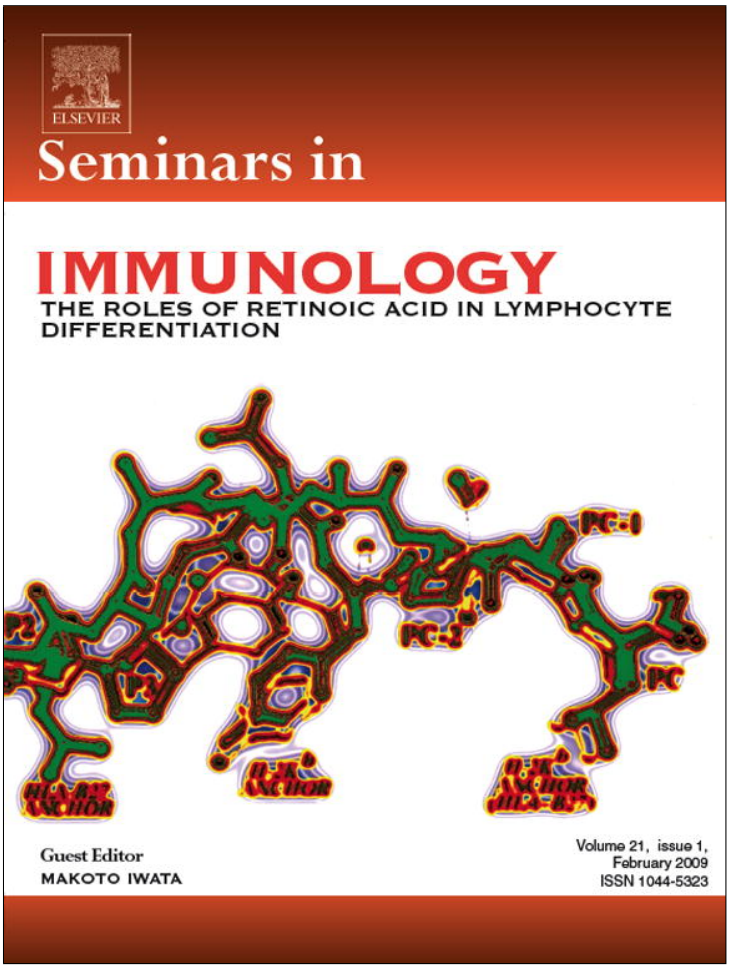

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Review

Role of retinoic acid in the imprinting of gut-homing IgA-secreting cells

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ABSTRACT

Antibody-secreting cells (ASCs) lodging in the mucosa of the small intestine are derived from activated B cells that are thought to arise in gut-associated lymphoid tissues (GALT). Upon leaving the GALT, B cells return to the blood where they must express the gut-homing receptors α4β7 and CCR9 in order to emigrate into the small bowel. Recent evidence indicates that gut-associated dendritic cells (DCs) in GALT induce gut-homing receptors on B cells via a mechanism that depends on the vitamin A metabolite retinoic acid (RA). In addition, although ASC associated with other mucosal tissues secrete IgA in an RA-independent fashion, the presence of high levels of RA in intestine and GALT can promote B cell class switching to IgA and thus, boost the production of IgA in the intestinal mucosa. Here, we discuss the role of RA in the imprinting of gut-homing ASC and the evidence linking RA with the generation of intestinal IgA-ASCs.

1. Introduction

IgA is the most abundant immunoglobulin isotype produced in the body (around 3 g/day) and it is estimated that around 80% of all IgA-antibody-secreting cells (ASCs) reside in the gut mucosa [1,2]. Mice either lacking IgA or impaired in its secretion are more susceptible to intestinal toxins and pathogens [3,4]. In addition, migration of B cells and ASCs to the gut is critical for conferring protection against intestinal pathogens [5–9]. Therefore, both IgA secretion and homing of ASCs to the gut are important in conferring protection at this anatomical site.

