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Regulation of mucosal IgA responses: lessons from primary immunodeficiencies

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Abstract

Adaptive co-evolution of mammals and bacteria has led to the establishment of complex commensal communities on mucosal surfaces. In spite of having available a wealth of immune-sensing and effector mechanisms capable of triggering inflammation in response to microbial intrusion, mucosal immune cells establish an intimate dialogue with microbes to generate a state of hyporesponsiveness against commensals and active readiness against pathogens. A key component of this homeostatic balance is IgA, a noninflammatory antibody isotype produced by mucosal B cells through class switching. This process involves activation of B cells by IgA-inducing signals originating from mucosal T cells, dendritic cells, and epithelial cells. Here, we review the mechanisms by which mucosal B cells undergo IgA diversification and production and discuss how the study of primary immunodeficiencies facilitates better understanding of mucosal IgA responses in humans.

Keywords

human; B cells; IgA; mucosa; immunodeficiency

Introduction

The intestinal mucosa is home to trillions of microbes present at densities that greatly exceed those found in other habitats, including soil.[1] These commensal bacteria confer many metabolic capabilities that our mammalian genome lacks, including the ability to break down otherwise undigestible dietary carbohydrates, generate essential vitamins and isoprenoids, and fill a niche that would otherwise be easily accessible to pathogens.[2] A single layer of intestinal epithelial cells separates commensals from the sterile milieu of our body.[3] By recognizing microbial molecular signatures through various families of pattern recognition receptors, such as Toll-like receptors (TLRs), intestinal epithelial cells establish a complex dialogue with innate and adaptive cells of the intestinal immune system.[4] This

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Conflicts of interest
The authors declare no conflicts of interest.

dialogue leads to the production of a vast array of immune mediators that generate a state of hyporesponsiveness against commensals and active readiness against pathogens.[1]

An important component of this homeostatic balance is IgA, a noninflammatory antibody iso-type generated by follicular B cells from Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles.[5,6] Collectively, these organized lymphoid structures form the gut-associated lymphoid tissue, which constitutes the major inductive site for intestinal IgA responses.[5,6] IgA-secreting plasma cells emerging from the gut-associated lymphoid tissue migrate to the effector site of the lamina propria, where they release large amounts of IgA onto the epithelial surface.[5,6] In addition to serving as a key effector site, the lamina propria has a nonorganized lymphoid tissue that includes dispersed B cells retaining some IgA-inducing function.[5,6] Here, we review the cellular and signaling pathways orchestrating intestinal IgA production and discuss how the analysis of patients with specific forms of primary immunodeficiency (PID) has improved our understanding of these pathways.

Function of mucosal IgA

The intestinal mucosa has evolved several strategies to control commensals and neutralize pathogens without causing inflammatory damage to the epithelial barrier. One of these strategies involves the production of massive amounts of IgA, the most abundant antibody isotype in our body. IgA reaches the intestinal lumen by interacting with the polymeric Ig receptor on the basolateral surface of epithelial cells.[5,6] After binding to polymeric Ig receptor through a joining chain, IgA dimers secreted by intestinal plasma cells translocate across epithelial cells onto the mucosal surface by undergoing transcytosis.[7,8] This process involves intracellular processing of polymeric Ig receptor into a polypeptide called secretory component, which remains associated with the joining chain of the IgA dimer to form a secretory IgA complex with noninflammatory protective function.[9–11] Indeed, secretory IgA can bind to bacteria without activating complement or stimulating the release of inflammatory mediators by innate immune cells.[12,13]

IgA neutralizes toxins, pathogenic bacteria, and inflammatory microbial molecules, such as, lipopolysaccharide.[14–21] IgA also prevents commensal bacteria from adhering to the epithelial surface by generating steric hindrance, by inducing bacterial agglutination, by masking adhesion epitopes, and by interacting with mucus through the secretory component.[22,23] These processes favor the growth of commensal bacteria in biofilms that prevent the outgrowth of pathogens through a mechanism involving competition for biological niches and sources of energy. Furthermore, IgA facilitates the maintenance of homeostasis by decreasing the inflammatory tone of the intestine and by favoring the maintenance of appropriate bacterial communities within specific intestinal segments.[21,24,25] Finally, IgA interacts with yet poorly defined receptors to facilitate the sampling of luminal antigen by intestinal dendritic cells (DCs) and microfold (M) cells, a subset of antigen-sampling intestinal epithelial cells located in the follicular epithelium of Peyer's patches and isolated lymphoid follicles.[17,26–28]

