

Vitamin A as a Regulator of Antigen Presenting Cells^{1,2}

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Abstract

Vitamin A has been long associated with immune system competence. Vitamin A deficiency is known to compromise many aspects of both innate and adaptive immune responses. Recent advances in retinol uptake and metabolism have identified the antigen presenting cell (APC) as a central immune cell capable of vitamin A metabolism. APC are now known to express retinaldehyde dehydrogenase and secrete retinoic acid. The retinoic acid produced has both autocrine and paracrine effects. Autocrine effects include upregulation of CD1d nonclassical major histocompatibility class I-like molecule and matrix metalloproteinase-9. Paracrine effects influence multiple lymphocyte lineage cell populations. Specifically, retinoic acid increases IgA isotype class switching by B lymphocytes, enhances regulatory T cell differentiation, and directs homing of lymphocytes to mucosa. CD1d lipid antigen presentation expands natural killer T cell populations. Previously, the focus of vitamin A action in adaptive immunity was on lymphocytes, but these recent advances suggest the APC may be the central player in carrying out the immune system functions of vitamin A. *J. Nutr.* 140: 1395–1399, 2010.

Historical vitamin A and immune function overview

The role of vitamin A in immune system maintenance has long been of interest to researchers. Vitamin A deficiency increases the neutrophil number in the spleen, peripheral blood, and bone marrow (1) while decreasing the monocyte numbers in the spleen and bone marrow (2,3). Deficiency also compromises the ability of macrophages and neutrophils to migrate to sites of infection, phagocytose, and kill bacteria (2,4). Vitamin A deficiency in rats leads to decreased natural killer (NK)⁵ cell cytotoxicity after infection, partially explained by decreased NK cell numbers, whereas treatment with dietary retinoic acid, a bioactive metabolite of vitamin A, can restore NK cell numbers within 1 wk (5). In adult men, whole body vitamin A stores are positively associated with peripheral blood NK cell and NK T cell numbers (6). Vitamin A deficiency has profound effects on the antibody-mediated immune response. Rodents deficient in vitamin A have impaired IgM and IgG response to tetanus toxoid vaccine (2), decreased specific IgM response to the

protein antigen hemocyanin (7), and a decrease in salivary IgA antibody during influenza A infection (8).

Vitamin A is required for CD4⁺ T helper (Th) lymphocyte stimulation of B cells to produce an appropriate antibody response to antigen. The addition of T cells from vitamin A-sufficient mice to B cells from vitamin A-deficient mice restores normal IgG₁ production by the B cells (9). Vitamin A deficiency enhances a Th1 response with increased secretion of interferon (IFN)- γ while suppressing the Th2 response (10). The addition of all-*trans* retinoic acid (atRA) inhibits the synthesis of IFN γ and enhances the development of CD4⁺ T cells into Th2 cells, partially through an antigen presenting cell (APC) intermediate via retinoic acid receptor (RAR)- α signaling (11,12). Recent advances in nutritional immunology have centered on APC in the metabolism and function of vitamin A (Fig. 1).

APC metabolize vitamin A

Adaptive immune responses by T lymphocytes require antigen processing and presentation by professional APC. Although B lymphocytes and macrophages express both major histocompatibility class I and II antigen-presenting molecules and can maintain T lymphocyte activation, dendritic cells (DC) are considered the principal professional APC capable of initiating naive T lymphocyte activation (13). As such, DC can and do play a pivotal role in determining T lymphocyte functional fate following activation.

In 2004, Iwata et al. (14) published a groundbreaking manuscript documenting that mucosal DC possessed the capability of metabolizing retinol to atRA. Importantly, these investigators also documented that CD11c⁺ cells (DC) from

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² A color version of Figure 1 is available with the online posting of this paper at jn.nutrition.org.

