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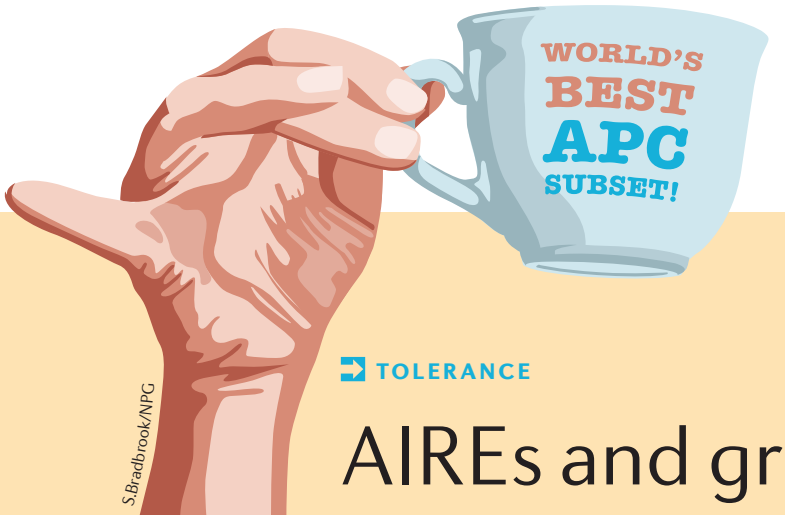

S.Bradbrook/NPG

TOLERANCE

AIREs and graces

Numerous distinct antigen-presenting cell (APC) populations in the thymic medulla are thought to contribute to self-tolerance — that is, the deletion of overtly autoreactive T cells and the generation of regulatory T (T_{Reg}) cells. But is one APC subset more important than the others in these tolerance mechanisms? A recent study suggests that bone marrow-derived APCs (BM-APCs) and medullary thymic epithelial cells (mTECs) both contribute to shaping the self-tolerant T cell repertoire. In addition, antigen transfer between mTECs and CD8α$^+$ dendritic cells (DCs) enables these subsets to share the burden of inducing tolerance to self-antigens that depend on autoimmune regulator (AIRE) for their expression.

> APC subsets contribute fairly equally to the presentation of AIRE-dependent antigens

The authors studied the mature T cell repertoire that is generated in mice with a selective reduction of MHC class II expression in mTECs or in BM-APCs. For easier analysis, T cell receptor (TCR) diversity was limited by using a transgenic fixed TCRβ chain. TCR repertoire analysis revealed that both BM-APCs and mTECs can mediate negative selection (of both conventional T cells and T_{Reg} cells) and induce T_{Reg} cell development, albeit with BM-APCs having a greater effect on the T_{Reg} cell repertoire than mTECs. However, different clusters of TCRs were negatively selected when repertoires were generated in mice with MHC class II ablation in BM-APCs or in mTECs, or in wild-type animals, which suggests that the different APCs select different TCR specificities. Consistent with this, 10 of the 15 most frequent TCRs were selected by BM-APCs, whereas only 6 of the 15 were selected by mTECs, which seem to select a substantial portion of the less frequent T_{Reg} cell TCRs. Their observations also implied that certain TCRs instruct developing conventional T cells or T_{Reg} cells to undergo negative selection. For example, a TCR clone that is rare in the normal T_{Reg} cell TCR repertoire is common when MHC class II is deleted in BM-APCs.

TECs are the only APCs in the thymus that express AIRE, which is responsible for driving thymic expression of tissue-specific antigens. So, are TCRs that are specific for AIRE-dependent antigens only selected by mTECs? Comparison of the T_{Reg} cell TCRs selected in *Aire*$^{-/-}$ mice and in mice lacking MHC class II on mTECs or BM-APCs showed that the APC subsets contribute fairly equally to the presentation of AIRE-dependent antigens. The authors explain the involvement of BM-APCs in AIRE-dependent antigen presentation by showing that antigens can be transferred from mTECs to BM-APCs (specifically CD8α$^+$ DCs).

So, spare the airs and graces, no one APC subset is better than another; the task of inducing tolerance is shared between APCs, although each APC subset is important for generating a diverse and self-tolerant T cell repertoire.

Lucy Bird

ORIGINAL RESEARCH PAPER Perry, J. S. A. *et al.* Distinct contributions of Aire and antigen-presenting-cell subsets to the generation of self-tolerance in the thymus. *Immunity* **41**, 414–426 (2014)
FURTHER READING Klein, L. *et al.* Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nature Rev. Immunol.* **14**, 377–391 (2014)