Binding modes and reactivity of mucosal IgA

Mucosal IgA antibodies emerge from B cells that follow either T cell–dependent (TD) or T cell– independent (TI) pathways (Fig. 1). Intestinal B cells generate IgA diversification and production thorugh V(D)J gene somatic hypermutation (SHM) and class switch recombination (CSR) from IgM to IgA.[5,6] These processes require the DNA-editing enzyme activation–induced cytidine deaminase (AID) and predominantly occur in the germinal center of Peyer's patches and mesenteric lymph nodes, although extrafollicular CSR and SHM have also been described.[29–36]

In mice, IgA forms both high-affinity and low-affinity binding systems that originate from different B cell types and likely serve distinct functions.[18] High-affinity IgA originates from monoreactive and antigen-selected conventional B-2 cells that express mutated Ig V(D)J gene sequences and occupy the follicles of Peyer's patches and mesenteric lymph nodes.[5,6] Low-affinity IgA would derive from polyreactive and nonantigen-selected B-1 cells that express unmutated Ig V(D)J gene sequences and occupy the peritoneal cavity and to some extent the lamina propria.[37–42] Additional low-affinity IgA may derive from conventional B-2 cells, such as those lodged in isolated lymphoid follicles.[39,40,43,44] Mutated, antigen-selected, and monoreactive IgA plays an important role in the control of commensal bacteria and the neutralization of pathogens and microbial toxins.[15,16,21,43] Unmutated, low-affinity, and polyreactive IgA would predominantly favor the exclusion of commensal bacteria from the surface of intestinal epithelial cells, but this distinction is not absolute, as there are examples of unmutated IgA antibodies that recognize commensal bacteria with high specificity.[2,25,41] Conversely, polyreactivity has been detected in mutated IgA antibodies with clear traces of antigen selection, at least in humans.[45]

In humans, 75% of IgA antibodies from intestinal plasmablasts are extensively mutated, have high specificity for commensal and enteropathogenic antigens, and carry signs of antigen selection.[45–47] Some of these antigen-specific antibodies seem to dominate the intestinal IgA repertoire in multiple individuals, which is remarkable considering the enormous diversity of the gut microbiota.[45] The remaining 25% of human intestinal IgA antibodies show polyreactivity for diverse microbial and autologous antigens, but also these antibodies are highly mutated and show traces of antigen selection.[45] It has been proposed that polyreactivity may be acquired through the introduction of somatic mutations and that selection of mutated variants of polyreactive germline gene-encoded antibodies may help to narrow down their antigen specificity.[45,48] Consistent with this possibility, some human polyreactive IgA antibodies show high reactivity to specific commensal bacteria and intestinal tissue structures, but low reactivity to other foreign or autologous antigens.[45] Another possibility is that mutation-induced polyreactivity enhances the binding affinity of human IgA for microbes by supporting heteroligation between one high-affinity combining site and a second low-affinity site on a different molecular structure of the microbe.[49] Clearly, more studies are needed to further elucidate the nature and reactivity of intestinal IgA in humans and to determine whether specific members of the microbiota elicit different IgA responses.

Although SHM plays a dominant role in the control of intestinal bacteria, CSR from IgM to IgA is crucial to lower the overall inflammatory tone of the intestine in face of the continuous stimulation exerted by the local microbiota.[21,25] The mechanism by which C_α confers noninflammatory-protective function to IgA remains poorly understood. The inability of C_α to effectively activate complement and the relative lack of high-affinity C_α-binding Fcα receptors on inflammatory intestinal immune cells likely play an important role.[18] Additional noninflammatory properties of C_α may relate to its ability to interact with the secretory component of the polymeric Ig receptor, which delivers regulatory signals to DCs via an unknown receptor.[10,11] C_α may deliver additional regulatory signals via a C-type lectin named DC-SIGN, which tunes down inflammatory signals from TLRs in antigen-sampling DCs.[50,51]

IgA induction in Peyer's patches and mesenteric lymph nodes

Peyer's patches are the major portal of entry of bacteria, and together with mesenteric lymph nodes, constitute the major IgA inductive site in the in-testine.[28,52] Peyer's patches develop during fetal life independently of gut colonization by bacteria and consist of large structures built on a stromal scaffold composed of several B cell follicles separated by areas containing

T cells and DCs.[5,6] In Peyer's patches there is an ongoing germinal center reaction that continuously drives IgA diversification and production.[52] This germinal center reaction is optimized by microbial signals, as mice depleted of intestinal bacteria have Peyer's patches with fewer and smaller germinal centers.[53,54] In both Peyer's patches and mesenteric lymph nodes, germinal center B cells produce IgA through a TD pathway involving activation of $CD4^+$ T cells by antigen-presenting DCs.[44,55,56] The phenotype, cytokine expression profile, and immune functions of these and other gut DCs are a matter of intense investigation (Table 1).

