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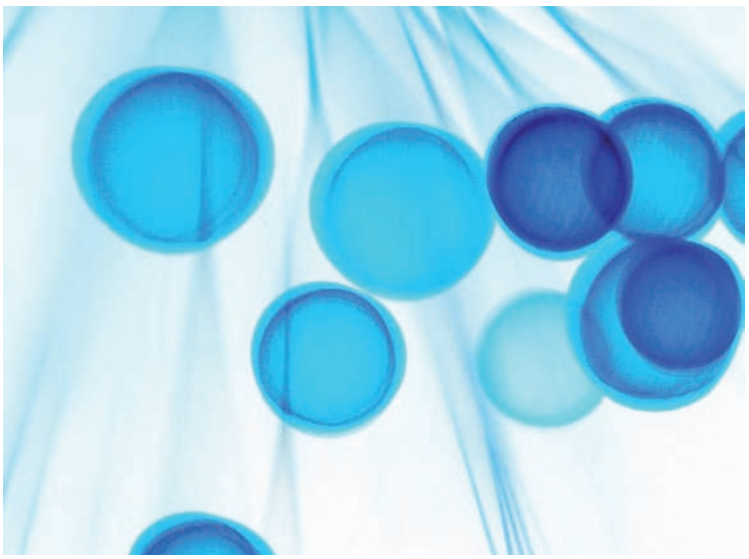
IMMUNE TOLERANCE

A T-cell-independent function for AIRE?

Mutations in the autoimmune regulator (*AIRE*) gene cause a breakdown in immune tolerance to self antigens, which leads to severe multi-organ autoimmunity and increased levels of circulating autoantibodies. Although this is thought to be mediated by self-reactive T cells that escape negative selection in the thymus, Karlsson and colleagues now provide evidence to suggest that AIRE is also important for controlling T-cell-independent B-cell responses in the periphery.

When the authors examined B-cell responses to a T-cell-independent antigen, they observed an increase in immunoglobulin production and activation level, but not in the total number, of B cells in *Aire*$^{-/-}$ mice compared with wild-type mice. Owing to the similarity between the phenotypes of *Aire*$^{-/-}$ mice and mice that overexpress the cytokine BAFF (B-cell activating factor), the authors then investigated whether BAFF might be responsible for B-cell hyperactivation in *Aire*$^{-/-}$ mice. Indeed, both mice and humans with AIRE mutations had increased serum levels of BAFF compared with wild-type controls. Furthermore, in agreement with the fact that marginal-zone B cells are highly responsive to BAFF, the authors found that the levels of immunoglobulin subclasses that are predominantly produced by marginal-zone B cells were increased in *Aire*$^{-/-}$ mice.

So, loss-of-function AIRE mutations cause an increase in circulating levels of BAFF, thereby promoting B-cell hyperactivation and antibody production, but what cells produce this cytokine? The authors used bone-marrow reconstitution experiments to show that the autoreactive T cells in *Aire*$^{-/-}$ mice do not seem to be involved in increased BAFF production; by contrast, bone-marrow-derived dendritic cells (DCs) from *Aire*$^{-/-}$ mice produced increased levels of BAFF in response to interferon-γ (IFNγ) compared with wild-type DCs. Although serum IFNγ levels were not increased in *Aire*$^{-/-}$ mice, the authors provided evidence to suggest that the increase in BAFF production might be caused by a cell-intrinsic dysregulation of DC responses to IFNγ: when *Aire*$^{-/-}$ DCs were treated with IFNγ *in vitro*, abnormal expression of a gene induced by signal transducer and activator of transcription 1, a key protein of the IFNγ-mediated signalling pathway, was observed.



Together, these results suggest that AIRE is important for immune homeostasis not only by ensuring the generation of a self-tolerant T-cell repertoire, but also through the regulation of peripheral DCs. In addition, this work helps to explain how mutations in AIRE contribute to the hyperactivation of B cells and, in particular, the BAFF-sensitive B-cell populations that are found in marginal zones.

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ORIGINAL RESEARCH PAPER Lindh, E. *et al.* AIRE regulates T-cell-independent B-cell responses through BAFF. *Proc. Natl Acad. Sci. USA* **105**, 18466–18471 (2008)