

Innate signals in mucosal immunoglobulin class switching

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List of Design Committee Members: Irene Puga, PhD, Montserrat Cols, PhD, and Andrea Cerutti, MD

Activity Objectives

1. To identify the role of innate immune cells, dendritic cells (DCs), epithelial cells, and stromal cells in gut lymphoid tissue and IgA production.
2. To be familiar with IL-10, B cell-activating factor (BAFF), a proliferation-inducing ligand (APRIL), and CD40 ligand (CD40L) in IgM-to-IgA class switching.
3. To understand how MyD88 is a critical signaling adaptor in intestinal IgA.
4. To understand the role of Toll-like receptors (TLRs) and the BAFF-APRIL signaling system.

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The intestinal mucosa contains large communities of commensal bacteria that process otherwise indigestible food components, synthesize essential vitamins, stimulate the maturation of the immune system, and form an ecologic niche that prevents the growth of pathogenic species. Conversely, the intestine provides the commensals with a stable habitat rich in energy derived from the ingested food. A delicate homeostatic balance maintains this mutualistic relationship without triggering a destructive inflammatory response. Commensals orchestrate intestinal homeostasis by entertaining an intimate dialogue with epithelial cells and immune cells lodged in the mucosa. Such a dialogue generates finely tuned signaling programs that ensure a state of hyporesponsiveness against noninvasive commensals and a state of active readiness against invasive pathogens. In this dialogue epithelial cells function as “interpreters” that

continuously translate microbial messages to “instruct” immune cells as to the antigenic composition of the intestinal lumen. This education process initiates sophisticated defensive strategies that comprise massive production of IgA, a noninflammatory mucosal antibody class that generates immunity while preserving homeostasis. (*J Allergy Clin Immunol* 2010;126:889-95.)

Key words: Mucosal immunity, B cells, immunoglobulin, class switching

The mucosal immune system generates frontline immune protection at the interface between the host and the environment by forming a highly integrated network of lymphoid organs collectively known as mucosa-associated lymphoid tissue.¹ This tissue can be further divided into anatomically distinct subregions that in human subjects are functionally independent of systemic lymphoid organs. One of these subregions is the gut-associated lymphoid tissue (Fig 1), which comprises highly organized lymphoid structures called Peyer’s patches, mesenteric lymph nodes, and isolated lymphoid follicles.¹ These inductive sites generate effector memory B cells that, under the influence of chemokines produced by intestinal epithelial cells (IECs), enter the general circulation and migrate to the diffuse lymphoid tissue of the intestinal lamina propria. At this effector site, B cells release IgA, which recognizes dietary antigens, commensal bacteria, and pathogens with both high- and low-affinity binding modes.¹

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Abbreviations used

AID:	Activation-induced cytidine deaminase
APRIL:	A proliferation-inducing ligand
BAFF:	B cell-activating factor of the TNF family
BCMA:	B-cell maturation antigen
CD40L:	CD40 ligand
CSR:	Class-switch recombination
DC:	Dendritic cell
FDC:	Follicular dendritic cell
IEC:	Intestinal epithelial cell
NF- κ B:	Nuclear factor κ B
pIgR:	Polymeric immunoglobulin receptor
SHM:	Somatic hypermutation
RA:	Retinoic acid
SLPI:	Secreted leukocyte protease inhibitor
TACI:	Transmembrane activator and calcium-modulating cyclophilin-ligand interactor
TD:	T cell dependent
T _{FH} :	Follicular T _H
TI:	T cell independent
tipDC:	TNF-inducible nitric oxide synthase-producing dendritic cell
TLR:	Toll-like receptor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin

In general, high-affinity IgA is thought to derive from follicular B cells that undergo T cell-dependent (TD) affinity maturation and IgA class switching on interacting with CD4⁺ T cells in the germinal centers of Peyer's patches and mesenteric lymph nodes.² Instead, low-affinity IgA originates from extrafollicular B cells that undergo T cell-independent (TI) IgA class switching but no or minimal affinity maturation after interacting with dendritic cells (DCs), stromal cells, and IECs in the lamina propria.² However, this picture is rapidly changing, and recent findings indicate that also follicular B cells can undergo TI IgA class switching by interacting with follicular dendritic cells (FDCs), DCs, and stromal cells in Peyer's patches and isolated lymphoid follicles.^{3,4}

