Vitamin A helps gut T cells find their way in the dark

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Once activated, some T cells home to distinct sites in the body, such as the intestine and inflamed skin. Research in mice shows that dendritic cells in the gut produce a derivative of vitamin A, retinoic acid, that gives T cells directions.

The immune system is capable of generating subsets of activated T cells with distinct tissue-homing potential. For example, T cells activated in the lymph nodes that drain the skin or intestine localize preferentially to these areas. Immunologically, this phenomenon makes sense, because it allows activated T cells to target those tissues that are most likely to contain cognate antigen. In a recent issue of *Immunity*, Iwata *et al.*[1] show how activated T cells are marked for transit to the gut. They report that dendritic cells in gut tissue generate retinoic acid, which prompts the generation of gut-tropic T cells.

Naive T cells recirculate between the blood and secondary lymphoid organs and gain access to peripheral tissues only upon activation. In the gut, naive T cells are activated in gut-associated lymphoid tissues (GALT), including Peyer's patches and mesenteric lymph nodes. There, T cells are induced to express the integrin $\alpha_4\beta_7$ and chemokine receptor CCR9 (refs. 2,3), whose subsequent interactions with molecules in the small intestine (MadCAM-1 and CCL25) are critical for T-cell entry to this site.

In vitro experiments suggest that dendritic cells direct the expression of these gut-homing markers on T cells. Dendritic cells isolated from GALT but not peripheral lymph nodes or spleen induce CCR9 and $\alpha_4\beta_7$ on responding T cells[4–6]. Until now the underlying mechanism for this selectivity has been undefined.

Vitamin A is known to participate in intestinal immunity and has been shown in developing countries to reduce infant mortality from persistent diarrhea caused by infectious organisms. The authors hypothesized that vitamin A or its metabolites may function, in part, by regulating T-cell homing to the intestine. One major metabolite, retinoic acid, is generated through the sequential intracellular oxidation of vitamin A (retinol) to retinal and then to retinoic acid (**Fig. 1a**).

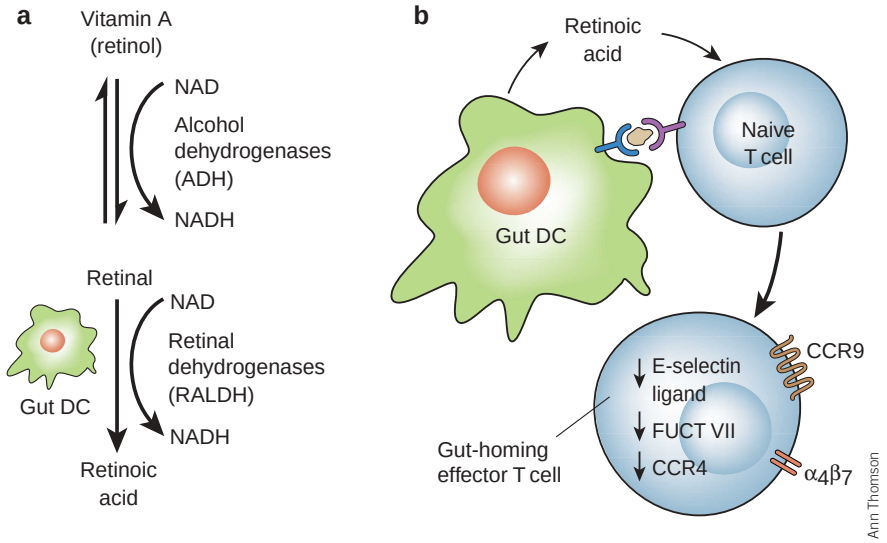

Figure 1 Retinoic acid–induced acquisition of gut-homing molecules during T-cell activation. (**a**) The generation of retinoic acid is dependent on the intracellular oxidative metabolism of retinol through retinal. Iwata et al. show that dendritic cells (DCs) isolated from gut-associated lymphoid tissue, but not spleen, are capable of generating retinoic acid from retinol, and suggest this ability to result from selective expression of retinal dehydrogenases (RALDH). (**b**) The presence of retinoic acid at low concentrations induces the gut-homing molecules CCR9 and $\alpha_4\beta_7$ on T cells and downregulates molecules implicated in skin homing (E-selectin ligands, CCR4).

Iwata *et al.* found that addition of picomolar concentrations of retinoic acid, but not retinol, to activated T cells *in vitro* induced the expression of $\alpha_4\beta_7$ and CCR9, while simultaneously suppressing expression of molecules associated with skin tropism. They went on to show that dendritic cells isolated from GALT (but not dendritic cells isolated from spleen) could convert vitamin A to retinoic acid.

Inhibition of an enzyme that catalyzes the final step of retinoic acid synthesis could abrogate the ability of these dendritic cells to induce $\alpha_4\beta_7$ expression on T cells—and an antagonist of the nuclear receptors for retinoic acid had the same effect. In the whole animal, the researchers found that removing vitamin A from the diet caused a reduction in the number of $\alpha_4\beta_7$-positive T cells in lymphoid organs and a dramatic depletion of $CD4^+$ T cells from the small intestinal mucosa (**Fig. 2**), but not from the liver or lung.

One approach to modulate the immune response in immune-related diseases is to interfere with the homing of effector T cells to specific tissues. The findings of Iwata *et al.* open the door for potential therapies targeting the vitamin A metabolic pathway, in order to regulate intestinal immune and inflammatory responses.

