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Retinoic acid dependent regulation of immune responses by dendritic cells and macrophages

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Abstract

Dendritic cells (DCs) control the strength and quality of antigen-specific T and B cell responses. Recent advances point to a novel mechanism, in which metabolism of vitamin A into retinoic acid (RA) in DCs, regulate critical parameters of lymphocyte differentiation. First, RA enhances the induction of Foxp3⁺ T regulatory cells by DCs. Thus, specific subsets of intestinal DCs and macrophages constitutively express RA synthesizing enzymes, and induce T regulatory cells. In addition, RA programs DCs to imprint mucosal homing properties on activated T and B cells, and enhanced induction of immunoglobulin-A (IgA) by B cells. Here, we review these recent advances, in the context of the pleiotropic effects of RA in regulating diverse biological processes.

Introduction

A central problem in immunology is how the immune system launches robust immunity against invading pathogens, while maintaining tolerance to self. This problem assumes a particular significance in the intestine because of the trillions of commensal microorganisms and food antigens that confront the intestinal immune system every day. Recent advances suggest that dendritic cells (DCs) play a fundamental role in maintaining the balance between immunity and tolerance [1–5]. We now know that there are multiple subpopulations of DCs that differentially regulate the immune response, and that these subsets display tremendous functional plasticity in response to instructive signals from microbes and microenvironments [1–8]. Thus, understanding the molecular mechanisms by which DCs regulate the balance between immunity and tolerance, and indeed of how DCs fine tune the immune response, will be useful in the rational design of therapies against various autoimmune disorders. Emerging evidence suggest that DCs play a role in suppressing immune responses through the generation of anergic or regulatory T cells in the gut, and fine tuning the response by altering the Th1/Th2/Th17 balance [1–8]. However, the signaling pathways and transcription factors within DCs that regulate these responses are poorly understood. Emerging evidence suggests that the catalysis of vitamin A into RA in specific subsets of DCs, plays a vital role in the induction of Foxp3⁺ T regulatory cells. In addition, RA generation in DCs is also thought to imprint intestinal homing properties on activated T and B cells, and enhanced IgA secretion by B cells.

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Vitamin A and the retinoic acid signaling pathway

Retinoic acid (RA) is an active derivative of vitamin A that regulates diverse biological processes such as cellular differentiation, apoptosis, embryonic development, reproduction, and vision [9,10]. Importantly, it has been known for decades that vitamin A deficiency is associated with enhanced susceptibility to virtually all types of infections, and defects in both the innate and adaptive immune systems [11–20]. However, it is only recently that its mechanism of action is beginning to be revealed [21–24]. Furthermore, accumulating evidence suggests that vitamin A plays a very important role in oral tolerance and its deficiency has been linked to various autoimmune diseases and inflammatory responses [17,19,23–25]. Thus, these studies suggest that this molecule could be therapeutically useful in treating various autoimmune diseases.

Vitamin A metabolism is a tightly regulated process that includes several key enzymes involved in RA synthesis[26,27] Within the cell, RA is produced from vitamin A (retinol) via a two-step enzymatic pathway that oxidizes retinol to retinaldehyde (retinal), and then retinaldehyde (retinal) to RA (Figure 1). Oxidation of retinol to retinaldehyde requires the activities of several alcohol dehydrogenases (ADH-1,-4,-5) and several of these enzymes are ubiquitously expressed. In contrast, oxidation of retinaldehyde to RA requires the action of retinaldehyde dehydrogenases (RALDH), and is generally believed to be the critical and rate-limiting step in the biosynthesis of all-trans retinoic acid (ARTA) (Figure 1). RA produced is released and acts on different cells in a paracrine or autocrine fashion. Furthermore, synthesized RA is catabolized in the cytoplasm by the CYP26 class of P450 enzymes.