INTESTINAL IgA CLASS SWITCHING

Antibody diversification is essential for B cells to generate protection. Bone marrow B-cell precursors generate immunoglobulin recognition diversity by assembling antigen-binding variable regions from individual V (variable), D (diversity), and J (joining) gene segments through an antigen-independent DNA-modifying process mediated by a recombination-activating gene endonuclease complex.² Peripheral mature B cells further diversify their immunoglobulin gene repertoire by undergoing class-switch recombination (CSR) and somatic hypermutation (SHM) through a DNA-editing enzyme called activation-induced cytidine deaminase (AID).^{2,5}

CSR replaces constant μ (C _{μ}) and C _{δ} exons encoding IgM and IgD with C _{γ} , C _{α} , or C _{ϵ} exons encoding IgG, IgA, or IgE, thereby providing antibodies with novel effector functions without changing their specificity for antigen; instead, SHM introduces point mutations within V(D)J exons, thereby providing the structural correlate for selection of high-affinity immunoglobulin mutants by antigen.^{2,5} By switching from IgM to IgA, B cells acquire an antibody class capable of undergoing transcytosis across epithelial cells, including IECs.² This process involves interaction

of IgA oligomers with polymeric immunoglobulin receptor expressed on the basolateral surface of epithelial cells.

Mucosal antigens initiate IgA production by activating follicular B cells through a TD reaction that takes place in the germinal center of Peyer's patches and mesenteric lymph nodes.^{1,2} This TD pathway involves an antigen-specific cognate interaction between B cells expressing the CD40 receptor and CD4⁺ T cells expressing CD40 ligand (CD40L), including T_{H2} cells, regulatory T (Treg) cells, and follicular T_H (T_{FH}) cells.^{1,2,6,7} Together with B-cell antigen receptor and receptors for cytokines such as IL-4, IL-5, IL-6, IL-10, IL-21, TGF- β , the CD40 receptor upregulates the expression of AID and triggers the induction of SHM and CSR from IgM to IgA.² Class-switched B cells emerging from such a CD40-dependent pathway ultimately differentiate into long-lived memory B cells and plasma cells that release high-affinity IgA antibodies in the lamina propria.²

Mucosal antigens can also initiate IgA production by activating follicular B cells through a TI reaction that takes place in Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles.^{1,4,8} This TI pathway involves noncognate interactions of B cells with FDCs, DCs, and stromal cells releasing innate IgA-inducing factors, such as B cell-activating factor of the TNF family (BAFF; also called BLyS), a proliferation-inducing ligand (APRIL), and TGF- β .^{1,4,8} Commensal bacteria drive this process by stimulating FDCs, DCs, stromal cells, and B cells through Toll-like receptors (TLRs).^{1,4,8} Together with many other germline gene-encoded pattern-recognition receptors, TLRs activate both innate and adaptive arms of the mucosal immune system after sensing highly conserved microbial products. In the intestine, commensals trigger multiple TLRs, including TLR4, TLR5, and TLR9, to stimulate FDC, DC, and stromal cell release of BAFF, APRIL, TGF- β , and other IgA-inducing cytokines.^{1,4,8-10} Similar innate signals can also initiate IgA CSR in B cells within the diffuse lymphoid tissue of the lamina propria.^{1,4,8} Class-switched B cells emerging from such a CD40-independent pathway ultimately release both low- and high-affinity IgA antibodies in the lamina propria.^{1,2}