Before these results are harnessed, many more experiments need to be done. Questions include: which signals imprint GALT dendritic cells with the selective ability to generate retinoic acid? And are there additional ways to induce expression of $\alpha_4\beta_7$ and CCR9? *In vivo* experiments that specifically block retinoic acid activity are also called for.

Future experiments should take into account findings that CCR9 and $\alpha_4\beta_7$ are not always linked in terms of their function or expression. For example, $\alpha_4\beta_7$, but not CCR9, is involved in effector T-cell localization to the colon, and few T cells at this site express CCR9. In contrast, CCR9 has been implicated in thymic T-cell development

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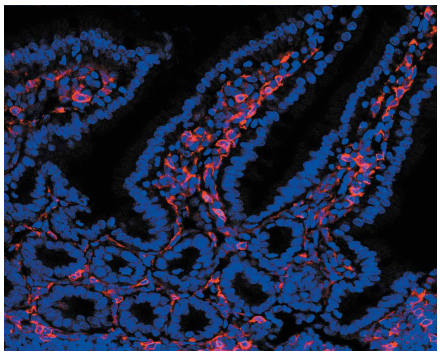

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Figure 2 T cells in the intestinal mucosa. In vitamin A–deficient mice, T cells do not localize to this site; nuclei in blue, T cells in red.

and the majority of thymocytes express CCR9, but do not express $\alpha_4\beta_7$ (ref. 7). It is possible that the thymus and small intestinal environment can imprint dendritic cells with the ability to induce CCR9 or $\alpha_4\beta_7$ and CCR9 on T cells, respectively. In this regard, epithelial cells in the thymus and gut may be developmentally related, because the thymic rudiment is in part derived from the embryonic gut tube[8]. The role of epithelial cells in dendritic cell imprinting warrants further study.

The body makes over 12 different types of retinoid dehydrogenase[9], the enzymes that catalyze the conversion of retinol through retinal to retinoic acid (**Fig. 1**). Although Iwata *et al.* show that dendritic cells from the mesenteric lymph nodes express higher levels of the retinal dehydrogenase RALDH-2 than peripheral lymph node and splenic dendritic cells, the picture with Peyer's patch dendritic cells is less clear. Whether selective expression of retinoid dehydrogenase underlies the ability of GALT dendritic cells to generate retinoic acid needs to be determined. Of note, the epithelium overlying Peyer's patches is a rich source of RALDH-1, and may contribute to the generation of retinoic acid at this site.

Perhaps most interesting from a potential therapeutic standpoint is how retinoic acid in GALT or other lymph nodes is regulated during infection or chronic inflammation. For example, intestinal inflammation boosts expression of the ligand of OX40, by dendritic cells in the mesenteric lymph nodes. OX40, a member of the tumor necrosis factor superfamily, in turn promotes the induction of $\alpha_4\beta_7$ on T cells and the subsequent localization of these cells to the intestinal mucosa in an animal model of colitis[10]. Because OX40 is preferentially expressed by activated T cells, T cells may themselves regulate dendritic cell expression of the enzymes involved in retinoic acid synthesis.

Retinoids have been used extensively in the treatment of T cell–mediated skin diseases such as psoriasis and in cutaneous T-cell lymphoma[11]. It seems possible that these beneficial effects are in part mediated by the ability of retinoic acids to downregulate markers of skin tropism on T cells. Similarly, retinol deficiency reduces insulitis in a mouse model of diabetes (nonobese diabetic mice); development of insulitis in these mice is partially dependent on $\alpha_4\beta_7$-positive T cells[12]. The best advice for now may be to take your vitamin A.

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Chipping away at gallstones

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Gallstones develop in response to an imbalance of lipids in bile, the digestive fluid produced in the liver. A compound that restores the balance prevents gallstone formation in mouse models (pages 1352–1358).

Gallstones are renowned for the severe pain they cause when they become lodged in the bile duct, an episode that often leads to surgery to remove the gallbladder. In this issue, Moschetta *et al.*[1] open the door to a more subtle approach. The researchers examine the mechanics of farnesoid X receptor (FXR), a transcription factor that regulates the composition of bile, the digestive fluid produced in the liver and stored in the gallbladder. They show that a pharmacological activator of FXR alters the composition of bile and alleviates cholesterol gallstone disease in mouse models.

Bile consists of a mixture of water, lipids, electrolytes and proteins. The primary lipid components of bile include bile acids, phospholipids and cholesterol. All of these molecules are secreted from the liver into the bile duct by active membrane transport systems (**Fig. 1a**).

Bile acids combine with phospholipids and cholesterol to form micelles consisting of a lipid-rich core and a water-soluble surface. Bile is concentrated and stored within the gallbladder and, when food enters the stomach, is released into the intestine where bile acids serve as detergents to emulsify dietary lipids and thereby facilitate their absorption.

Cholesterol gallstones develop when the capacity of bile acids and phospholipids to solubilize cholesterol is exceeded by the amount of cholesterol secreted into the bile[2]. As a result of the lipid imbalance, the micelles become supersaturated with cholesterol, giving rise to the formation of liquid crystals, an intermediate state in which cholesterol simultaneously has the physical properties of a liquid and solid.

As the condition progresses, the gallbladder secretes excess mucus. This mucus nucleates the formation of solid cholesterol crystals which become trapped in the gallbladder, form a mucus sludge and impair emptying of the gallbladder[2]. The cholesterol crystals aggregate into larger crystals and eventually form discrete gallstones[2].

Even after the formation of cholesterol gallstones, medical treatment is not always required and individuals may remain asymptomatic for several years. Biliary cholic may develop after gallstones become temporarily impacted in the gallbladder

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