In Peyer's patches, DCs expressing the chemokine receptor CX3CR1 are found in close contactwith the follicle-associated epithelium and should be equivalent to $CX3CR1^+$ DCs present in the lamina propria.[57,58] In general, $CX3CR1^+$ DCs originate from circulating monocytes, express the DC molecule CD11c together with the macrophage molecule CD11b, and extend cellular projections across interepithelial junctions to sample antigen from the intestinal lumen, including segmented filamentous bacteria.[57,59–64] Although unable to migrate to the interfollicular areas of Peyer's patches to present antigen to T cells,[65] $CX3CR1^+$ DCs might contribute to TD IgA responses by transferring antigen to migratory $CD103^+$ DCs. In Peyer's patches, DCs expressing the integrin CD103 have an uncertain location but seem phenotypically and functionally similar to $CD103^+$ DCs found in the intestinal lamina propria.[66] In general, $CD103^+$ DCs originate from circulating pre-DCs, express CD11c but no or little CD11b, and migrate to the interfollicular area of Peyer's patches and mesenteric lymph nodes to present antigen to T cells.[62,63,65,67] $CD103^+$ DCs do not seem to form interepithelial projections and, therefore, might acquire antigen from $CX3CR1^+$ DCs or M cells.

Peyer's patches contain additional DC subsets, including $CD11c^+$ DCs secreting the noninflammtory cytokine IL-10 and $CD11b^+$ DCs secreting the antibody-inducing cytokine IL-6.[68,69] An additional DC subset expressing the chemokine receptor CCR6 is found in the subepithelial dome, which lies just underneath the follicle-associated epithelium of Peyer's patches.[58,70] Subepithelial $CCR6^+$ DCs can initiate T cell immunity and may give rise to $CCR7^+$ DCs, which are typically detected in the T cell-rich interfollicular area of mesenteric lymph nodes.[71] The relationship of all these DC subsets with $CX3CR1^+$ DCs and $CD103^+$ DCs remains unclear.

As they sample antigen across epithelial cells, intestinal DCs receive "conditioning" signals from intestinal epithelial cells, including thymus stromal lymphopoietin (TSLP).[72] These signals mitigate DC production of IL-12, a cytokine that stimulates the formation of T helper type-1 (Th1) cells producing the inflammatory cytokine IFN-γ.[59,72,73] Instead, intestinal DCs, including $CD103^+$ DCs, release IL-10 and retinoic acid (a derivative of vitamin A) to promote the development of $Foxp3^+$ T regulatory (T_{reg}) cells.[72–75]

By expressing the TNF family member CD40 ligand (CD40L) and releasing IL-10 and TGF-β1, intestinal T_{reg} cells elicit IgA CSR and production in B cells while inhibiting the formation of inflammatory Th1 cells.[56,76] Furthermore, intestinal T_{reg} cells differentiate into T follicular helper cells, which induce germinal center B cell differentiation as well as IgA CSR and production via CD40L, IL-21, and TGF-β1.[56,77,78] Yet, it is currently unclear whether intestinal T follicular helper cells arise from natural or induced T_{reg} cells, and whether T_{reg} and T follicular helper cells play specific roles in the generation of commensal-reactive versus pathogen-reactive, or low-affinity versus high-affinity IgA antibodies. In addition to T_{reg} and T follicular helper cells, Th2 cells producing IL-4 may further contribute to IgA CSR and production in intestinal follicles. $CD11b^+$ DCs appear to be particularly efficient in the induction of Th2 cells in Peyer's patches.[68,79]

Together with TGF-β, CD40L is a key element in the TD pathway for IgA CSR and production.[80–82] Engagement of CD40 on B cells by CD40L causes recruitment of TNF receptor–associated factor (TRAF) adaptor proteins to the cytoplasmic tail of CD40.[83] This event is followed by translocation of the transcription factor NF-κB from the cytoplasm to the nucleus and by NF-κB-dependent transcription of the AID gene promoter.[84] In contrast, NF-κB is not required for the activation of the C_α gene promoter, which rather involves SMA-homologue mothers against decapentaplegic (SMAD) transcription factors induced by the TGF-β receptor.[84]

In spite of requiring $CD4^+$ T cells to develop a germinal center reaction, Peyer's patches can promote IgA responses in the absence of the B cell antigen receptor (BCR or Ig receptor).[54] The BCR is central to antigen-driven cognate T–B cell interactions and is required for the survival of peripheral B cells and the development of a germinal center reaction in systemic lymphoid follicles.[54,85] This has led to the proposal that B cells from Peyer's patches may undergo IgA diversification and production by utilizing a noncanonical TD pathway involving cosignals from TLRs instead of cosignals from the BCR.[86] Additional BCR-independent signals may originate from TNF-inducible nitric oxide synthase (iNOS)-producing DCs, which enhance TD IgA responses by upregulating the expression of the TGF-β receptor on follicular B cells from Peyer's patches via nitric oxide.[87]