Naïve B lymphocytes migrate to secondary lymphoid organs (SLOs), such as lymph nodes, Peyer's patches (PPs) and the spleen, where they are activated by their cognate antigen [10]. Conventional (B2) B cells can be activated by T cell-dependent (TD) antigens, i.e., antigens that elicit concomitant "helper" CD4 T cell responses (usually proteins), and become either ASCs or memory B cells (B_{Mem}) [11]. On the other hand, B cells can also be activated by T cell-independent (TI) antigens, either type-I (polyclonal activators, such as LPS, CpG, poly-IC) or type-II (polysaccharides, such as capsular bacterial polysaccharides) and become mostly short-lived IgM-ASCs [11].

Peyer's patches, and to a lesser extent mesenteric lymph nodes (MLNs), are the main SLOs where B cells differentiate into IgA-ASCs [2,12]. As we will discuss below, the preferential induction of IgA-ASCs in these sites also explain why they acquire preferential migration to the gut [13–15]. Homing of ASCs to the intestinal mucosa requires the expression of the integrin α4β7 [16,17], which binds to its receptor MAdCAM-1, which is displayed on intestinal postcapillary endothelial cells [18]. Moreover, in the case of the small bowel, ASCs also need to express the chemokine receptor CCR9 in order to migrate efficiently to this compartment [19–21]. Another chemokine receptor, CCR10, has been proposed as a "general" mucosal homing receptor [22–25]. In fact, most IgA-ASCs express CCR10 [24,26] and one of its ligands, the chemokine CCL28/MEC, is expressed by most mucosal epithelia [23,27]. However, although CCR10 is apparently necessary for the homing of ASCs to the colon [21] and the lactating mammary gland [22], its role in ASC migration to the small bowel remains controversial [21,28].

Peritoneal B1 B cells can also give rise to intestinal IgA-ASCs, although the extent of their contribution remains controversial, ranging from 1 to 50% of all intestinal lamina propria IgA-ASCs, depending on the experimental system and readout [29–32]. In addition, it has been described that conventional B1 B cells are not being found in most mammals (including several mouse strains). Instead, another B cell subset (Bw B cells) has been described in most mouse strains [33]. These cells are mostly found in the peritoneal cavity and the spleen and they may play an important role in the production of natural autoantibodies. However, the migratory properties of this particular B cell subset has not been characterized. Moreover, in humans, peritoneal B1 B cells do not seem to be a significant source of intestinal IgA-ASCs [34]. Thus, the relative contribution of B1 B cells to the pool of intestinal IgA-ASCs

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and their relevance to gut immunity remain to be determined. It is also unknown what traffic molecules B1 cells need to home to the gut mucosa. Interestingly, a recent study showed that the peritoneal cavity environment can also imprint gut-homing capacity and induce IgA class-switching/secretion on plasmablasts [35]. In this setting, TLR ligands [36] and sphingosine-1-phospate (S1P) [37] may also play important roles allowing the mobilization of peritoneal B1 B cells in order to become intestinal IgA-ASCs. Regarding the latter, it is important to highlight that S1P and S1P receptor type 1 ($S1P_1$) are also essential for lymphocyte exit from lymphoid compartments, such as lymph nodes and PP [38,39]. Consistent with this notion, S1P is also important for the egress of IgA plasmablasts from PPs [40].

2. Gut-associated dendritic cells and retinoic acid in the imprinting of gut-tropic ASCs

It has been shown that oral vaccination induces higher levels of the gut-homing integrin α4β7 on B cells and ASCs than parenteral administration of the same antigen [5,6,41–44]. Thus, the site of antigen entry into the body determines the microenvironment where B cells are activated, which in turn strongly influences the homing commitment of the resulting ASCs. In the lymphoid microenvironment, dendritic cells (DCs) are not only essential for T cell activation [45,46], but they can also influence B cell responses by enhancing their differentiation to ASCs and survival [47,48]. Moreover, DCs can present unprocessed antigens to B cells *in vivo* [49–51]. Since several reports have shown that DCs from PPs and MLNs (gut-associated lymphoid tissues (GALT)-DCs) are sufficient to induce α4β7 and CCR9 and gut-homing capacity on activated T cells [52–57], it was plausible that they could also modulate B cells in a tissue-specific manner. In fact, previous data showed that DCs from PPs, but not from the spleen, promoted IgA class switching in activated B cells [58,59]. These findings were recently reproduced and extended to other systems [60–63]. Moreover, similar to their effect on T cells, it was recently shown that PP-DCs and DCs from the lamina propria of the small intestine can also imprint α4β7, CCR9 and gut-homing capacity on ASCs [61,62].