RA exists in two different isomeric forms in mice and humans: ATRA is the most abundant form, where as 9-*cis*-RA is present at significantly lower concentration. The transcriptional activities of RA (both ARTA and 9-*cis*-RA) are mediated through its binding to retinoid nuclear receptors such RA receptor (RAR) and the retinoid X receptor (RXR) [28]. Each class of retinoid receptor includes three isoforms encoded by separate genes: α , β , and γ and each gene has multiple splice variants that regulate several genes[28,29]. RARs form heterodimers with RXRs α , β or γ , which only bind to 9-*cis*-RA. In contrast, ARTA only binds to RARs[28]. These receptors form heterodimers (RAR/RXR) or homodimers (RXR/RXR) and are known to regulate more than 500 genes[30]. Specifically, these complexes bind to specific retinoic acid response element (RARE) or RX response elements (RXRE) in the promoter regions of target genes functioning as either ligand-inducible transcriptional enhancers or repressors [28,31].

RA is also known to directly influence the activation of many transcription factors through the phosphorylation of the transcription factor CREB, the mitogen activated kinase ERK1/2, JNK and p38[32–34]. Further, RA is known to repress the activation of AP1, another transcription factor, by inhibiting the induction of c-Jun and c-fos[35,36].

Recent studies have shown that RA regulates other nuclear receptors such as peroxisome proliferators-activated receptors (PPAR), vitamin D receptor, the liver X receptor and farnesoid X receptor which heterodimerizes with RXR and thereby regulates the activation of a number of transcription factors, e.g., NF- κ B, AP-1 and STAT-1 [37–39]. Recent work suggests that RA can exert opposing effects on cell growth, via the alternative activation of RARs versus PPAR β/δ [39].

Retinoic acid production in dendritic cells and macrophages

RA directly influences the development and effector functions of various immune cell types [2,21–23,40–42]. Emerging evidence suggest that RA plays a significant role in regulating the functions of APCs in the intestinal immune system. RA is produced by many subsets of

intestinal APCs, and facilitates the induction of T regulatory cells by these APCs. Here we will review the emerging data on the importance of specific DC and macrophage subsets in the intestine that express RALDH enzymes, and facilitate the induction of T regulatory cells.

It is now clear that there are several phenotypically distinct subsets APCs in the intestine, and the evidence suggests that they may differentially regulate Th1/Th2/Th17/T regulatory responses [2,3,4,5,43]. These subsets are situated in three major locations: the lamina propria (LP), Peyer's patches (PP) and mesenteric lymph nodes (MLN) [2,3,4,5,43]. Several years ago, Iwata and colleagues described that DCs in the mesenteric lymph nodes and Peyer's patches expressed RA producing enzymes, and were capable of producing RA from retinol [44]. Subsequently, much effort has gone into identifying the specific subsets of APCs in the intestine that produce these enzymes, and their roles in inducing T regulatory cells.

In the lamina propria (LP), there are two major subsets of DCs: CD11c⁺CD8 α ⁻CD11b⁺ and CD11c⁺CD8 α ⁺CD11b⁻ DCs (Figure 2). Lamina propria DCs can also be classified, based on the expression of the chemokine receptor CX3CR1 (the receptor of CX3CL1, fractalkine) [45] and the α - integrin CD103 [43,46–51]. The correlation between CX3CR1, CD103 and the “traditionally defined” subsets is at present murky, but our recent work suggests that CD11c⁺CD8 α ⁻CD11b⁺ DCs in the LP are CX3CR1⁺ and a major fraction of this subset also expresses CD103 [52]. In addition, a proportion of the CD11c⁺CD8 α ⁺CD11b⁻ DCs in the LP are CX3CR1⁻ and CD103^{bright} [52]. The functional properties of various subsets of DCs in the LP are only now beginning to be appreciated.