⁵ Abbreviations used: α -GalCer, α -galactosylceramide; atRA, all-*trans* retinoic acid; APC, antigen presenting cell; CC, C-C chemokine; DC, dendritic cell; FoxP3, forkhead box P3; iTreg, inducible T regulatory; IFN, interferon; IL, interleukin; iNKT, invariant natural killer T cell; MMP, matrix metalloproteinase; NK, natural killer; poly(I:C), polyinosinic:polycytidylic; RALDH, retinaldehyde dehydrogenase; RAR, retinoic acid receptor; STRA6, stimulated by retinoic acid 6; Th, T helper; TGF, transforming growth factor; TLR, Toll-like receptor.

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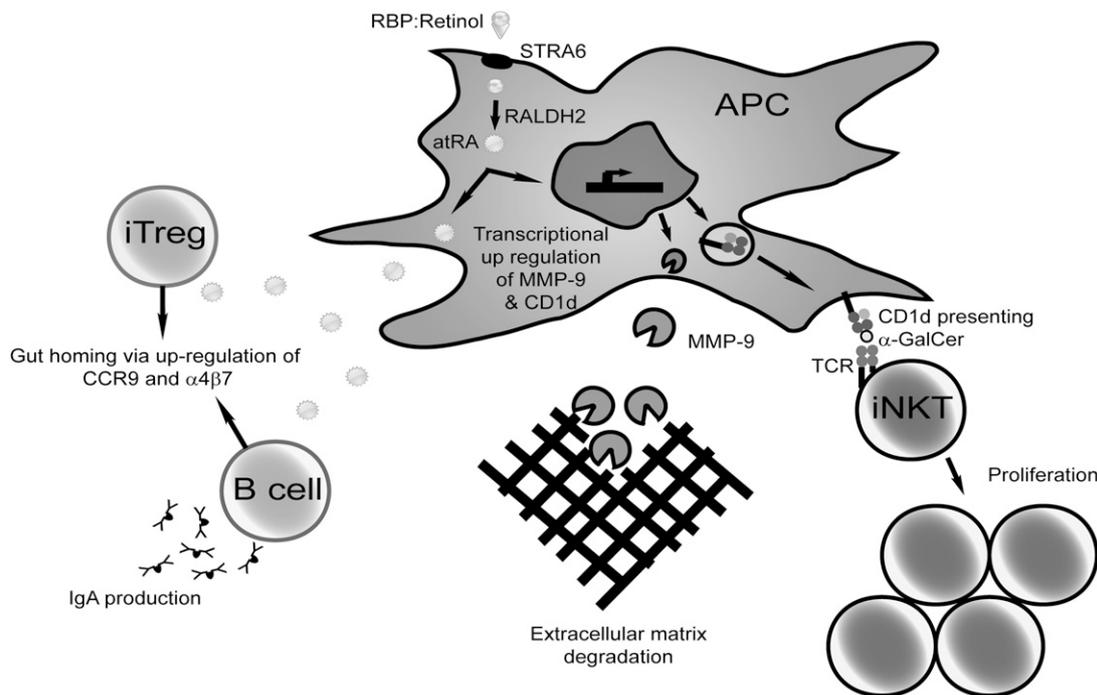


FIGURE 1 The metabolism and function of vitamin A in APC. The APC expresses STRA6, which binds RBP and allows the APC to acquire retinol. The APC expresses RALDH 2 for the metabolism of retinol to atRA. Secreted atRA, synthesized by the APC, acts on CD4⁺ T lymphocytes to induce a regulatory T cell phenotype (iTreg) and stimulates isotype class switching to IgA by B lymphocytes. In addition, both B and T lymphocytes upregulate CCR9 and $\alpha 4\beta 7$ in response to atRA, leading to the homing to gut mucosa. Synthesized atRA upregulates transcription of MMP-9 and CD1d by the APC. CD1d presents lipid antigens such as α -GalCer to invariant iNKT cells causing their proliferation. The secretion and activation of MMP-9 degrades gelatin, types I and IV collagen, and laminin in the extracellular matrix.