Follicular B cells from Peyer's patches can receive additional IgA-inducing signals from follicular DCs.[88] These cells release CD40L-related factors known as B cell-activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) upon "priming" by mucosal signals, such as commensal TLR ligands and retinoic acid.[88] Mucosal follicular DCs also release large amounts of active TGF-β1 and use their dendrites to organize commensal antigens in "periodic" arrays.[88] By releasing TGF-β1, BAFF, and APRIL and stimulating BCRs and TLRs on B cells, follicular DCs would enhance the IgA-inducing function of T follicular helper cells in Peyer's patches.[56,88] A similar mechanism may enable follicular DCs to trigger IgA production in a TI manner.[89,90] Follicular B cells from Peyer's patches and mesenteric lymph nodes further undergo TI switching to IgA in response to plasmacytoid DCs.[91] These cells are "primed" by type-I IFNs from intestinal stromal cells to release large amounts of BAFF and APRIL.[91]

IgA induction in isolated lymphoid follicles

Together with Peyer's patches and mesenteric lymph nodes, isolated lymphoid follicles represent another important site for IgA induction.[92] These lymphoid structures are scattered throughout the intestine and consist of solitary B cell clusters built on a scaffold of stromal cells with a few interspersed $CD4^+$ T cells and more abundant perifollicular DCs expressing CD11c.[56,92] Unlike Peyer's patches, which develop in the sterile fetal microenvironment, isolated lymphoid follicles develop from smaller anlagen structures called cryptopatches after postnatal bacterial colonization of the intestine.[92–94] These cryptopatches contain lymphoid tissue-inducer cells expressing the retinoic acid orphan receptor RORγt and stromal cells that recruit DCs, B, and T cells in response to bacterial signals, including TLR signals.[92–94]

Similar to Peyer's patches, isolated lymphoid follicles have a follicular epithelium comprising antigen-sampling M cells as well as a subepithelial area containing $CX3CR1^+$ DCs.[92] After capturing bacteria from the intestinal lumen or M cells, $CX3CR1^+$ DCs may present TI antigens to local follicular B cells, thereby, eliciting the activation of TLR and perhaps BCR signaling pathways. $CD11c^+$ DCs associated with isolated lymphoid follicles also express TNF, a powerful inducer of matrix metalloproteases 9 and 13 that process active TGF-β1 from a latent precursor protein.[44] In addition to forming active TGF-β1, DCs

cooperate with stromal cells to release BAFF and APRIL through a pathway that is enhanced by microbial TLR signals.[44] These cytokines induce IgA CSR and production through a TI pathway that does not require germinal center formation.[5,44,95]

IgA induction in the lamina propria

The diffuse tissue of the lamina propria can support some IgA CSR and production in the absence of follicular structures.[44,96,97] Consistent with this possibility, some B cells from the lamina propria contain molecular hallmarks of ongoing IgA CSR, including AID, H2AX (a nuclear protein associated with AID-induced double-strand DNA breaks), S_α–S_μ switch circles, and I_α–C_μ switch circle transcripts.[34,96,98–101] In general, lamina propria B cells are scattered and express fewer molecular byproducts of IgA CSR than Peyer's patch B cells, which may explain why some groups failed to detect IgA CSR in the lamina propria.[89,90,102] Discrepancies seem particularly evident with regard to AID expression.[89,90,102] Yet, this expression has been confirmed in the lamina propria by means of a green fluorescent protein-AID reporter mouse model and through the use of *in situ* hybridizaton techniques.[34,96]

IgA CSR in the lamina propria likely involves *in situ* activation of B cells by DCs.[34,44,87,97,103,104] In the mouse lamina propria, TNF-iNOS–producing DCs initiate TI IgA CSR and production by releasing BAFF and APRIL through a TLR-dependent mechanism involving induction of nitric oxide production by iNOS.[87] Another lamina propria DC subset with IgA-licensing function is represented by $TLR5^+$ DCs.[97,105] In addition to TLR5, these DCs express CD11c, CD11b, and CD103 and induce TI IgA production by releasing retinoic acid and IL-6 upon sensing bacteria through the flagellin receptor TLR5.[97,105] Also epithelial cells deliver IgA-inducing signals to lamina propria B cells by releasing BAFF and APRIL after recognizing bacteria via TLRs.[34,103] Epithelial cells would further amplify IgA production by enhancing DC release of BAFF and APRIL through TSLP.[34,103]