Insights into the mechanism by which gut-associated DCs imprint gut-homing T cells was provided in a seminal study by Iwata et al. [64] in which it was shown that the vitamin A metabolite *all-trans* retinoic acid (RA) is sufficient to induce α4β7 and CCR9 on activated T cells, and that blocking RA-receptors of the RAR family decreased the induction of gut-homing receptors by PP-DCs and MLN-DCs. Consistent with a pivotal role of RA in gut-homing imprinting, it was shown more recently that RA is also necessary for the induction of gut-homing receptors on B cells and IgA-ASCs [61,62] (Fig. 1). These findings provided a molecular explanation for older observations that vitamin A-deficient rats exhibit impaired migration of recently activated MLN lymphocytes to the intestinal mucosa [65], and that these animals had also a marked decrease in the number of IgA-ASCs and CD4 T cells in their ileum [66].

Of note, subcapsular sinus macrophages can also present lymph-borne antigens and activate naïve B cells in skin-draining lymph nodes [67–69]. Since macrophages can secrete BAFF (B-cell activating factor/Blys) [47] and intestinal lamina propria macrophages secrete RA [70], it will be interesting to determine whether subcapsular sinus macrophages in the GALT can also imprint tissue-specific homing and/or promote specific IgA class switching.

The reason why GALT-DCs and lamina propria DCs can secrete RA is explained, at least in part, by their selective expression of retinal dehydrogenases (RALDH), which are critical enzymes for RA synthesis [62–64,71]. However, other cells in the gut, e.g., intestinal epithelial cells (IEC), also express RALDH and can synthesize RA [64,72]. Also, extraintestinal sources of RA have been identified in lungs [73] and liver [74]. However, the role of RA in those extraintestinal anatomic sites remains to be defined. Of interest, it has been reported that recently activated B cells (plasmablasts) are also imprinted with gut-tropism in the peritoneal cavity [35]. It will be interesting to assess whether this "peritoneal imprinting" also relies on RA.

Even though CCR10 is expressed on most IgA-ASCs, it is unknown how this receptor is induced on ASCs *in vivo*. 1,25(OH)2VD3, the active form of vitamin D, has been reported to induce CCR10 on *ex vivo* activated human T cells [75] and ASCs [76]. However, the physiological relevance of 1,25(OH)2VD3 for CCR10 induction is presently unclear. Interestingly, a recent report showed that CCR10 is induced on murine ASCs upon intra-rectal, but not oral, immunization [77]. In the latter study it was proposed that CCR10 upregulation happens in the cecal patches and iliac lymph node, although the molecular mechanism for the induction of this receptor remains to be determined [77].

B cells may also exhibit homing plasticity [44]. In fact, they can be reeducated and acquire or lose gut-homing potential when they are restimulated with or without RA, respectively [61] (Fig. 1). Similar homing malleability has been documented for T cells [56,57]. Given that plasma cells are terminally differentiated cells and do not divide, it is likely that homing plasticity operates at the level of B_{Mem} when they are reactivated and proliferate to become ASC. In addition, during a restimulation, and depending on the activation conditions, B cells may also switch to another immunoglobulin isotype. For example, B_{Mem} expressing either IgM, IgG or IgE may, in theory, switch to IgA when reactivated in MALT. In fact, sequential immunoglobulin switching from IgG2b to IgA or, in humans, from IgA1 to IgA2, has been described in Ref. [78].

3. Role of gut-associated DCs and RA in the generation of intestinal IgA-ASCs

The different and complex mechanisms implicated in inducing mucosal IgA-ASCs have been reviewed in detail elsewhere [10,79–81]. Here we will focus on summarizing and discussing the evidence linking RA with the generation of IgA-ASCs, which also establishes a mechanistic link between the imprinting signals for gut homing and the modulation of B cell effector function.

