TOLERANCE

Attack of the eTACs

A population of extrathymic autoimmune regulator (AIRE)-expressing cells (eTACs) found in secondary lymphoid organs can delete self-reactive T cells in the periphery, according to a study by Gardner and colleagues in *Science*.

The expression of a large number of peripheral tissue-specific antigens (TSAs) by medullary thymic epithelial cells (mTECs) under the control of AIRE is a well-known mechanism of central tolerance, but additional mechanisms must maintain self tolerance after T cells have left the thymus; this study now shows that AIRE might also be important for peripheral tolerance.

The authors used a transgenic mouse model in which the mouse *Aire* locus drives the expression of the gene encoding green fluoresent protein (*Gfp*) fused to the gene encoding islet-specific glucose-6-phosphate-related protein (*Igrp*) — known as *Adig* (*Aire*-driven *Igrp*–*Gfp*) mice. IGRP is a pancreatic β-cell-specific self antigen that is targeted by $CD8^+$ T cells in mouse and human autoimmune diabetes. In addition to the expected expression of GFP by mTECs in *Adig* mice, a distinct population of extrathymic GFP-expressing cells was observed in the T-cell zones of the lymph nodes and spleen. These cells — which were named eTACs — did not express CD45 or markers of B cells, dendritic cells or fibroblastic reticular cells, but were shown to be stromal in origin and shared some characteristics with mTECs, such as the expression of MHC class II molecules and epithelial-cell adhesion molecule (EpCAM). These $CD45^-$MHC class II^+EpCAM^+ cells were also shown to express high levels of *Aire* mRNA when sorted from non-transgenic mice.

Microarray analysis of eTACs from transgenic mice confirmed that AIRE is an active transcriptional regulator in these cells. The total number of AIRE-regulated genes and the percentage change in their expression level were lower in eTACs compared with mTECs, but there was a significant enrichment for TSAs among these genes, including several that are known autoantigens in human autoimmune diseases. Interestingly, the set of AIRE-regulated TSAs in eTACs was distinct from the set of AIRE-regulated TSAs in mTECs.

When congenic IGRP-specific, T-cell-receptor-transgenic T cells, known as 8.3 T cells, were transferred into *Adig* mice, they proliferated rapidly and then died within 2 weeks of transfer. The deletion of 8.3 T cells also occurred in irradiated *Adig* mice reconstituted with β_2-microglobulin-deficient bone marrow, in which only stromal cells can present antigen to T cells. This shows that the stromal eTACs are sufficient to mediate deletion of self-reactive cells in the periphery. In support of this, two-photon microscopy showed that stable, long-term interactions between eTACs and 8.3 T cells occurred in the lymph nodes of *Adig* mice early after T-cell transfer.

Additional studies are required to confirm the physiological relevance of eTACs in a non-transgenic setting, but these results indicate that a previously unknown population of AIRE-expressing cells in the periphery might have an important role in deletional self tolerance, perhaps functioning as a 'safety net' to target autoreactive T cells specific for TSAs that are not expressed in the thymus.

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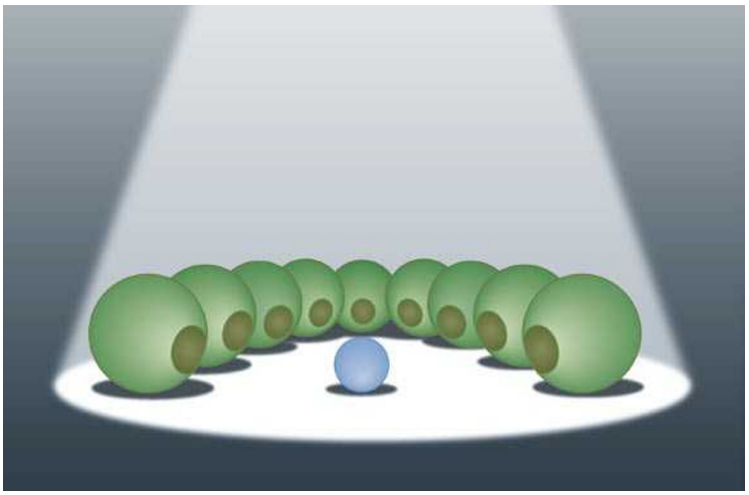

ORIGINAL RESEARCH PAPER Gardner, J. M. *et al.* Deletional tolerance mediated by extrathymic Aire-expressing cells. *Science* **321**, 843–847 (2008)