Recent work by Sun et al., suggests that DCs in the LP (some of which express CD103) induce T regulatory cells via a mechanism dependent on RA [51]. The conversion of naïve T cells to T regulatory cells could be impaired by adding inhibitors of retinal dehydrogenases, indicating that the RA produced by the DCs facilitated the conversion. Importantly RA alone could not induce the conversion of naïve T cells to T regulatory cells, but enhanced the conversion in the presence of TGF- β . Furthermore, both the CD103⁺ and CD103⁻ DC subsets in the lamina propria seemed capable of converting naïve T cells to T regulatory cells. In the mesenteric lymph node (MLN), it is only the CD103⁺ DCs, (and not the CD103⁻ DCs) which express *aldh1a2*, a retinal dehydrogenase involved in the conversion of retinal into RA [49], and, induce T regulatory cells, in the presence of TGF- β .

In addition to DCs, the gastrointestinal tract contains large number of macrophages (10–20% of all mononuclear cells). Mucosal macrophages are derived from unique blood monocytes precursors and are recruited to the lamina propria by the non-inflamed tissues [53–55]. Recent work from our laboratory has identified a population of CD11b⁺ F4/80⁺CD11c⁻ macrophages in the lamina propria of the small intestine (Figure 2) [52]. In the “steady-state” condition, these macrophage subsets are functionally different from splenic macrophages. For example, unlike splenic macrophages, intestinal macrophages constitutively produce high levels of the anti-inflammatory cytokine IL-10 [52], and produce lower amounts of pro-inflammatory cytokine upon stimulation with TLR ligands. Furthermore, these macrophages express higher levels of *aldh1a1* and *aldh1a2*, relative to their splenic counterparts. Importantly, these macrophages convert naïve CD4⁺ T cells to Foxp3⁺ T cells in vitro, in the presence of exogenous TGF- β , and via a mechanism dependent on both IL-10 and *aldh1a1* and *aldh1a2*. The question of whether this particular subset of macrophage is restricted to the lamina propria, or whether equivalent cells can also be found in the mesenteric lymph nodes, and whether they bear any relation to the *aldh1a2*⁺ DCs found in the lamina propria deserves further study. Furthermore, since naïve T cells are not thought to be present in the lamina propria, the question of whether these macrophages can present antigens to activated or memory T cells in situ to induce tolerance remains to be determined. Indeed, under non-

inflamed conditions, these cells may play a role in the induction and maintenance of T cell tolerance to food antigens and normal flora.

However, not all lamina propria APC subsets induce T regulatory cells. For example, our recent work also suggests that the CD11c⁺CD11b⁺ subset of DCs in the lamina propria of the small intestine, induces robust Th17 responses[52]; this is consistent with recent data demonstrating the potent capacity of these CD11c⁺CD11b⁺ lamina propria DCs, to promote the differentiation of Th17 cells[56]. Intriguingly, this latter study also showed a concentration dependent effect of RA in promoting Th17 responses – with low doses (1 nM) stimulating Th17 responses, and higher doses (10 μM) suppressing both Th17 and Th1 responses[56]. What could explain the apparent differences between the studies demonstrating potent T regulatory versus Th17 induction by DCs in the lamina propria? One likely reason is the nature of the particular subset of DC being studied; alternatively, the differences could reflect distinct isolation procedures involved.

In contrast to the gut DCs, DCs in the periphery are not thought to express *aldh1a1* and *aldh1a2*, but do constitutively express different isoforms of ADH and hence, they lack the ability to convert vitamin A to RA[44]. Although current studies have shown that RA is constitutively produced by several subsets of DCs and macrophages in the intestine several questions remain unanswered. For example, is this dependent on innate signals from commensals? If so, is it dependent on stimulation of APCs via TLRs, or other non-TLRs such as NOD like receptors, and C-type lectins. In this context, the question of whether RA synthesizing enzymes can be induced in APCs in other tissues, and if so, the mechanisms of their regulation are currently not known. Indeed, vitamin A is stored in other organs such liver, lungs and bone marrow[27,57]. So, it is not know whether DCs present in these organs constitutively express vitamin A metabolizing enzymes or it can be induced under certain conditions. It is interesting to note that a recent report suggests that IL-4 induces *aldh1a2* in MLN DCs in vitro[58]. Further research will be required to see the how these enzymes are regulated in different subpopulation of APCs during infection or in other inflammatory disease conditions.