It had been known for some time that GALT-DCs can induce IgA-ASCs when cocultured with activated B cells *in vitro* [58–63], even in the absence of T cells [61–63]. As mentioned above, RA is synthesized/secreted by GALT-DCs and it is essential for the imprinting of gut-homing receptors on T and B cells [61,64]. Since RA also induces IgA secretion in LPS-activated splenocytes [82–87], we tested the possibility that GALT-DCs may rely on RA for inducing IgA class switching (Fig. 2). Indeed, we and others recently demonstrated that the IgA-promoting effect of GALT-DCs or lamina propria DCs is at least partially dependent on RA [61–63]. The effect of RA on IgA secretion may be mediated, at least in part, by increased IgA class switching in RA-exposed B cells [87]. However, the extent to which RA directly influences class switching [87] or enhances the proliferation/differentiation of already switched IgA plasmablasts [88,89] remains to be determined. Nonetheless, consistent with the effect of RA on IgA secretion *in vitro*, oral administration of a RA receptor (RAR)-agonist significantly increases serum IgA levels in rats [90].

RA may also have effects on other immunoglobulin isotypes. Although vitamin A depletion (hence RA depletion) increases total serum IgG levels [91,92], antigen-specific IgG1 responses are decreased [93]. The latter effect probably reflects the impaired Th2 differentiation observed in the setting of vitamin A deficiency [94,95] and not a direct effect on B cells. In fact, supplementation of RA inhibits IgG1 production *in vitro* and *in vivo* [82,90,96,97]. Finally, it has been reported that RA also blocks the production of