In humans, APRIL is particularly effective at inducing IgA2, an IgA subclass abundant in heavily colonized mucosal districts, such as, the distal intestine.[34,106,107] Consistent with studies showing the germinal center–independent origin of IgA2-producing B cells,[108] APRIL triggers IgM-to-IgA2 CSR independently of CD40L.[34] In addition, APRIL elicits sequential IgA1-to-IgA2 CSR, thereby, allowing hypermutated IgA1-expressing B cells from Peyer's patches to acquire a protease-resistant IgA2 subclass in the lamina propria.[34] This model could explain why IgA2 antibodies have mutated V(D)J genes in spite of emerging from a seemingly TI pathway.[45]

BAFF and APRIL trigger IgA CSR by engaging a CD40-related receptor known as transmembrane activator and calcium modulator and cyclophylin ligand interactor (TACI).[109,110] In the presence of cosignals from cytokine receptors and TLRs (Fig. 2), TACI induces AID expression via NF-κB, followed by CSR, antibody production, and plasma cell differentiation.[110,111] An important property of TACI relates to its ability to establish a close functional cooperation with B cell-intrinsic TLR signals.[110] Indeed, TACI uses the adaptor protein myeloid differentiation primary response gene 88 (MyD88) and TRAF6 to activate NF-κB, as TLRs do.[110] However, TLRs recruit MyD88 and downstream kinases, such as, IL-1 receptor–associated kinase 1 (IRAK-1) and IRAK4 through a cytoplasmic Toll-interleukin-1 receptor (TIR) motif, whereas TACI uses a cytoplasmic motif different from TIR.[110] Given that TLR signals are also important to generate the production of TACI ligands by innate immune cells,[34,103,104] these findings highlight the intimate cooperation between the innate and adaptive immune systems at both cellular and

signaling levels and provide an additional mechanistic explanation for studies linking intestinal IgA responses to MyD88.[54,87]

Lessons from PID

In addition to neutralizing specific mucosal pathogens, IgA modulates the interaction of commensal bacteria with the mucosal immune system to mitigate the overall inflammatory tone of the intestine.[25] Therefore, it is not surprising that a large proportion of patients with primary antibody disorders, such as selective IgA deficiency (SIgAD), common variable immune deficiency (CVID), and hyper-IgM (HIGM) syndrome, develop not only gastrointestinal infections, but also inflammatory bowel disease.[112–116] Gastrointestinal inflammation is somewhat less prominent in patients with X-linked agammaglobulinemia (XLA), a primary antibody disorder in which deleterious substitutions of the BCR-associated enzyme Bruton's tyrosine kinase (Btk) cause developmental arrest of B cell precursors in the bone marrow and severe depletion of mature B cells in the periphery.[117,118] Perhaps, the lack of functional Btk in XLA attenuates BCR-independent inflammatory signals, such as, TLR signals in mucosal DCs, macrophages and epithelial cells.[119,120] Alternatively, XLA patients may be protected from intestinal disease by the lack of heterogeneous T cell and DC abnormalities often present in patients with CVID.[121–124]

Patients with SIgAD or CVID also develop gut nodular lymphoid hyperplasia, a benign lymphoproliferative disorder that consists of multiple nodular lesions made up of lymphoid aggregates usually confined to the lamina propria of the small intestine.[115,116,123,125] Nodular lymphoid hyperplasia is thought to originate from polyclonal activation of intestinal B cells by commensal bacteria undergoing aberrant expansion in the small intestine.[126] Consistent with this interpretation, patients with SIgAD and CVID develop small bowel bacteria overgrowth syndrome, which leads to heterogeneous clinical manifestations associated with malabsorption.[115,116,123] Nodular lymphoid hyperplasia and small bowel bacteria overgrowth syndrome are also present in patients with HIGM syndrome caused by deleterious AID substitutions that impair both CSR and SHM.[127] The molecular basis of impaired mucosal IgA responses and gastrointestinal disorders in SIgAD and CVID remain largely unknown, but some CVID patients have deleterious TACI substitutions.[128–131]

Nodular lymphoid hyperplasia and bacterial overgrowth have also been observed in AID knockout mice and in mice with deleterious AID substitutions that abrogate the induction of SHM but not CSR.[21,24] The small intestine of these mice shows uncontrolled expansion of segmented filamentous bacteria as well as a prominent antibiotic-sensitive hyperplasia of isolated lymphoid follicles.[21,24] Together, these observations indicate that specific recognition of commensals by somatically hyper-mutated IgA plays an important role in the control of the composition and compartimentalization of the intestinal microbiota. The lack of this function would lead to increased bacterial growth in the small intestine, with subsequent polyclonal hyperactivation of local as well as systemic B cells. Over time, this process may lead to the aberrant expansion of allergen-reactive, autoreactive, and clonal B cells, which could contribute to the increased frequency of allergy, autoimmunity (celiac disease, hemolytic anemia, immune thrombocytopenic purpura), and Bcell tumors (mostly non-Hodgkin lymphoma) observed in individuals with SIgAD, CVID, or HIGM syndrome.