CONNECTIVITY OF IgA-INDUCING SIGNALS

In spite of having available a wealth of sensing and effector mechanisms capable of triggering inflammation in response to microbial intrusion, our intestinal immune system establishes homeostatic conditions based on a fine discrimination between commensals and pathogens. IECs and DCs play a key role in this process because these cell types can sense luminal bacteria through a complex arsenal of pattern-recognition receptors, including TLRs. Signals from TLRs "instruct" the immune system as to the composition of the local microbiota and thereafter instruct the generation of effector and regulatory lymphocytes, the main function of which is to dampen inflammation while eliciting immune protection. This education process involves intertwined signaling networks that ultimately lead to the production of massive amounts of a noninflammatory antibody class, such as IgA. In these networks the adaptor MyD88 is at a center of a signaling hub because most TLR ligands from commensal bacteria require MyD88 to activate those B-cell, T-cell, DC, FDC, stromal cell, lymphoid tissue inducer cell, and IEC signaling programs required for the initiation of IgA CSR and production. Consistent with this scenario, lack of MyD88 in genetically engineered mice leads to a profound impairment of intestinal IgA responses and homeostasis.^{3,10}

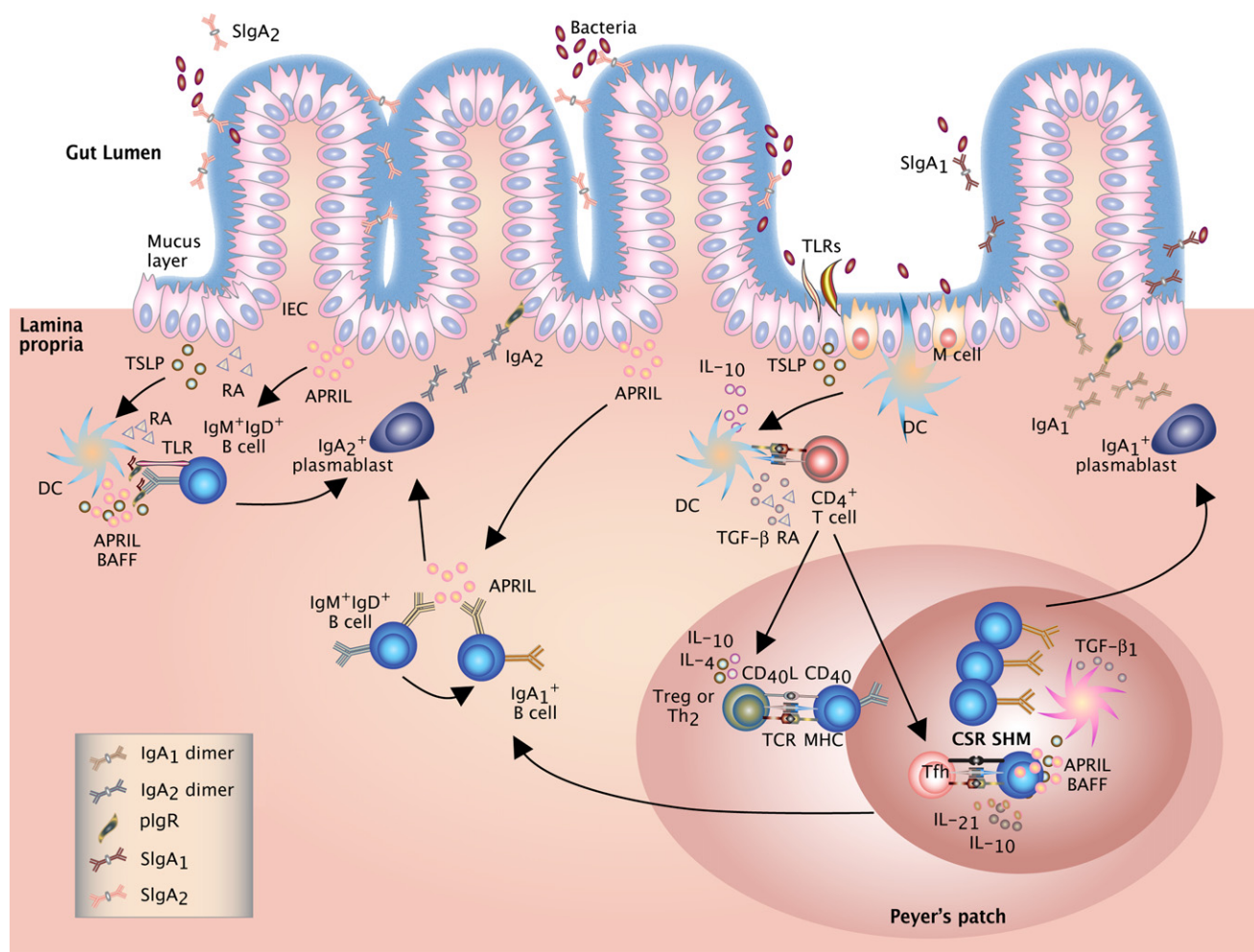


FIG 1. Architecture of intestinal TD and TI IgA responses. Antigen-sampling DCs receive conditioning signals from TLR-activated IECs through TSLP and RA and thereafter differentiate into various DC subsets releasing TGF- β , IL-10, RA, and nitric oxide. These DCs initiate TD IgA responses in Peyer's patches by inducing T_H2, Treg, and Treg-derived T_{FH} cells that activate follicular B cells through CD40L, TGF- β , IL-4, IL-10, and IL-21. IgA-expressing B cells emerging from this TD pathway differentiate into plasma cells in mesenteric lymph nodes and lamina propria. Plasma cells release IgA dimers and IgA oligomers comprising a joining (J) chain that binds to the polymeric immunoglobulin receptor (plgR) on the basolateral membrane of IECs. This binding triggers endocytosis of polymeric IgA, protease-mediated cleavage of plgR, and formation of a plgR-derived