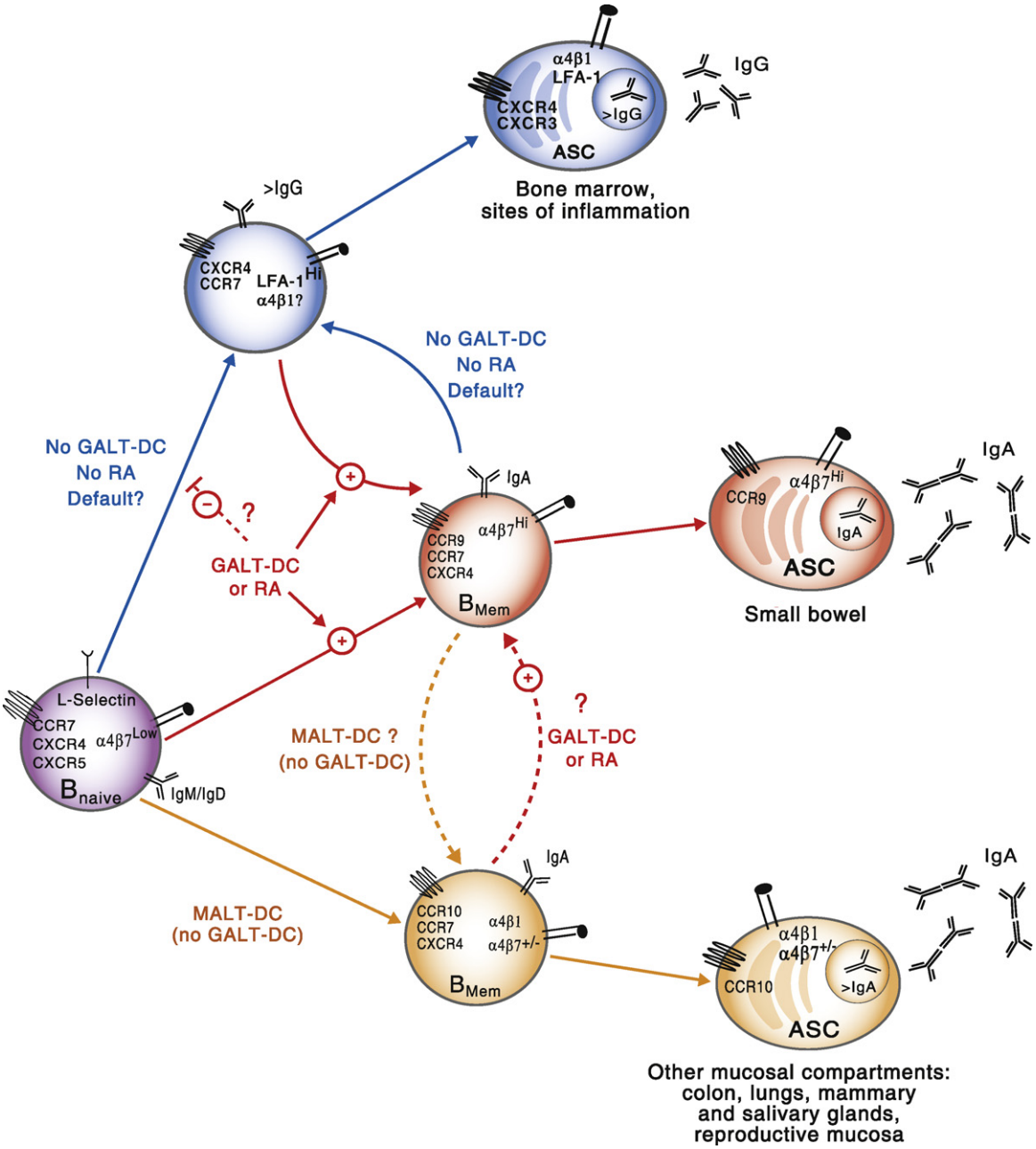

Fig. 1. Homing imprinting on B cells and ASC. GALT-DC or *all-trans* retinoic acid (RA) induce the expression of α4β7 and CCR9 on ASC and probably also on memory B cells (B_{Mem}), endowing them with the capacity to home to the small bowel. In addition, IgA-ASC migrating to all mucosal tissues express CCR10 and the CCR10 ligand MEC/CCL28 is expressed in all mucosal compartments. However, it is unknown how CCR10 is induced on ASC. Like T cells, B cells also show plasticity regarding their homing commitment. If nongut-homing B cells are restimulated in the presence of RA, they readily upregulate α4β7 and CCR9. On the other hand, B cells with gut-homing capacity lose α4β7 and CCR9 if they are reactivated without RA. Since ASC are terminally differentiated and do not divide, it is likely that the capacity to be "reprogrammed" in their homing potential resides at the level of B_{Mem}. Finally, whether homing to the bone marrow or sites of inflammation represents a default pathway in the absence of RA or other mucosal signals remains to be determined. (+) Agonist/inductive effect. (−) Antagonist/blocking effect. Dashed lines: hypothetical/speculative scenario.

IgE *in vitro* [98]. However, this IgE-blocking effect was not observed *in vivo* [99].

4. The interplay of RA and other DC-derived signals in the induction of IgA-ASCs

It has been reported previously that either IL-5 or IL-6 can influence IgA secretion [100–110]. In fact, RA-induced IgA secretion requires either exogenous IL-5 or the presence of T cells producing this cytokine [84,96]. Also, RA induces autocrine production of IL-6 by B cells, which may further contribute to IgA secretion [111]. Moreover, both RA and IL-6 are required for optimal IgA induction by GALT-DCs *in vitro* [60,61]. Furthermore, RA plus either IL-5, IL-6 or LPS synergize and are sufficient to induce IgA secretion by activated B cells in the presence of non-intestinal DCs [61,62]. However, IL-5, IL-6 or LPS are probably not directly involved in specific IgA class switching but are rather permissive for immunoglobulin class switching by inducing activation-induced cytidine deaminase (AID, an essential enzyme for immunoglobulin class-switching and somatic hypermutation) [79,112] or by promoting