In cases characterized by specific gene defects, PIDs can be regarded as an "experiment of nature" that may help immunologists to better understand the regulation of mucosal IgA responses. In HIGM syndrome caused by deleterious CD40 substitutions,[132] the intestinal lamina propria includes IgA-producing B cells and plasmablasts that contain AID, a hallmark of ongoing CSR.[34,101,133] Consistent with the key role of CD40 in the germinal center reaction,[134] AID expression and IgA CSR are virtually abolished in germinal center B

cells from mucosal follicles of individuals with HIGM syndrome.[104,132] In contrast, subepithelial B cells from the intestinal and respiratory mucosal surfaces of these patients show AID expression and active IgA CSR.[104,132] IgA CSR is also conserved in subepithelial B cells from chronically infected HIV-infected patients with massive depletion of intestinal $CD4^+$ T cells.[100] These patients also show a profound impairment of the germinal center reaction.[100] Overall, these findings suggest that human B cells can produce IgA through a germinal center–independent pathway that does not require help to B cells by $CD4^+$ T cells expressing CD40L.

In humans, CD40-independent IgA production may mostly rely on APRIL signaling to B cells via TACI.[110] Accordingly, IgA production is decreased in CVID patients with deleterious TACI substitutions, whereas patients with deleterious BAFF-R substitutions have normal IgA, at least in the circulation.[128,129,135] Additional studies show that B cells from patients with MyD88 or IRAK4 deficiency, two PIDs associated with invasive bacterial infections, are less responsive to CSR signals from BAFF and APRIL, indicating a possible role of MyD88 and IRAK-4 in the generation of class-switched antibodies to bacterial TI antigens, such as, polysaccharides.[110,136,137] Consistent with this possibility, MyD88-deficient mice have defective intestinal IgA production, and their B cells do not effectively undergo CSR in response to TACI engagement by BAFF or APRIL.[5,54,87,95] Of note, patients lacking MyD88 or IRAK-4, a kinase downstream of MyD88, have normal levels of total IgA in the serum.[136–138] However, mucosal IgA responses have never been measured in these patients.

Conclusions

IgA is the predominant antibody isotype of the gut-associated lymphoid tissue that has been selected throughout evolution to provide protection against mucosal microorganisms. IgA has long been known for its importance in the protection against pathogens, but its role in the selection and maintenance of a spatially diversified bacterial community in the gut has become clear only in recent years. A number of studies have revealed that IgA responses involve B cells from both follicular and extrafollicular districts and follow multiple TD and TI pathways. Yet, the precise cellular and signaling components of these pathways, and their relative contribution to mucosal immunity and homeostasis remain to be fully elucidated. Further studies are also needed to characterize the mechanisms by which IgA controls the inflammatory tone of the intestine and regulates the composition and compartimentalization of the intestinal microbiota. PIDs with genetic alterations affecting known B cell–regulating pathways may provide excellent models to address some of these questions in humans.