secretory component protein that remains associated with the polymeric IgA-J chain complex to form secretory IgA (SlgA). This latter traffics toward the apical membrane of IECs and ultimately gets transcytosed onto the mucosal surface, where it recognizes dietary antigens, commensal bacteria, and pathogens with both high- and low-affinity binding modes. In the lamina propria IECs and DCs can initiate TI IgA responses, including sequential switching from IgA1 to IgA2, by releasing BAFF, APRIL, and RA in response to TLR stimulation by microbial ligands. TSLP from IECs further amplifies IgA production by enhancing DC production of BAFF and APRIL. Together with RA, BAFF and APRIL from DCs and IECs can stimulate plasma cell differentiation and survival in addition to eliciting IgA CSR and production.

THE TLR LIGAND-BAFF-APRIL SIGNALING SYSTEM

BAFF and APRIL are CD40L-related TNF family members released by innate immune cells, stromal cells, and epithelial cells, including IECs.² Chronic release of low amounts of BAFF and APRIL trimers delivers survival signals to B cells and plasma cells, whereas acute release of larger amounts of higher-order BAFF and APRIL oligomers signals CSR and antibody production to B cells. In the intestine TLR signals from commensals upregulate BAFF and APRIL release by DCs, stromal cells, FDCs, and IECs and thereby trigger induction of TI IgA CSR and production in Peyer's patches, isolated lymphoid follicles, and the lamina propria.²⁻⁴ This induction involves engagement of transmembrane activator and

calcium-modulating cyclophilin-ligand interactor (TACI), BAFF receptor, and B-cell maturation antigen (BCMA) on B cells.²

Although TACI signals CSR and antibody production, BAFF receptor and BCMA signal B-cell and plasma cell survival.² Of note, BAFF and APRIL require cosignals from microbial TLR ligands to efficiently elicit IgA CSR and production in B cells.² This cooperation involves upregulation of TACI expression by B cell–intrinsic TLR-mediated signals.¹¹ The TLR pathway further cooperates with the TACI pathway by converging on a distal signal transducer, such as nuclear factor κ B (NF- κ B), which is essential for the induction of both *AID* and germline C_H gene transcription.¹¹ Thus TLR signals from commensals