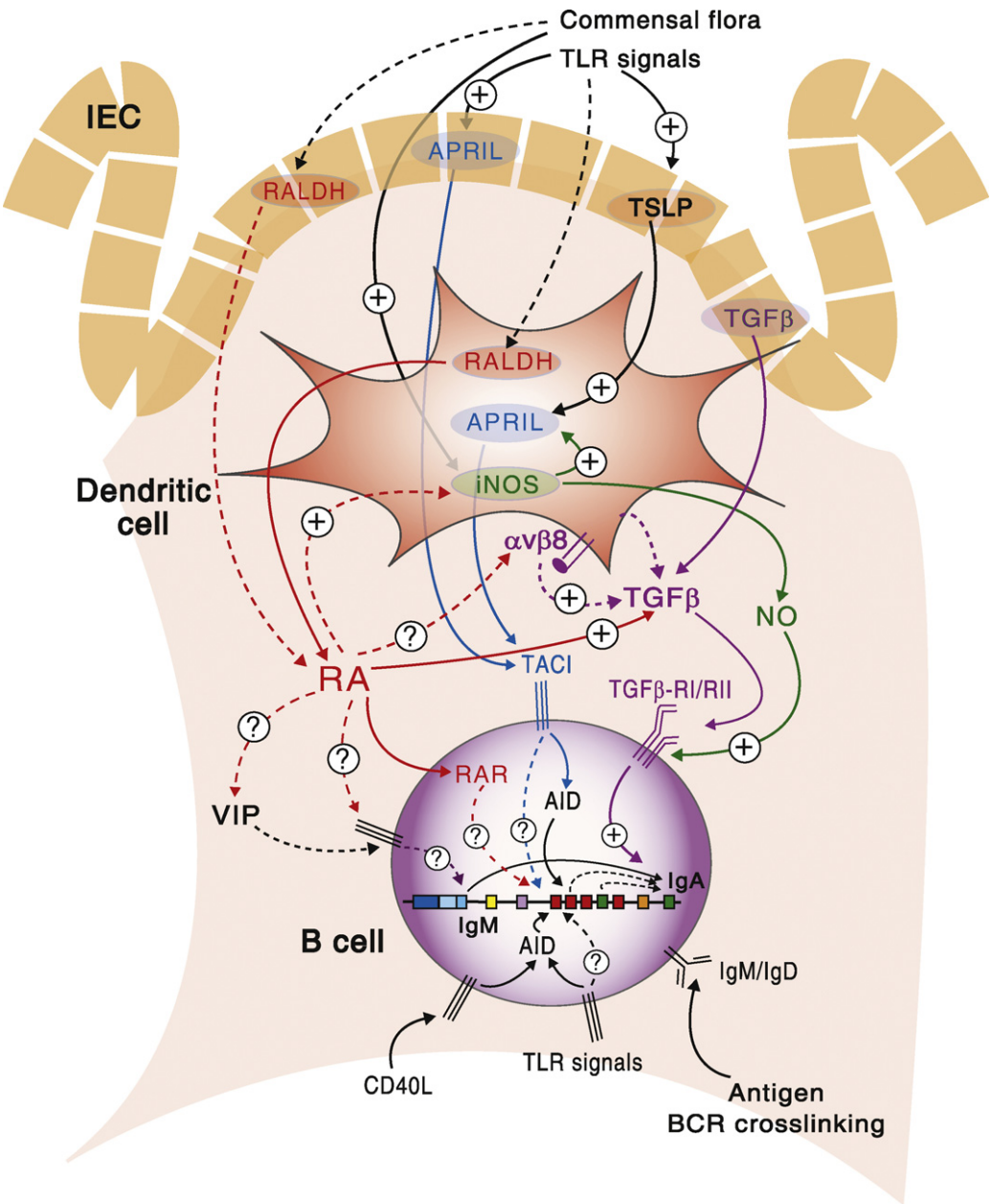

Fig. 2. Retinoic acid and induction of IgA-ASC. TGFβ is directly involved in IgA class switching and is virtually essential for IgA responses in all mucosal compartments. In the gut, intestinal epithelial cells (IEC) and GALT-DC are among the potential sources of TGFβ. DCs also express the integrin αvβ8, which is essential for TGFβ activation *in vivo*. Gut IgA responses to thymus-independent (TI) antigens require APRIL binding to TACI on B cells. APRIL is produced by IEL upon stimulation by commensal flora or TLR signals. These stimuli also induce TSLP secretion by IEL, which in turn induces more APRIL expression by GALT-DC. Mucosal DC (including GALT-DC) express the inducible form of nitric oxide synthase (iNOS), which is also induced by commensal flora and TLR signals. iNOS generates nitric oxide (NO), which is critical for both TD and TI IgA responses. NO synthesis is necessary for proper TGF-β signaling on B cells and also for APRIL synthesis by GALT-DC. CD40L, APRIL and TLR ligands contribute to IgA class-switching by upregulating the enzyme activation-induced cytidine deaminase (AID), which is essential for both immunoglobulin class-switching and somatic hypermutation. APRIL and TLR ligands may also directly contribute to IgA class switching. Vasoactive intestinal peptide (VIP) can also induce IgA class switching *in vitro*, although its significance *in vivo* remains to be determined. RA, which can be synthesized by intestinal epithelial cells (IEC) and GALT-DC, is probably interrelated to some of the IgA inducing mechanism mentioned above. RA plus IL-5, IL-6, or TLR signals can promote the differentiation of IgA-ASC in the presence of DC. Whether the latter effect represents mainly a direct effect of RA on IgA class-switching remains to be clarified. RA may also induce IgA class switching indirectly by upregulating TGF-β secretion and iNOS/NO. RA has also been shown to induce VIP and its receptors in some cell lines. However, whether this is also relevant for DC and/or B cells remains to be defined. It will also be interesting to determine whether RA can induce the expression of αvβ8 on DC. (+) Synthesis, induction or activation. Dashed lines: hypothetical speculative scenario. Questions marks: unknown mechanism.

proliferation/differentiation of already switched IgA plasmablasts [10,113].