Effects of RA on Lymphocytes

Effect of RA on imprinting mucosal homing properties on T cells

Emerging evidence shows that activated T cells with distinct phenotypes can home to different tissues depending on the expression of specific homing receptors. For example, activated T cells expressing $\alpha 4\beta 7$ and CCR9 preferentially migrate to the gut epithelium in response to thymus-expressed chemokine called TECK (also known as CCL25), and in response to the mucosal addressin cell adhesion molecule (MAdCAM)-1[44,47,59–62]. Early studies showed that antigenic stimulation T cells with DCs isolated from PP or MLN have the capacity to imprint gut-homing specificity on T cells. Importantly, a subsequent study by Iwata et al., has shown that the expression of $\alpha 4\beta 7$ and CCR9 on T cells and homing to the intestine is dependent on RA [44]. Consistent with this observation, DCs from PP and MLN can convert retinol to RA in vitro [44]. Furthermore, this study has shown that RA at very low concentration (1 nM) is sufficient to induce $\alpha 4\beta 7$ expression on T cells, even under Th-1 and Th-2 inducing conditions [44]. Finally, the expressions of CCR9 and $\alpha 4\beta 7$ on T cells, and the tropism of T cells to intestine can be effectively blocked by the RALDH inhibitor (citral) or the RAR inhibitor (LE540)[44]. Subsequently, several groups have shown that CD103⁺ DCs residing within the lamina propria, Peyer's patches, and MLN can imprint naïve T cells with the property of gut tropism [44,58,63–66]. These observations collectively suggest RA plays an important role in mucosal homing of activated T cells.

Effect of RA on modulating T regulatory cell differentiation

Recent studies have shown that RA, in concert with TGF- β , has ability to induce Foxp3 in CD4⁺ T cells [49,51,52,63,67,68]. As discussed above, specific subsets of intestinal APCs, have the capacity to produce RA and induce to Foxp3⁺ regulatory T cells in vitro, in the presence of TGF- β [49,51,52]. In addition to its role in inducing T regulatory cells, accumulating evidence suggest RA, at high concentrations, suppresses Th-1 and Th-17 differentiation by suppressing the lineage specific transcription factors and also by suppressing the expression of effector cytokines IFN- γ and IL-17 [63,67,69,70]. In contrast, a recent study by Uematsu et al. has shown that RA at very low concentrations promotes Th-17 response [56]. Furthermore, it should be noted that very low concentrations of RA (1 nM) can induce α 4 β 7 on T cells and induce mucosal homing properties [44]. The mechanisms underlying the concentration dependent effects of RA on T cell differentiation are not understood, but may very well depend on differences in the receptors through which RA signals.

Effect of RA on B cells

In addition to its well-established role in the induction of regulatory T cells in the gut, vitamin A is also required for B cell mediated IgA antibody responses to bacterial polysaccharide antigens [71,72,73]. RA produced by GALT-DCs is critical for B cell IgA class-switching and induction of IgA production by B cells in the gut without T cell help involving IL-6 or IL-5 [64]. B cell activated with RA express high levels gut homing receptors α 4 β 7 and CCR9. Furthermore, several studies have demonstrated that DCs isolated from Peyer's patches or MLN were able to induce gut homing receptors on both T and B cells. Similarly, a recent study by Uematsu et al. has shown that CD11c^{hi} CD11b^{hi} LPDCs induced the differentiation of naïve B cells into IgA-producing plasma cells by a mechanism dependent on RA [56].