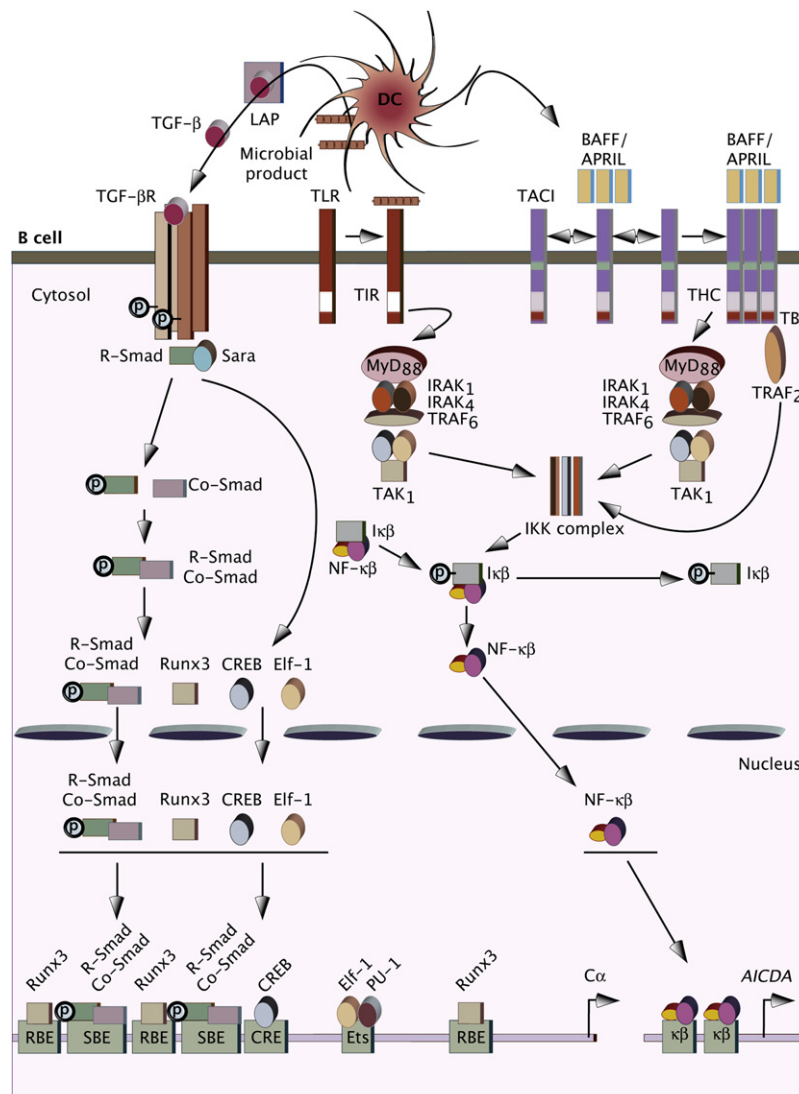


FIG 2. Innate IgA-inducing signaling pathways. Mucosal DCs induce IgA CSR and production by releasing BAFF, APRIL, and TGF- β on sensing microbial TLR ligands. Active TGF- β originates from cleavage of a latency-associated peptide (LAP) by TLR-induced matrix metalloproteases. Engagement of TACI on B cells by BAFF and APRIL triggers association of the adaptor MyD88 to a TACI highly conserved domain that activates NF- κ B through a pathway involving IL-1 receptor-associated kinase (IRAK) 1, IRAK-4, TGF- β activated kinase-1 (TAK1), and I κ B kinase (IKK)-mediated degradation of the inhibitor of NF- κ B (I κ B). Additional NF- κ B activation involves binding of TNF receptor-associated factor (TRAF) 2 to a TRAF-binding site (TBS) in the cytoplasmic domain of TACI. NF- κ B initiates CSR by binding to κ B motifs on the *AID* gene promoter. Engagement of TLRs by microbial ligands enhances IgA CSR and production through a Toll-IL-1 receptor domain (TIR)-dependent pathway that shares MyD88 with the TIR-independent pathway emanating from TACI. Further CSR-inducing signals are provided by TGF- β , which forms a heteromeric TGF receptor (TGF- β R) complex on B cells. TGF- β activates TGF- β R kinases that induce phosphorylation of receptor-regulated SMAD (R-SMAD) proteins. After forming homo-oligomeric and hetero-oligomeric complexes with a common-partner SMAD (Co-SMAD) protein, R-SMAD proteins translocate to the nucleus, where they bind to SMAD-binding elements (SBEs) on the *C α* gene promoter. These Smad complexes further associate with constitutive and TGF- β R-induced cofactors, including Runt-related transcription factor 3 (RUNX3), which binds to RUNX-binding elements (RBEs); cyclic adenosine monophosphate response element-binding protein (CREB), which binds to a cyclic adenosine monophosphate response element (CRE); and Ets-like factor-1 (ELF-1), which binds to an Ets-binding site, to enhance CSR from *C μ* to *C α* .

not only induce BAFF and APRIL expression but also cooperate with BAFF and APRIL to induce B-cell activation through TACI. However, recent studies suggest that the interconnectivity of TLR and TACI receptors have further layers of complexity (Fig 2).

