Nature Reviews Immunology | AOP, published online 7 February 2014; doi:10.1038/nri3626

INNATE LYMPHOID CELLS

Nutrients direct immune balance

Immune cells can sense dietary components, and vitamin A deficiency is associated with immunosuppression, but how the immune system responds to the nutritional state of the host has been unclear. Now, Belkaid and colleagues report that a lack of vitamin A results in altered intestinal immune homeostasis, with a decrease in the frequency of group 3 innate lymphoid cells (ILC3s) and an increase in that of ILC2s.

> vitamin A deficiency affects developing ILCs and is associated with an increased frequency of ILC2s

To investigate the effects of vitamin A on intestinal barrier function, the authors examined ILCs — which have important roles in maintaining barrier integrity — in vitamin A-deficient mice. The frequency of ILC3s and production of the ILC3-derived cytokines interleukin-17 (IL-17) and IL-22 was substantially reduced by vitamin A deficiency in both wild-type and lymphocyte-deficient mice (*Rag1*$^{-/-}$ mice) compared with controls, whereas the number of ILC2s and their production of IL-4, IL-5 and IL-13 was increased. Inhibition of signalling by the vitamin A metabolite retinoic acid also resulted in decreased numbers of ILC3s and an increase in the frequency of ILC2s in both wild-type and immunocompromised mice. This indicates that retinoic acid controls the balance of these two ILC subsets in the mouse intestine.

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Next, the authors investigated whether retinoic acid signalling influences the development or maintenance of ILCs. Transfer of wild-type common lymphoid progenitors into ILC-deficient (*Rag1*$^{-/-}$*Il2rg*$^{-/-}$) mice resulted in the accumulation of both ILC2s and ILC3s in the intestinal tract. Treatment with retinoic acid led to increased numbers of ILC3s, whereas inhibition of retinoic acid signalling resulted in the accumulation of ILC2s. However, when purified mature ILC2s and ILC3s were exposed to retinoic acid or its inhibitor *in vitro*, there was no effect on their phenotype. Furthermore, the expression of IL-7 receptor α-chain (IL-7Rα), which is important for the development and survival of ILCs, was increased on both mouse and human ILC2s in the absence of retinoic acid signalling, and blocking IL-7 signalling *in vivo* halted the proliferation and accumulation of ILC2s in mice treated with a retinoic acid inhibitor, but not in control-treated mice. Thus, vitamin A deficiency affects developing ILCs and is associated with an increased frequency of ILC2s, which could be mediated by increased responsiveness to IL-7.

As ILC3s are important for the immune response against bacterial infections, the authors examined the effect of vitamin A on immunity to *Citrobacter rodentium* infection. Both wild-type vitamin A-deficient mice and mice treated with the retinoic acid inhibitor showed increased susceptibility to infection compared with control mice. The authors speculate that this could partly explain the observation that children with vitamin A deficiency have a predisposition to gastrointestinal bacterial infections.

So, what is the benefit of shifting to an enhanced ILC2-mediated response during vitamin A deficiency? ILC2s have an important role in protection against nutrient-consuming helminth infections. Indeed, the authors found that, compared with controls, both vitamin A-deficient mice and mice treated with retinoic acid inhibitors exhibited enhanced protection against infection with *Trichuris muris*. This enhanced protection was associated with an increased frequency of IL-13-producing ILC2s and was independent of adaptive immune cells. Furthermore, as type 2 immunity is associated with tissue repair and increased mucus production, this could improve barrier integrity.

This study shows that nutrient deficiency is not associated with a global immunosuppression, but instead can result in the specific activation of a distinct branch of barrier immunity. Furthermore, it emphasizes the role of ILCs as important mediators of intestinal immune homeostasis.

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ORIGINAL RESEARCH PAPER Spencer, S. P. *et al.* Adaptation of innate lymphoid cells to a micronutrient deficiency promotes type 2 barrier immunity. *Science* **343**, 432–437 (2014)
FURTHER READING Artis, D. & Peterson, L. W. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. *Nature Rev. Immunol.* In the press (2014)