URLs

TOLERANCE

Function of AIRE clarified

By inducing the expression of otherwise tissue-specific proteins by medullary thymic epithelial cells (mTECs), the transcriptional regulator AIRE (autoimmune regulator) ensures that developing thymocytes are exposed and tolerized to the variety of self-proteins that they might encounter while patrolling the body. Although this function of AIRE is now well described, a recent study indicates that this might not be its only tolerance-promoting function.

A key role for AIRE in central tolerance was first proposed following the observation that humans or mice with mutations in *AIRE* suffer a range of organ-specific autoimmune diseases. Until now, studies have been unable to distinguish between two possible models of how AIRE might influence central tolerance. In the first, AIRE might promote the diversion of self-reactive thymocytes into $CD4^+CD25^+$ regulatory T (T_{Reg}) cells. In the second, AIRE might somehow increase the clonal deletion of self-reactive thymocytes.

To test the first possibility, Anderson *et al.* compared the number and function of T_{Reg} cells in wild-type and AIRE-deficient mice. Consistent with previous reports, the authors found no difference in the number or *in vitro* function of T_{Reg} cells in either group of mice. Moreover, in an *in vivo*-transfer model, AIRE-deficient T_{Reg} cells were as efficient as wild-type T_{Reg} cells at inhibiting the symptoms of autoimmune colitis induced in lymphopaenic mice by co-transfer of self-reactive T cells.

To rule out a role for defects in the positive selection of other regulatory-cell populations, the authors carried out thymus-transplant experiments. Athymic mice that received thymic-stroma grafts from AIRE-deficient donors developed autoimmune disease, similar to AIRE-deficient mice. When both AIRE-deficient and wild-type stroma grafts were transferred to athymic mice, no improvement in disease was observed, indicating that, under these conditions, autoreactive cells that were selected on the AIRE-deficient stroma could not be controlled by the wild-type regulatory-cell populations that were selected on the wild-type stroma.

To address the second possibility, that AIRE controls negative selection of self-reactive thymocytes, the authors studied mice that are transgenic for T-cell receptors (TCRs) that recognize tissue-specific antigens that are thought to be expressed in the thymus under the control of AIRE. In the presence of AIRE, thymocytes expressing a TCR transgene specific for an ovalbumin (OVA)-derived peptide were deleted on encounter with their cognate ligand expressed by mTECs. In AIRE-deficient mice, however, these TCR-transgenic thymocytes failed to be deleted, and organ-specific autoimmune disease rapidly ensued.

Although the prediction was that negative selection failed because of reduced expression of OVA in the absence of AIRE, this was not the case. There was no difference in the level of transcripts encoding OVA between wild-type and AIRE-deficient mTECs, implying another function of AIRE in mediating negative selection. It turns out that OVA-transgenic AIRE-deficient mTECs were less efficient at inducing proliferation of OVA-specific T cells than their AIRE-expressing counterparts. This defect was not because of reduced MHC or co-stimulatory molecule expression but, instead, might rest in differences in expression of chemokines, or antigen presentation or processing factors.

So, AIRE functions by ensuring negative selection of self-reactive cells and not positive selection of regulatory cells, and it achieves this not only through its ability to induce promiscuous gene expression but also by providing mTECs with the means for effective antigen presentation.

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References and links

ORIGINAL RESEARCH PAPER Anderson, M. S. *et al*. The cellular mechanism of Aire control of T cell tolerance. *Immunity* **23**, 227–239 (2005)