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The Biology of Intestinal Immunoglobulin A Responses

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Abstract

The gut mucosa is exposed to a large community of commensal bacteria that are required for the processing of nutrients and the education of the local immune system. Conversely, the gut immune system generates innate and adaptive responses that shape the composition of the local microbiota. One striking feature of intestinal adaptive immunity is its ability to generate massive amounts of noninflammatory immunoglobulin A (IgA) antibodies through multiple follicular and extrafollicular pathways that operate in the presence or absence of cognate T-B cell interactions. Here we discuss the role of intestinal IgA in host-commensal mutualism, immune protection, and tolerance and summarize recent advances on the role of innate immune cells in intestinal IgA production.

Introduction

The gastrointestinal mucosa is a unique environment that becomes exposed to a massive and diverse microbial ecosystem shortly after birth (Macpherson, 2006). The stomach and proximal segments of the small intestine, including the duodenum and jejunum, have relatively low bacterial densities of approximately 10^3–10^5 organisms per gram of luminal contents, at least in mice. Higher bacterial densities of 10^8 organisms per gram can be found in the ileum, which is the distal portion of the small intestine. In the large intestine or colon, bacteria can reach a density of 10^{10}–10^{12} organisms per gram and comprise more than 1000 species, including obligate anaerobes, such as *Bacteroides*, bifidobacteria, fusobacteria, and peptostreptococci, as well as obligate and facultative aerobes, such as enterobacteria and lactobacilli. Because of this massive colonization, the number of prokaryotic cells in our body is estimated to exceed that of eukaryotic cells by one order of magnitude.

In general, intestinal bacteria establish a mutualistic relationship with the human host. The peaceful nature of this relationship can be traced in the word commensal, which originates from the Latin *cum mensa*, “sharing a table.” Indeed, the intestinal lumen provides bacteria with a stable habitat rich in energy sources derived from the ingested food (Macpherson and Harris, 2004). Conversely, bacteria breakdown otherwise indigestible food components, generate essential nutrients, compete with incoming invasive species, stimulate the growth and protective functions of intestinal epithelial cells, and facilitate the development of the intestinal immune system (Macpherson and Harris, 2004; Rakoff-Nahoum et al., 2004; Rhee et al., 2004). Thus, it is not surprising that the intestine has evolved multiple immune

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strategies to confine commensals to the intestinal lumen while preserving their number and composition. An additional remarkable feature of the intestine is its capacity to select appropriate effector and regulatory immune mechanisms to neutralize pathogens while preventing bystander tissue damage (Holmgren and Czerkinsky, 2005). In this fashion, the intestine provides immune protection without compromising the integrity of the epithelial barrier.

A key intestinal strategy to generate immune protection in a noninflammatory manner is the production of immunoglobulin A (IgA), the most abundant antibody isotype produced in our body (Macpherson et al., 2008). IgA provides mucosal immune protection as a result of its ability to interact with the polymeric Ig receptor (pIgR), an antibody transporter expressed on the basolateral surface of epithelial cells (Mostov and Deitcher, 1986). After binding to pIgR, IgA dimers secreted by intestinal B cells translocate to the surface of epithelial cells, thereby generating secretory IgA (SIgA) complexes that play multiple protective roles (Mestecky et al., 1999). SIgA promotes immune exclusion by entrapping dietary antigens and microorganisms in the mucus, downmodulates the expression of proinflammatory bacterial epitopes on commensal bacteria, and, in general, promotes the maintenance of appropriate bacterial communities within specific intestinal segments (Fagarasan et al., 2002; Peterson et al., 2007; Phalipon et al., 2002). In addition, SIgA blocks or sterically hinders microbial components involved in epithelial attachment, mediates intraepithelial neutralization of incoming pathogens and microbial inflammatory products, and facilitates antigen sampling by binding to microfold (M) cells, an epithelial-like cell type specialized in antigen-capturing functions (Brandtzaeg et al., 1999; Fernandez et al., 2003; Huang et al., 2005; Kadaoui and Corthesy, 2007; Mantis et al., 2002; Rhee et al., 2004). Furthermore, IgA dimers locally released by plasma cells remove microorganisms that have breached the epithelial barrier in two ways: by transporting them back into the lumen through the pIgR and by promoting their clearance via FcαRI (also known as CD89), an IgA receptor expressed by dendritic cells (DCs), neutrophils, and other phagocytes (Pasquier et al., 2005; Phalipon and Corthesy, 2003).

