MUCOSAL IMMUNOLOGY

# Innate control of IgA

> ILC-derived soluble $LT\alpha_3$ controls IgA induction through regulation of T cell homing to the lamina propria

IgA is important for protecting against intestinal pathogens and maintaining a healthy gut flora. But it is not known exactly how it is regulated. New data published in *Science* show that soluble and membrane-bound forms of the cytokine lymphotoxin (LT) that are produced by innate lymphoid cells (ILCs) control the induction of IgA through distinct mechanisms.

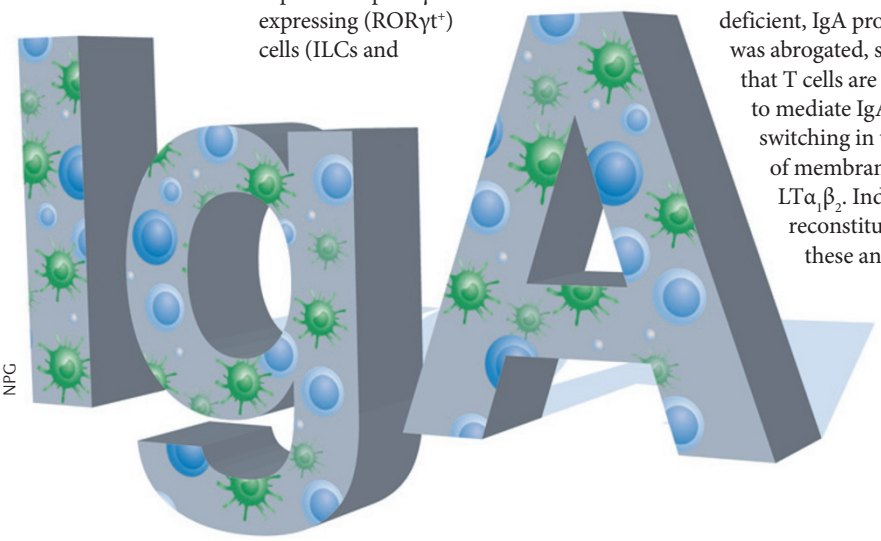
LT occurs in trimeric soluble ($LT\alpha_3$) or membrane-bound ($LT\alpha_1\beta_2$) forms. Previous studies have shown a crucial role for membrane-bound $LT\alpha_1\beta_2$ on ILCs in the generation of IgA through the formation of isolated lymphoid follicles (ILFs). So the authors were surprised to find that mice with a specific ablation of LTβ in retinoic acid receptor-related orphan receptor-γt-expressing ($ROR\gamma t^+$) cells (ILCs and double-positive thymocytes) lacked ILFs but had normal fecal IgA levels and only slightly reduced blood IgA levels compared with wild-type controls. By contrast, deletion of the gene encoding LTα in $ROR\gamma t^+$ cells led to a marked decrease in both fecal and blood IgA levels. This reduction in IgA levels altered the composition of the commensal bacteria: segmented filamentous bacteria were increased and Bacteroidetes were reduced in LTα mutant mice compared with controls. Consistent with a role for soluble $LT\alpha_3$ in intestinal IgA production, mice lacking its receptors — tumour necrosis factor receptor 1 (TNFR1) or TNFR2 — had reduced IgA levels.

When mice that lacked LTβ in ILCs were also made T cell deficient, IgA production was abrogated, suggesting that T cells are required to mediate IgA class switching in the absence of membrane-bound $LT\alpha_1\beta_2$. Indeed, reconstitution of these animals with wild-type or CD40 ligand (CD40L)-deficient T cells confirmed the involvement of CD40–CD40L signalling in T cell-dependent IgA class switching mediated by soluble $LT\alpha_3$. Further experiments suggested that ILC-derived soluble $LT\alpha_3$ controls IgA induction through regulation of T cell homing to the lamina propria.

Finally, in mice with $LT\alpha_1\beta_2$-deficient ILCs, dendritic cells expressed lower levels of inducible nitric oxide synthase and were less potent in inducing IgA *in vitro*. This suggests that membrane-bound $LT\alpha_1\beta_2$ on ILCs controls T cell-independent IgA production through the regulation of dendritic cells.

So, ILC-derived soluble and membrane-bound LTs — acting through T cell-dependent and T cell-independent mechanisms, respectively — organize adaptive immune responses in the gut and control the commensal composition.

*Lucy Bird*

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**ORIGINAL RESEARCH PAPER** Kruglov, A. A. *et al.* Nonredundant function of soluble $LT\alpha_3$ produced by innate lymphoid cells in intestinal homeostasis. *Science* **342**, 1243–1246 (2013)