Since it is well established that TGFβ is critical for IgA responses *in vivo* [114–117], it is likely that GALT-DCs rely, at least partially, on TGFβ for their IgA-inducing capacity. In fact, GALT-DCs can produce active TGFβ [70,71,118,119] and blocking TGFβ decreases the capacity of PP-DCs to induce IgA-ASCs [63]. Moreover, mucosal DCs express the integrins αvβ6 and αvβ8, which play an essential role in activating latent TGFβ (TGFβ non-covalently associated to the latency-associated peptide) *in vivo* [119–123] (Fig. 2). Nonetheless, it is possible that GALT-DCs also promote IgA in a TGFβ-independent manner. In fact, blocking TGFβ does not com-

pletely abrogate the capacity of PP-DCs to induce IgA-ASCs [63]. Moreover, although RA also induces TGFβ activity in LPS-activated splenocytes and other cells [82,124,125], the IgA-inducing effect of RA is only partially dependent on this cytokine [63,82]. These observations are in line with the notion that while the essential *in vivo* role of TGFβ in IgA class-switching is well demonstrated, its *in vitro* effects on IgA class-switching/secretion seem to vary significantly depending on the experimental system (this issue is discussed in detail elsewhere [10]).

Interestingly, the inducible form of nitric oxide synthase (iNOS) and nitric oxide (NO) play essential roles for both thymus-dependent and thymus-independent IgA responses [126]. iNOS/NO seem to be important for the normal expression of TGF-βRII and Smad proteins (involved in TGFβ signal transduction) in B cells as well as for the production of APRIL (a proliferation-inducing ligand) and BAFF by DCs [126] (Fig. 2). Of note, iNOS is expressed by DCs from small intestinal lamina propria and GALT-DC, but not by spleen DC, and its expression depends on signals driven by commensal flora and TLR signals [126], which may contribute to explaining the lower induction of IgA by GALT-DCs isolated from germ-free mice [63]. Regarding a potential relationship of iNOS/NO and RA, the iNOS gene promoter has a RA-response element (RARE) that is directly activated by RA bound to its nuclear RARα/RXR heterodimeric receptor [127,128]. In fact, intraperitoneal administration of RAR-agonists, including RA, potentiates LPS-induced iNOS expression in several organs, and also increases plasma levels of nitrate/nitrite in rats [128,129]. Thus, RA may also indirectly contribute to IgA secretion by inducing iNOS/NO expression.

