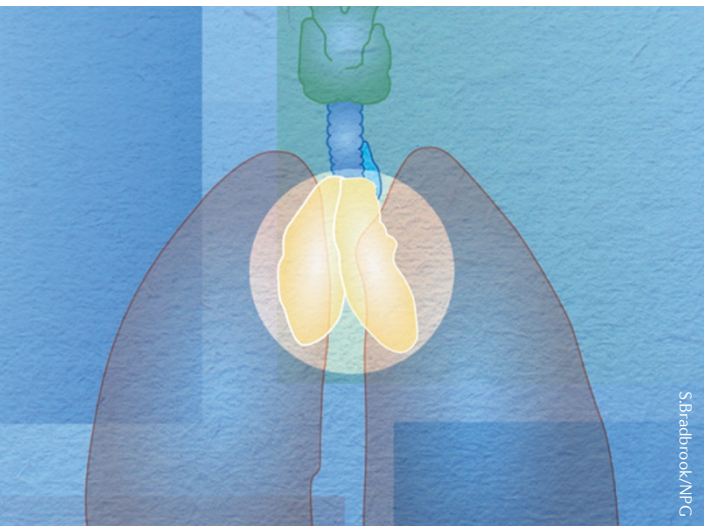
B CELLS

# Mediators of central tolerance

The deletion of self-reactive T cells during thymocyte development (a process termed central tolerance) is thought to be mediated mainly by medullary thymic epithelial cells (mTECs) and dendritic cells (DCs) via distinct mechanisms. Reporting in *Immunity*, Klein and colleagues now show that B cells can also mediate central tolerance following 'licensing' by thymocytes.

mTECs express the autoimmune regulator (AIRE) protein — which, in addition to other functions, mediates the promiscuous expression of tissue-restricted antigens (TRAs) — and directly present TRAs for T cell tolerance induction. By contrast, DCs acquire self-antigens from the serum or the periphery, or by 'handover' from mTECs, to mediate central tolerance. While assessing the expression pattern of AIRE in the thymus, the authors noted a non-epithelial AIRE$^+$ cell population, the majority of which also expressed the B cell marker CD19. Further analysis confirmed their B cell identity and showed that only thymic B cells, and not peripheral B cells, expressed AIRE. Thymic B cells were also MHC class II$^{hi}$CD80$^+$ and had undergone class switching. These thymic B cells expressed some AIRE-dependent transcripts, although they were not enriched for TRAs.

> B cells that migrate into the thymus are licensed through CD40 ligation by CD4 SP thymocytes to mediate T cell central tolerance



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The phenotypic characteristics of thymic B cells were shown to emerge following the migration of mature peripheral B cells into the thymus and were dependent on ligation of CD40 by CD4 single-positive (SP) thymocytes; the authors referred to this microenvironmental reprogramming as thymic B cell licensing. Adoptively transferred MHC class II-deficient B cells failed to upregulate AIRE following entry into the thymus, which suggests that thymic B cell licensing requires CD40 signals in the context of MHC class II-restricted cognate B cell–CD4 SP thymocyte interactions.

B cells are extremely efficient at presenting antigen that has been taken up by the B cell receptor (BCR), and therefore it is possible that the BCR might have a role in self-antigen presentation in the thymus. However, the authors found that thymic B cell licensing did not depend on the BCR. In fact, BCR signalling in conjunction with CD40 ligation suppressed AIRE upregulation, which may explain why B cells in germinal centres (which receive both BCR and CD40 signals) do not express AIRE. However, the upregulation of MHC class II expression and immunoglobulin class switching was AIRE dependent, suggesting that AIRE influences thymic B cell licensing in a cell-intrinsic, feedforward manner.

Finally, using various experimental approaches with transgenic mice expressing haemagglutinin (HA) under the control of *Aire*, the authors showed that thymic B cells, but not peripheral B cells, can directly present an endogenous self-antigen (HA), the expression of which is induced upon thymic B cell licensing, and can promote the negative selection of HA-specific CD4 SP thymocytes.

These data show that B cells that migrate into the thymus are licensed through CD40 ligation by CD4 SP thymocytes to mediate T cell central tolerance through the direct presentation of a licensing-dependent endogenous self-antigen. However, the exact nature of the self-antigens remains to be determined.

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**ORIGINAL RESEARCH PAPER** Yamano, T. *et al.* Thymic B cells are licensed to present self antigens for central T cell tolerance induction. *Immunity* http://dx.doi.org/10.1016/j.immuni.2015.05.013 (2015)

**FURTHER READING** Klein, L. *et al.* Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). *Nat. Rev. Immunol.* **14**, 377–391 (2014)