mesenteric lymph nodes expressed high levels of retinaldehyde dehydrogenase (RALDH) 2 (also known as aldehyde dehydrogenase 1A2), which is critical for cellular production of atRA. These authors also showed that Peyer's patch DC express RALDH1 mRNA and protein, albeit at much lower levels than RALDH2 expression in mesenteric lymph node DC. Interestingly, CD11c⁻ Peyer's patch cells expressed higher levels of RALDH1 compared with Peyer's patch DC. Lamina propria DC and liver stellate cells have also shown the capability to produce retinoic acid (15,16).

Others have also shown that interleukin (IL)-4 signaling in mesenteric lymph node DC induces CCR9 expression in naïve T cells through a mechanism requiring atRA (17). Spleen- and bone marrow-derived DC cultured with granulocyte-macrophage colony-stimulating factor and IL-4, as well as toll-like receptor (TLR) ligands in the case of bone marrow-derived DC, produce RALDH2 (18). TLR2 ligation induced expression of RALDH2 in splenic DC to increase atRA production (19). Lamina propria DC also express RALDH2 (15). Finally, treatment of DC with a synthetic activator of PPAR γ , rosiglitazone, results in increased RNA and protein production of retinol dehydrogenase 10, dehydrogenase/reductase 9, and RALDH2, resulting in increased production of atRA by DC (20).

atRA production effects on lymphocytes

Lymphocyte homing to gut mucosa. Compromised mucosal immunity is a well-established hallmark of vitamin A deficiency. New insights demonstrate that the production of atRA by APC is crucial for imprinting gut homing of lymphocyte populations. It has been documented that the membrane receptor for retinol: retinol binding protein, stimulated by retinoic acid (STRA) 6, is expressed in the spleen and that mesenteric lymph node DC can induce STRA6 expression in T lymphocyte cocultures (21–23).

In response to gut APC stimulation, mucosal addressin cell adhesion molecule 1, or integrin $\alpha 4\beta 7$, is increased on both mucosal B and T lymphocytes. In addition, atRA upregulates the expression of C-C chemokine (CC) receptor 9 and migration to its ligand CCL 25 on CD4⁺ Th cells and IgA secreting B cells. AtRA producing DC increase expression of gut-homing receptors CCR9 and integrin $\alpha 4\beta 7$ and the Treg-associated transcription factor forkhead box P3 (FoxP3) in naïve T cells in coculture experiments (18,24). Recent studies have also shown that CD103⁺ mesenteric lymph node DC are capable of inducing CCR9 expression on cytotoxic CD8⁺ T cells for gut homing through RAR signaling (25). Although liver DC and stellate cells express RALDH2, they are poor inducers of T cell mucosal homing phenotype (26). Thus, gut-associated DC increased the homing of B and T lymphocytes to the small intestine in the presence of physiological doses of atRA, and dietary depletion of vitamin A decreased the numbers of IgA secreting B cells and T cells in the lamina propria (14,27).

B lymphocyte IgA class switching. A key component of impaired mucosal immunity of vitamin A-deficient populations is depressed antigen-specific IgA synthesis and secretion. As described above, mucosal DC imprint gut homing to B lymphocytes, but Ig class switching to IgA also requires secretion of atRA by DC (27). The class switching was T cell independent but dependent on mucosal DC and further augmented by atRA alone and in combination with IL-6 and/or IL-5 (27). B cells, when cocultured with lamina propria DC but not with spleen-derived DC, increased IgA production through a mechanism involving retinoic acid, with even greater expression after addition of flagellin, a TLR5 ligand. Splenic DC were able to increase B cell IgA production after addition of the TLR4 ligand lipopolysaccharide (15). Additionally, transforming growth fac-

tor (TGF) β and atRA signal through Runx proteins to induce IgA class switching of B cells (28). Therefore, the depressed antigen-specific IgA responses found in vitamin A-deficient individuals may be a result of the lack of atRA production by APC.

