond to self antigens, although the process is not foolproof. Tolerance involves both central tolerance (mediated by thymic epithelial cells and dendritic cells (DCs)) and peripheral tolerance mechanisms. However, a role for DCs in maintaining peripheral T-cell tolerance during steady-state conditions remains controversial. Now, Ohnmacht and colleagues have generated DC-depleted mice that spontaneously develop autoimmunity, demonstrating a role for DCs in preventing autoimmunity under steady-state conditions.



To generate DC-depleted mice, the authors crossed mice expressing the Cre recombinase specifically in DCs (CD11c–Cre mice) with mice carrying the diphtheria toxin α-chain (DTA) under the control of a ubiquitously expressed locus (ROSA26); this led to the expression of DTA in DCs and to their constitutive elimination. A 90% reduction in DC numbers in the thymus, spleen and lymph nodes was observed in DC-depleted mice compared with controls, and this depletion affected the main DC subsets (including myeloid, lymphoid and plasmacytoid DCs), as well as Langerhans cells. Negative selection of $CD4^+$ T cells was impaired in the thymi of DC-depleted mice, as shown by the 30% increase in CD4 single positive thymocytes compared with control animals.

The DC-depleted mice were smaller than the control mice at 6 weeks of age and had enlarged spleens and lymph nodes. These mice developed spontaneous autoimmunity that was characterized by inflammation in the intestines, autoantibody development and high numbers of T helper 1 (T_H1) and T_H17 cells. Several organs showed signs of infiltrates by both $CD4^+$ T cells and neutrophils, and 40% of the mice died by 8 weeks of age. When bone marrow chimeras were generated, autoimmune pathology developed following transfer of bone marrow from DC-depleted mice into wild-type mice, but co-transfer of bone marrow from wild-type and DC-depleted mice prevented the pathology. So, a specific lack of peripheral DCs leads to autoimmune pathology, demonstrating a role for DCs in peripheral tolerance.

This study shows that DCs are crucial in tolerance induction at many stages of T-cell development and homeostasis. The authors propose that the discrepancy between the results of this study and others in which DC depletion has had no effect on the development of autoimmunity might be the result of inefficient depletion of sufficient numbers of DCs to detect an effect on negative selection — it is known that even low numbers of antigen-presenting cells can mediate negative selection of thymocytes. Further work will be needed to determine whether the autoreactive $CD4^+$ T cells were primed by the few remaining DCs or by other antigen-presenting cells.

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ORIGINAL RESEARCH PAPER Ohnmacht, C. *et al.* Constitutive ablation of dendritic cells breaks self-tolerance of CD4 T cells and results in spontaneous fatal autoimmunity. *J. Exp. Med.* 23 Feb 2009 (doi:10.1084/jem.20082394)