Summary and Future directions

The central role of RA in regulating diverse biological processes has been appreciated for a long time. Even immunologists have recognized for decades that vitamin A deficiency is associated with enhanced susceptibility to most infections, and defects in both the innate and adaptive immune systems [11,12,16,18]. However, it is only recently that immunologists have begun to explore the cellular and molecular mechanisms by which vitamin A exerts its effects on the innate and adaptive immune systems. Recent observations have highlighted that certain intestinal APC subsets metabolize vitamin A into RA and enhance the TGF- β -dependent conversion of naïve T cells into regulatory T cells, and in the acquisition of mucosal homing properties by the T and B cells. A key finding of these studies is that only certain subsets of APCs seem competent to produce RA, and induce T regulatory cells. These observations raise some important questions. For example, what are the receptors and signaling pathways involved in the expression of RALDH in APCs in the gut? Why do only specific subset DCs express RA synthesizing enzymes? To what extent does RA modulate the function of the APCs themselves? Furthermore, it is clear that RA mediates its effects through several receptors, including RARs, RXRs and PPAR β/δ . what is the functional consequence of triggering via these different receptors, on the immune system? Can the paradoxical findings of RA inducing T regulatory cells [49,51,52,63,68] versus Th17 cells [56] be explained by effects on different receptors? Could differential action via different receptors also explain the diverse biological effects of RA on lymphocytes – such as imprinting of mucosal homing versus IgA secretion? Clearly, discovering the answers to these questions is likely to illuminate molecular mechanisms that play a pervasive and central role in regulating lymphocyte function and homeostasis in health and disease. This in turn is likely to be of great value in the design of intelligent therapies against a whole range of immunological disorders.

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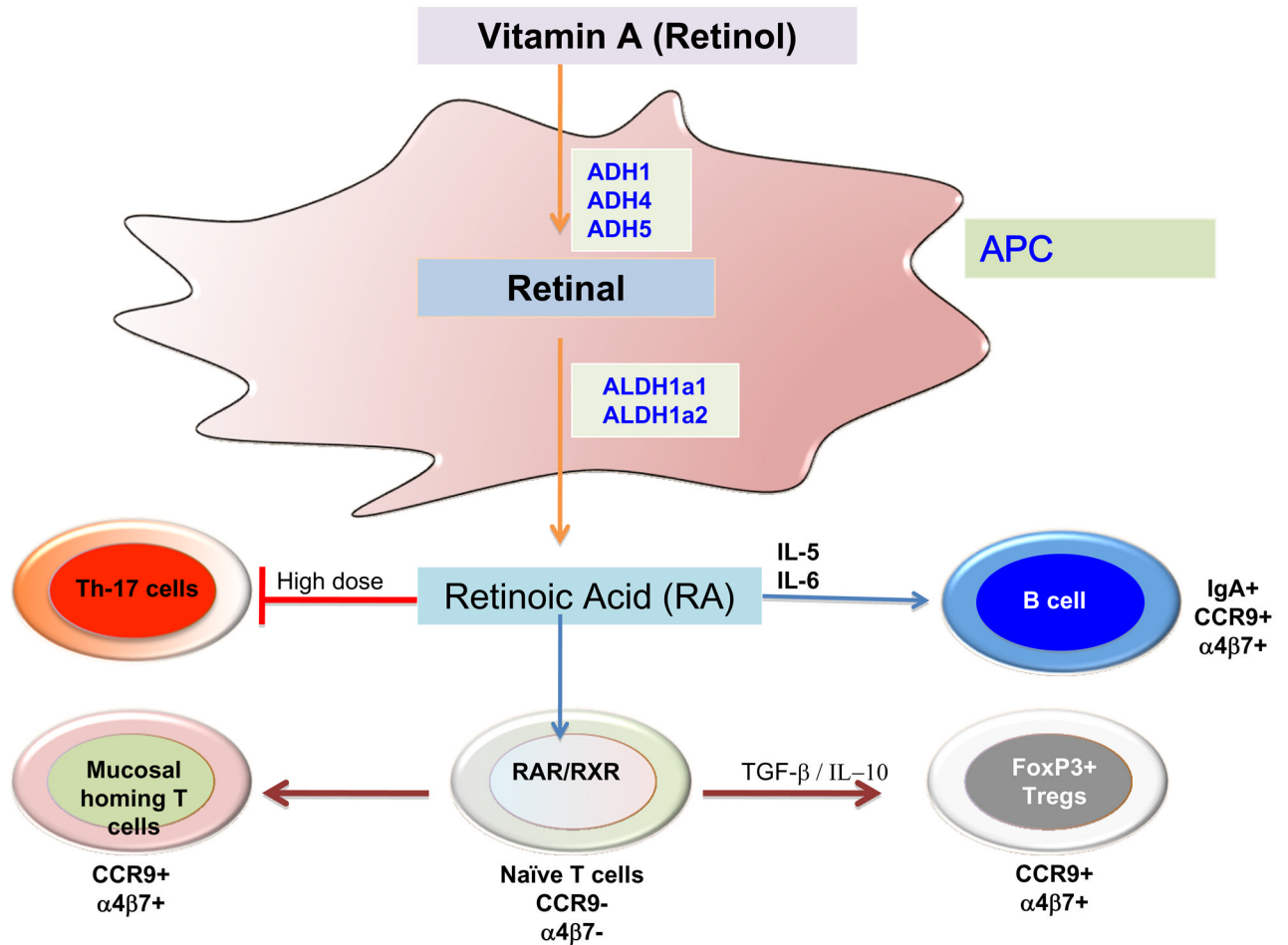