Indeed, engagement of TACI by BAFF or APRIL triggers recruitment of MyD88 to a highly conserved cytoplasmic domain of TACI distinct from the canonical cytoplasmic Toll-IL-1 receptor domain of TLRs.¹¹ Interaction of TACI with MyD88 is followed by activation of a TLR-like pathway that elicits AID

TABLE I. IgA in primary immunodeficiencies affecting class switching

Immunodeficiency	Mechanism	Systemic IgA	Intestinal IgA	Intestinal disease
SIgAD	Unknown	Impaired	Impaired	Infections,* celiac disease, nodular hyperplasia
CVID	TACI†	Impaired	Impaired	Infections,* bacterial overgrowth,‡ nodular hyperplasia, inflammation§
HIGM-1	CD40L	Impaired	Unknown	Infections,¶ bacterial overgrowth
HIGM-2	AID	Impaired	Impaired	Infections,¶ bacterial overgrowth
HIGM-3	CD40	Impaired	Partly conserved	Infections,¶ bacterial overgrowth
MyD88 deficiency	MyD88	Conserved#	Unknown	None reported
IRAK-4 deficiency	IRAK-4	Conserved#	Unknown	None reported

CVID, Common variable immunodeficiency; HIGM, hyper-IgM syndrome; SIgAD, selective IgA deficiency.

*Cytomegalovirus, *Helicobacter pylori*, and *Cryptosporidium* and *Giardia* species, among others.

†Three percent to 8% of cases associated with heterozygous TACI substitutions. The *in vivo* effect of these substitutions is still poorly understood.

‡Bacterial overgrowth takes place in the small intestine and causes malabsorption.

§Inflammatory bowel disease–like disorder in 6% to 10% of patients.

||Likely partially conserved, as in hyper-IgM syndrome type 3.

¶*Cryptosporidium* species, among others.

#Only *in vitro* immunoglobulin defects; however, the kinetics and affinity of *in vivo* IgG and IgA responses to certain antigens might be altered.

expression and CSR through NF- κ B.¹¹ These findings could provide an alternative molecular explanation to previously published *in vivo* data demonstrating an essential role of MyD88 in systemic TI IgG responses induced by BAFF and, together with other studies, suggest that TACI and TLRs might converge on MyD88 to generate intestinal IgA production.^{3,10,12}

DC IgA-INDUCING SIGNALS

Together with M cells, DCs directly sample antigen from the intestinal lumen by emanating transepithelial projections through a process controlled by TLR-activated IECs.^{13,14} Antigen-loaded DCs eventually migrate to mucosal follicles to induce T_H2, Treg, and T_{FH} cell differentiation in an antigen-specific way.² Of note, the generation of these noninflammatory CD4⁺ T-cell subsets with IgA-inducing function requires “conditioning” of antigen-sampling DCs by various IEC factors, including thymic stromal lymphopoietin (TSLP), an IL-7–like cytokine that impedes formation of inflammatory T_H1 cells and enhances formation of T_H2 cells by attenuating DC production of IL-12 but not IL-10.^{2,13,14} In addition to facilitating T_H2-mediated IgA responses, TSLP amplifies TI IgA responses by stimulating DC production of IL-10, BAFF, and APRIL.² Indeed, in the presence of cosignals from TLRs, TSLP-conditioned DCs trigger CD40-independent IgA CSR by stimulating B cells through BAFF, APRIL, and IL-10.^{8,15}

In mice a DC subset that triggers IgA production through either TD or TI pathways is that of TNF- α –inducible nitric oxide synthase–producing DCs (tipDCs).¹⁰ Like other DC subsets, tipDCs are lodged in Peyer’s patches, where they enhance TD IgA CSR by upregulating the expression of TGF- β receptor on follicular B cells through nitric oxide.¹⁰ However, tipDCs are also lodged in the lamina propria, where they elicit TI IgA CSR by upregulating the release of BAFF and APRIL in response to nitric oxide.¹⁰ In both pathways tipDCs deliver IgA-inducing signals as they sense the presence of commensals through TLRs.¹⁰