RA enhances germinal center expansion. B cells, after activation by Th cells, migrate to lymphoid tissue secondary follicles where they proliferate, creating germinal centers where the B cells differentiate and mature through antibody class switch recombination and somatic hypermutation (29). In experiments where mice fed complete diets were immunized with tetanus toxoid in the presence or absence of the TLR3 ligand polyinosinic:polycytidylic acid [poly(I:C)], then given an oral dose of atRA or oil for 5 d, mice given both poly(I:C) and retinoic acid had a greater antibody response to immunization than with either treatment alone. The combination of atRA and poly(I:C) also increased the frequency of IgG₁ secreting plasma cells in the periarteriolar sheath, the T cell area of the spleen where naïve B cells are initially activated. Both treatments also increased the size of the germinal centers within the spleen, with the combination of treatments increasing the fraction of isotype switching within the germinal centers to IgG₁ isotype greater than with either treatment alone. The authors found that poly(I:C) treatment increased the frequency of follicular DC in the germinal centers, but the addition of oral atRA treatment did not markedly change the extent of the follicular DC network (30).

Inducible T regulatory cell development. Vitamin A deficiency impairs Th2 and enhances Th1 immune responses. Recently described inflammatory Th17 cells have a similar reciprocal relationship with inducible T regulatory (iTreg) cells. Addition of atRA in combination with TGF β favors iTreg cell development even in the presence of the Th17 inducing cytokine IL-6, whereas blocking atRA signaling increases Th17 cell development at the expense of iTreg cells (31). Vitamin A stores in men have been shown to be negatively associated with IL-17 and IL-6 serum concentrations. However, 1 wk of vitamin A supplementation did not change these concentrations (6). Others have shown no change in IL-17. Addition of atRA to cultured peripheral blood mononuclear cells after stimulation of the T cell receptor did not result in a change in IL-17 production (32). Subsequently, atRA activated suppressor of cytokine signaling 3 in spleen DC leading to development of iTreg cells (19). TGF β enhances IL-10 and FoxP3 expression by iTreg cells. However, atRA production by mucosal DC increases iTreg cell expression of only FoxP3 but not IL-10 (33,34). FoxP3 expression is increased via atRA-mediated histone acetylation of the *FoxP3* promoter (35). AtRA, in the presence of TGF β , blocks IL-4-mediated STAT6 binding to the *FoxP3* promoter, also resulting in increased histone acetylation (36). It has also been found that atRA increases TGF β -induced *FoxP3* expression in naïve T cells through an indirect mechanism involving atRA decreasing expression of IL-4, IL-21, and IFN γ produced from memory CD44^{hi} T cells through RAR α signaling, which otherwise inhibit naïve CD4⁺ T cell FoxP3 expression (37). Thus, atRA produced by APC helps to minimize inflammatory Th17 cells and promote iTreg cell development to prevent gut inflammation (38,39).

AtRA synthesis effects on DC

atRA enhances CD1d antigen presentation to invariant NK T cells. CD1d, a nonclassical major histocompatibility-I like

molecule expressed on APC, presents lipid antigen to activate invariant NK T (iNKT) cells. Upon activation by lipid antigens, iNKT cells promote a cell-mediated immune response (40). Treatment of DC with either PPAR γ or RAR α agonist enhances production of CD1d, presentation of the lipid antigen α -galactosylceramide (α -GalCer) and activation of iNKT cells (20). AtRA treatment of the monocytic cell line THP-1cell upregulated *CD1d* gene expression via a retinoic acid response element in the *CD1d* upstream promoter. It was also found that atRA treatment enhanced cultured spleen cell proliferation in response to the glycolipid antigen α -GalCer, indicating that CD1d upregulated by atRA may increase glycolipid presentation to iNKT cells (41).