Figure 1. Retinoic acid synthesis pathway in dendritic cells and its effects on lymphocytes
 Retinoic acid (RA) is produced from vitamin A (retinol) via a two-step enzymatic pathway that oxidizes retinol to retinaldehyde and then retinaldehyde to RA. Oxidation of retinol to retinaldehyde requires the activities of several alcohol dehydrogenases (ADH-1,-4,-5) and subsequently, retinaldehyde is oxidized to retinoic acid by retinal dehydrogenases (RALDH). RA produced by DCs acts on T- and B-lymphocytes, and induces the mucosal homing receptors $\alpha 4\beta 7$ -integrin, and CCR9. RA in the presence of TGF- β promotes the conversion of naive T cells into Foxp3+ regulatory T cells, and at high concentration inhibits the differentiation of Th-17 cells. In addition, RA synergizes with IL-6 and IL-5 and promotes class switching to IgA in B cells.

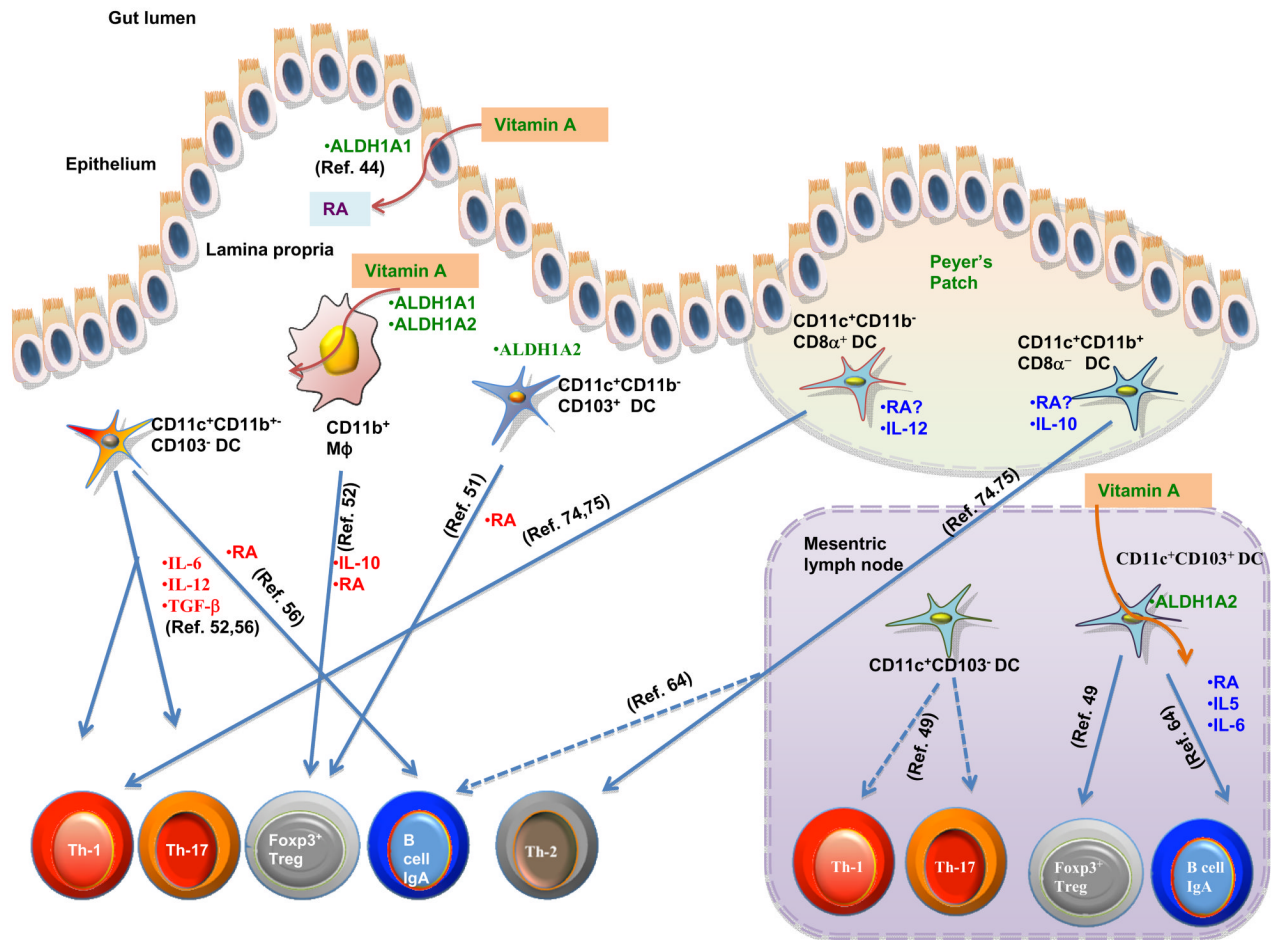


Figure 2. Subsets of intestinal antigen presenting cells produce RA and induce T regulatory cells