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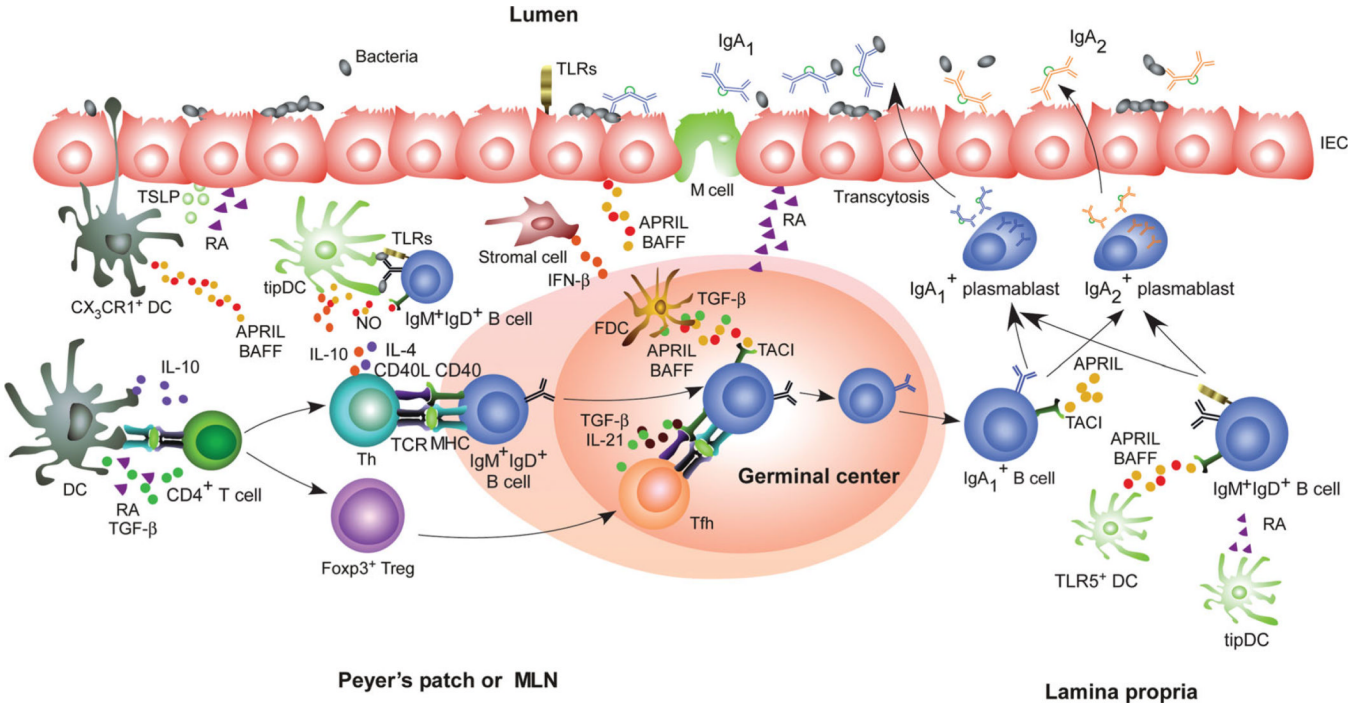

Figure 1.

Cellular networks underlying mucosal IgA responses. Intestinal epithelial cells (IECs) "condition" dendritic cells (DCs) by releasing thymic stromal lymphopoietin (TSLP) and retinoic acid (RA) in response to TLR ligands from commensal bacteria. Different subsets of intestinal DCs release TGF-β, IL-10, RA, and nitric oxide (NO) that promote IgA responses in Peyer's patches and mesenteric lymph nodes (MLNs) by inducing T regulatory (T_{reg}) and T helper (Th) cells, including T_{reg}-derived T follicular helper cells, which activate follicular B cells via CD40L, TGF-β, IL-4, IL-10, and IL-21. Follicular DCs further enhance IgA production by releasing B cell–activating factor of the TNF family (BAFF), a proliferation-inducing ligand (APRIL), and TGF-β upon exposure to TLR ligands and RA. Some subsets of intestinal DCs also induce T cell–independent IgA production in mesenteric lymph nodes or the lamina propria by releasing BAFF, APRIL, RA, and NO in response to TLR ligands from commensals or IFN-β from stromal cells. In humans, these T cell–independent signals would induce switching from IgM or IgA1 to IgA2. The IgA antibodies emerging from these pathways undergo transcytosis across IECs via the polymeric Ig receptor.