Transcriptional upregulation of matrix metalloproteinase-9. Matrix metalloproteinase (MMP)-9 is a gelatinase produced and secreted as a zymogen that becomes active upon cleavage of its pro-peptide. MMP-9 degrades the extracellular matrix by cleaving gelatin, collagen types I and IV, and laminin (42). DC require MMP-9 activity to migrate in response to inflammation and through tight epithelial junctions (43,44). Immature DC cultured with pharmacological levels of supplemental atRA (1 μ mol/L) have increased migratory ability in vitro and when injected into tumors compared with that of DC cultured in medium containing physiological concentrations of atRA. This migration is greatly diminished by inhibiting MMP (45). Treatment of bone marrow-derived DC cultures with physiological concentrations of atRA after cells are cultured with an RAR α antagonist upregulated expression of *Mmp-9* within 4 h with maximal expression after 24 h and increased secretion of pro-MMP-9 into the culture medium, corresponding with decreased DC adhesion in these cultures (46).

Future directions

A subset of mucosal DC expressing the α E integrin CD103 induces iTreg cell development and diminishes experimental colitis pathology (47,48). Development of iTreg cells by mucosal CD103⁺ DC stimulation depends on atRA and TGF β (47). In addition, the mucosal CD103⁺ DC also induce the expression of CCR9 on iTreg cells (48). Recently, CD103⁺ DC were described as a subset of CD8 α ⁺ DC present in the marginal zone of the spleen that functions to promote tolerance to self antigens (49). It is not known if the spleen CD103⁺ DC, like their mucosal counterpart, are dependent on atRA for induction of tolerance to self antigens. In vitro addition of atRA to peripheral DC induced a mucosal DC phenotype (50). The overwhelming evidence that vitamin A is essential for iTreg development in mucosal sites suggests that vitamin A deficiency may contribute to the development of food allergies and other gastrointestinal diseases such as inflammatory bowel disease.

Vitamin A deficiency alters the numbers and function of NK cells (5). IL-15, produced by hepatic and pancreatic stellate cells and DC, supports memory CD8⁺ T, NK, and NKT cell numbers (16,51). Importantly, hepatic stellate cells store vitamin A and thereby play a prominent role in the regulation of circulating vitamin A. Although there is no published evidence that retinoic acid directly regulates IL-15 production or APC function of stellate cells, one might hypothesize that vitamin A deficiency could upregulate IL-15 production by stellate cells. Chang et al. (52) recently demonstrated that Langerin⁺ DC expand greatly in number in the mesenteric lymph nodes and lamina propria of vitamin A-deficient mice. These Langerin⁺ DC produce more IL-15 than their Langerin negative counterparts, but unlike mesenteric lymph node DC from control animals, they have

lower expression of RALDH2 and are compromised in their ability to induce regulatory T cell development. Therefore, there appears to be a close inter-relationship between DC, T cells, and NK cells dependent on vitamin A, with the precise mechanism currently unclear. Does retinoic acid production by DC influence T cell and NK cell numbers and function? Further, do altered DC numbers and function in vitamin A deficiency lead to the altered T cell and NK cell responses observed? The vitamin A status of individuals may have far reaching effects on immune parameters that are based on atRA production by APC.

Currently, for convenience, national vaccination days in developing countries provide large-dose vitamin A supplements at the same time as vaccines (53). In their role as APC, DC are targets for vaccine delivery (54). In light of the fact that DC can synthesize atRA, there is a potential risk in the simultaneous high-dose vitamin A supplementation and vaccination. In fact, a recent study in Ghana found that vitamin A supplementation at the time of vaccination is only beneficial for children with no previous vaccination history, whereas vitamin A supplementation of girls who had previously been vaccinated against measles and had received a follow-up diphtheria-tetanus-pertussis vaccination was associated with increased mortality (55). These are all areas of continued research into the role of APC in vitamin A function and metabolism and their impact on vaccination efficacy.

Acknowledgments

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