 Recent studies show the existence of multiple subsets of antigen-presenting cells in the lamina propria (LP), mesenteric lymph node (MLN) and Peyer's patches (PP). In the lamina propria CD11b⁺ intestinal macrophages induce the differentiation of Foxp3⁺ regulatory T cells via retinoic acid, via a mechanism dependent on both RA and IL-10[52] and these cells can also inhibit the induction of Th-17 responses induced by CD11b⁺ DCs in the lamina propria [52, 56]. In contrast, it has also been shown that lamina propria DCs induce Foxp3⁺ T regulatory cells [51]. In the MLN, CD103⁺ DCs that produce RA promote the differentiation of Foxp3⁺ regulatory T cells [49], as well as IgA-secreting B cells [64]. In contrast, CD103⁻ DCs in the MLN do not promote Foxp3⁺ T regulatory cells, but can be stimulated to produce greater levels of the pro-inflammatory cytokines TNF- α , IL-6, IL-12p40 and IL-23 [49], raising the possibility that they may induce Th1/Th17 responses. In the PP, CD11c⁺CD11b⁻CD8 α ⁺ DCs can be induced to secrete high amounts of IL-12p70 promote Th1 responses [43,74,75]; in contrast, CD11c⁺CD11b⁺CD8 α ⁻ DCs secrete high amounts of IL-10 promote Th2 responses [43,74,75]. Solid lines represent published data. Dotted lines represent speculations.