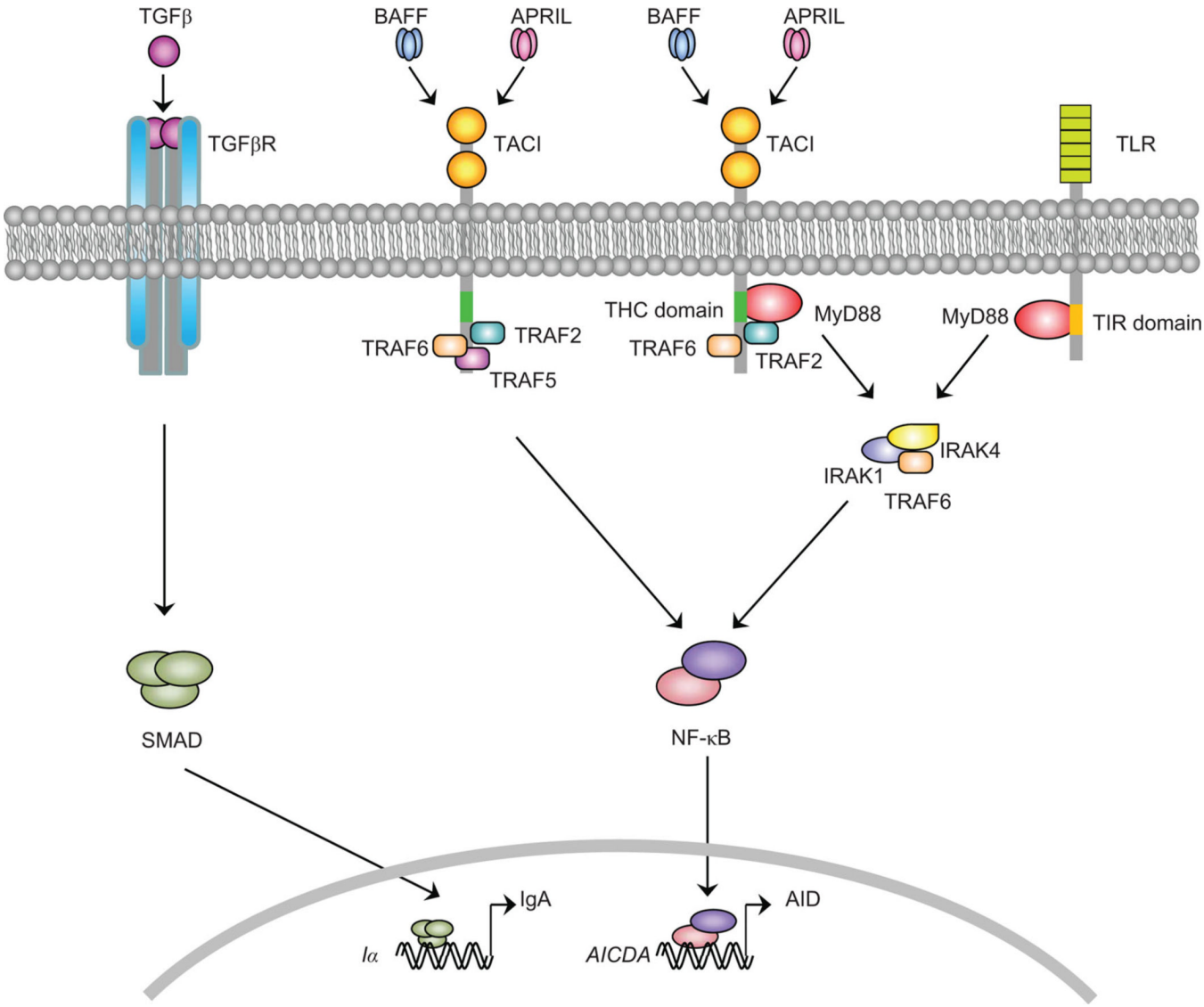

Figure 2.

Signaling pathways emanating from transmembrane activator and calcium modulator and cyclophylin ligand interactor (TACI). The TGF-β receptor (TGF-βR) initiates germline C_α gene transcription by activating the I_α promoter via SMA-homologue mothers against decapentaplegic (SMAD) proteins. At the same time, engagement of TACI by BAFF and APRIL triggers the recruitment of myeloid differentiation primary response gene 88 (MyD88) to a TACI highly conserved (THC) motif located in the cytoplasmic domain of TACI receptor. TACI also recruits TNF receptor–associated factor 2 (TRAF2) to a motif located immediately downstream of THC. The THC motif is distinct from the Toll-interleukin-1 receptor (TIR) motif, which mediates the recruitment of MyD88 by Toll-like receptors (TLRs). Recruitment of IL-1 receptor–associated kinase 1 (IRAK-1), IRAK-4, and TRAF6 by TACI and TLRs leads to the activation and nuclear translocation of NF-κB, which initiates transcriptional activation of the *AICDA* gene encoding activation-induced cytidine deaminase (AID). Together, germline C_α gene transcription and AID induction cause class switch recombination from IgM to IgA in B cells.

Table 1

Mucosal cell types involved in IgA class switching and production

Mucosal cell type	Mucosal topography	Mechanism of IgA induction
T_{reg} cell	PP, LP	CD40L, TGF-β, possibly IL-10
T_{FH} cell	PP, MLN	CD40L, IL-21, TGF-β
Th2 cells	PP	IL-4, IL-10
FDC	PP, MLN	BAFF, APRIL, TGF-β
Stromal cell	ILF, LP	BAFF, APRIL, TGF-β
IEC	LP	BAFF, APRIL, RA, TSLP, IL-10, TGF-β
$iNOS^+TNF^+$ DC (tipDC)[a]	PP, LP	BAFF, APRIL, nitric oxide
$CD11c^{hi}CD11b^{hi}$ DC ($TLR5^+$ DC)[a]	LP	RA, IL-6
$CX3CR1^+$ DC[a]	PP, LP	Unknown
$CD103^+$ DC[a]	PP, LP, MLN	Induction of T_{reg} and possibly T_{FH} cells via RA
$CD11c^+$ DC	PP	Induction of Th2 cells via IL-10
$CD11b^+$ DC[a]	PP	IL-6

[a] Described mostly in mice. T_{FH}, T follicular helper cell.