APRIL and BAFF (which signal through TACI and BCMA on B cells) can also induce IgA-ASCs, and these factors are important during thymus-independent B cell responses [10,79]. It has been reported that the intestinal flora and TLR signals induce BAFF and APRIL in DCs [78,130]. Therefore, the decreased IgA induction by GALT-DCs isolated from germ-free mice [63] may be explained, at least in part, by a reduced production of APRIL and BAFF. In addition, since iNOS/NO is necessary to induce BAFF and APRIL secretion by GALT-DC [126], RA may also play an indirect role in APRIL/BAFF-mediated IgA responses by upregulating iNOS [128,129]. However, it should be mentioned that PP-DCs can still induce IgA responses on TACI- and BCMA-deficient B cells when they are activated with either CD40L or LPS [63]. This is analogous to the IgA induction by TGF-β1 plus LPS, which is also TACI- and BCMA-independent [131]. Thus, the relative role of APRIL and BAFF in IgA induction will ultimately depend on the B cell activation context.

Vasoactive intestinal peptide (VIP) can also induce IgA secretion by human activated B cells [132–134]. Interestingly, it has been reported that RA can induce both VIP and VIP receptors in a neuroblastoma cell line [135,136]. However, whether RA plays a role influencing VIP responses on B cells and/or DCs remains to be determined.

To summarize, RA has a direct IgA-promoting effect on activated B cells and it also appears to synergize with several other mechanisms that are thought to promote IgA production in the gut. Consistent with an important *in vivo* role of RA in gut IgA production, rats depleted of vitamin A have decreased levels of total IgA in intestinal lavages and decreased mucosal antigen-specific IgA responses [137–141]. Similarly, vitamin A-depleted mice show impaired IgA secretion and protection at mucosal sites [92,142], as well as impaired IgA responses to bacterial toxins either after oral [143] or transcutaneous [144] immunization. However, it should be kept in mind that vitamin A deficiency may have other effects on the immune system. In fact, the greater susceptibility to intestinal infections and toxins observed in vitamin A-deficient animals may also be explained, at least in part, by a decreased epithelial expression of the polymeric immunoglobulin receptor (pIgR) and therefore, a decreased IgA secretion to the intestinal lumen [137,141,142,145]. Moreover, although vitamin A-deficient mice have a greatly reduced number of IgA-ASCs in the small bowel [61,66], they have normal serum IgA levels [61]. This indicates that retinoids are not absolutely required for IgA production in tissues other than the small intestine. Nonetheless, the critical role of RA in T and B cell gut-homing imprinting [61,64], as well as its IgA-ASC promoting potential in the gut [61,82], may contribute to explain the classical epidemiological observation that vitamin A deficiency is associated with impaired intestinal immune responses [91,92,143,137–142] and markedly increased mortality in children in the developing world [146]. It also provides a plausible mechanism to explain the empirical observation that vitamin A supplementation decreases diarrhea and mortality in HIV-infected or malnourished children [147–151].

5. Concluding remarks

It is already well established that gut-associated DCs, including DCs from GALT and lamina propria, can strongly influence T and B cell responses in a tissue-specific manner. Gut-associated DCs, owing to their selective ability to produce and secrete RA, imprint gut-homing capacity on both T and B cells. Moreover, gut-associated DCs can induce B cells to become IgA-ASCs by a mechanism that is, at least in part, dependent on RA. Thus, gut-associated DCs and RA modulate intestinal immune responses by affecting both lymphocyte migration and effector activity.

As discussed above, it is also apparent that RA can potentially interact with other mechanisms inducing IgA-ASCs, such as TGFβ, iNOS/NO and probably others. However, the overall relevance of RA for TD and/or TI IgA responses *in vivo* remains to be defined. Also, although RA influences the steady-state lymphocyte composition/numbers in the gut, it has been recently reported that during some viral vaccinations gut-homing imprinting and induction of IgA-ASC may also happen outside the GALT [152]. Thus, it will be important to determine how essential RA is for lymphocyte migration during acute immune responses or in various settings of inflammation.

Finally, it will be important to address how gut-associated DCs are "educated" to acquire the capacity to synthesize RA and, thus, to imprint gut-homing lymphocytes and IgA-ASCs. Recent work suggests that commensal flora is necessary to confer GALT-DCs with the capacity to induce IgA-ASCs. Whether this is also true for imprinting gut-homing lymphocytes remains to be determined. If so, it will be interesting to address whether TLR signals and/or commensal bacteria are sufficient to confer non-gut DCs or their precursors with gut imprinting and/or IgA inducing capacity.

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