Another DC subset that triggers IgA production through a TI pathway in the lamina propria is that of CD11c^{hi}CD11b^{hi} DCs.¹⁶ These DCs release retinoic acid (RA) and IL-6 on sensing bacteria through TLR5, a receptor for the microbial protein flagellin.¹⁶ Like other DC subsets, CD11c^{hi}CD11b^{hi} DCs upregulate the expression of vitamin A–processing RA-inducing enzymes in response to signals from TLRs.¹⁶ In addition to upregulating gut-homing receptors, RA triggers IgA CSR and plasma cell

differentiation by stimulating B cells in cooperation with microbial TLR ligands and IL-6.^{2,16} The relationship of tipDCs and CD11c^{hi}CD11b^{hi} DCs with antigen-sampling CX₃CR1⁺ DCs and CD103⁺ DCs remains unclear.^{13,14}

FDC IgA-INDUCING SIGNALS

Recent data show that Peyer’s patches and mesenteric lymph nodes contain FDCs that have powerful IgA-inducing function.³ Ontogenetically, phenotypically, and functionally distinct from their cousin DCs, FDCs provide a scaffold that favors the homing, survival, and selection by antigen of follicular B cells. Compared with FDCs from systemic lymphoid follicles, FDCs from intestinal lymphoid follicles induce IgA CSR and production through a TI pathway involving FDC production of BAFF, APRIL, TGF- β –processing matrix metalloproteases, and the B cell–attracting chemokine CXCL13.³ Of note, FDCs activate this pathway as they sense commensals through TLRs.³

EPITHELIAL CELL IgA-INDUCING SIGNALS

In addition to TSLP, IECs release TGF- β and RA, which stimulate the development of CD103⁺ DCs.¹⁴ These DCs promote the formation of Treg cells through TGF- β and RA and suppress the development of inflammatory T_H1 and T_H17 cells.¹⁴ As indicated by recent research, similar Treg cells might also induce IgA CSR in B cells by expressing CD40L and releasing TGF- β .^{6,7} Of note, IECs, as well as other mucosal epithelial cells, such as respiratory epithelial cells, release BAFF, APRIL, and IL-10 in response to TLR signals.^{8,15} In human subjects APRIL is very effective at inducing IgA2, an IgA subclass particularly abundant in the distal intestine.⁸ In addition to direct IgM-to-IgA1 CSR, APRIL elicits sequential IgA1-to-IgA2 CSR in the lamina propria of the distal intestine.⁸ This process allows B cells arriving from Peyer’s patches to acquire an IgA2 subclass more resistant than IgA1 to degradation by bacterial proteases.⁸ Importantly, BAFF and APRIL also enhance the survival of plasma cells and therefore might be involved in the generation of sustained intestinal IgA responses.^{17,18} In addition to releasing BAFF, APRIL, and BAFF/APRIL-inducing cytokines, such as TSLP, IECs produce IL-10, TGF- β , and RA, which are critical to generating homeostasis through Treg cells.^{2,14,19} Furthermore, IECs release secreted leukocyte protease inhibitor (SLPI), which restrains BAFF and APRIL signaling in B cells.¹⁵

In general, SLPI promotes homeostasis by inactivating proinflammatory proteases released by macrophages and granulocytes, including elastase.¹⁵ Moreover, SLPI attenuates the production of proinflammatory cytokines, such as IL-12 and TNF, by TLR-activated macrophages and DCs.¹⁵ Furthermore, SLPI mitigates IgA (and IgG) CSR in B cells by dampening the activation of NF- κ B as induced by BAFF and APRIL.¹⁵ This process might be implicated in intestinal IgA attrition, which involves dampening of ongoing IgA responses by dominant bacterial species.¹⁷

STROMAL CELL IgA-INDUCING SIGNALS

Stromal cells play an important role in TI IgA responses taking place in isolated lymphoid follicles.⁴ Together with DCs, stromal cells entertain an intimate cross-talk with lymphoid tissue inducer cells, another key cell type lodged in isolated lymphoid follicles.⁴ By sensing commensals through TLRs, lymphoid tissue inducer cells release lymphotoxin, which in turn triggers stromal cell (and DC) expression and release of BAFF, APRIL, and matrix metalloproteases endowed with TGF- β processing activity.⁴

CONCLUSIONS

In spite of recent breakthroughs on the lineage, functional heterogeneity, and plasticity of the immune and nonimmune cell types orchestrating intestinal immunity and homeostasis, more work is needed to better understand the cellular and signaling networks involved in intestinal IgA responses. A better understanding of these networks is critical to devise mucosal vaccines capable of providing rapid, robust, and sustained protection against mucosal pathogens without causing inflammation or tolerance. A more detailed knowledge of intestinal IgA responses is also needed to gain new insights into the pathogenesis of intestinal disease. Similar to genetically engineered mice lacking AID, some IgA-deficient patients with selective IgA deficiency, common variable immune deficiency, and hyper-IgM syndrome (type 2, caused by AID deficiency) have gut nodular lymphoid hyperplasia (a B cell–lymphoproliferative disorder) and in some cases gut inflammation.^{2,20–23} These intestinal disorders can arise as a result of an exaggerated stimulation of the local immune system by specific components of the microbiota.^{2,20,24} In particular, IgA deficiency might cause aberrant expansion of commensal species with increased inflammatory potential.²⁰ In this regard IgA has been recently found to dampen intestinal inflammation by attenuating bacteria-induced activation of the innate immune system through immunoselection of bacterial epitope expression.²⁴ Disturbances of IgA-mediated homeostasis could also explain the increased frequency of allergy, autoimmunity, and lymphoma observed in some IgA-deficient patients with selective IgA deficiency and common variable immune deficiency.^{2,21,22} As a final remark, basic immunologists can learn informative lessons from primary immunodeficiencies (Table I) because some of these disorders represent experiments of nature capable of providing precious information as to the effect of specific gene products on our systemic and mucosal immune responses. This is exemplified by our recent studies with specimens from patients with deleterious substitutions of CD40L, CD40, TACI, MyD88, IL-1 receptor–associated kinase 4 (a signal transducer downstream of MyD88), or AID,^{8,11,25,26} which have provided important new insights into the regulation of antibody production in multiple mucosal districts.

What do we know?

- Commensal bacteria orchestrate intestinal homeostasis, including IgA production.
- IgA class switching mainly occurs in intestinal follicular inductive sites.
- IgA class switching additionally involves extrafollicular sites.
- Intestinal IgA responses involve a close cooperation between immune cells and epithelial cells.
- Microbial TLR ligands stimulate epithelial cell and DC release of innate IgA-inducing factors.
- BAFF and APRIL are TLR-inducible mediators that induce class switching from IgM to IgA.
- BAFF and APRIL can stimulate IgA class switching in the absence of T cells and CD40L.
- BAFF and APRIL require cosignals from IL-10 or TGF- β to induce IgA class switching.
- BAFF and APRIL require cosignals from TLR ligands to generate IgA-secreting plasma cells.
- BAFF and APRIL trigger class switching through TACI receptor on B cells.
- BAFF and APRIL promote plasma cell survival through BCMA receptor on plasma cells.
- TACI is functionally intertwined with TLRs in B cells.

What is still unknown?

- The contribution of follicular and extrafollicular IgA responses to gut homeostasis and immunity
- The mechanism by which IgA controls the size and composition of commensal bacteria
- The role of human IgA1 and IgA2 subclasses in gut homeostasis and immunity
- The nature of human B cells mediating TD and TI intestinal IgA responses
- The precise mechanism by which TACI initiates IgA gene transcription
- The contribution of human TGF- β in BAFF and APRIL signaling, including induction of IgA
- The role of human MyD88 in intestinal IgA responses
- The pathogenesis of IgA loss in selective IgA deficiency and common variable immunodeficiency
- The protective function of CD40-independent IgA responses in patients with hyper-IgM syndrome

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