Here we discuss the function of intestinal IgA antibodies, the follicular and extrafollicular inductive sites for intestinal IgA production, the T cell-dependent and T cell-independent pathways regulating intestinal IgA responses, and the mechanisms mediating homing of IgA-producing B cells to the intestinal lamina propria.

Follicular Inductive Sites for Intestinal IgA Production

Craig and Cebra were the first to show that Peyer's patches are a source of IgA precursor cells (Craig and Cebra, 1971). Using an elegant adoptive-transfer system based on different Ig allotypes, they demonstrated that cells derived from Peyer's patches were able to replenish lethally irradiated rabbits with IgA-producing cells. They clearly showed that the intestinal lamina propria of recipient animals was repopulated with IgA-secreting cells of donor origin after transfer of Peyer's patches, but not of popliteal lymph node cells.

Peyer's patches are characterized by three important features. First, Peyer's patches include germinal centers that promote the interaction between antigen-specific T cells and B cells as well as the expression of activation-induced cytidine deaminase (AID), a B cell-specific enzyme required for the diversification of Ig genes through class-switch DNA recombination (CSR) and somatic hypermutation (Muramatsu et al., 2000). Second, Peyer's patches contain a higher proportion of B cells versus T cells (four to six times more) as compared to peripheral lymph nodes (Stevens et al., 1982). Third, Peyer's patches are rich in cytokines with IgA-inducing functions, including transforming growth factor β (TGF-β) (Gonnella et al., 1998).

TGF-β cooperates with CD40 ligand (CD40L, also known as CD154), a tumor necrosis factor (TNF) family member expressed by $CD4^+$ T cells, to trigger IgA CSR and generate antigen-specific IgA^+ B cells (Figure 1), which represent nearly 70% of germinal-center B cells in Peyer's patches (Butcher et al., 1982;Cazac and Roes, 2000;Cerutti, 2008b;Coffman et al., 1989;Islam et al., 1991;McIntyre et al., 1995;Shockett and Stavnezer, 1991). Indeed, B cell-conditional TGF-β-receptor-deficient mice show severely impaired steady-state and antigen-induced IgA responses both systemically and in intestinal sites (Cazac and Roes, 2000). In addition to TGF-β, Peyer's patches contain inter-leukin-4 (IL-4), IL-6, and IL-10, which facilitate the expansion of IgA-expressing B cells and their differentiation to IgA-secreting plasma cells (Defrance et al., 1992;Fayette et al., 1997;Okahashi et al., 1996;Sato et al., 2003;Xu-Amano et al., 1993).

Peyer's patches are covered by the follicle-associated epithelium (Figure 1), an epithelial area rich in M cells (Neutra and Kozlowski, 2006). M cells are specialized epithelial cells that deliver antigen from the gut lumen to intra- and subepithelial DCs through a vesicular transport system (Neutra, 1999). Not all antigens can gain access to M cells, given that size restrictions are set by a glycocalix (Frey et al., 1996). Antigen-loaded DCs migrate from epithelial and subepithelial areas to the T cell-rich interfollicular regions of Peyer's patches, where they initiate a polarized T helper type-2 (Th2) response characterized by the release of noninflammatory cytokines with B cell-activating functions, including IL-4 (Rimoldi et al., 2005). This response requires the "conditioning" of DCs by epithelial cells via thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine (Figure 2). TSLP stimulates DC production of IL-10, an IgA-inducing cytokine that inhibits the generation of proinflammatory Th1 cells releasing interferon-γ (IFN-γ) (Rimoldi et al., 2005). This inhibitory effect stems from the ability of TSLP to block DC production of IL-12, a cytokine essential for the initiation of Th1 responses (Rimoldi et al., 2005). Thus, intestinal epithelial cells may educate DCs to initiate noninflammatory T cell-dependent immune responses in Peyer's patches, including IgA responses.

TSLP-conditioned DCs may further enhance IgA production by releasing TGF-β (I.D. Iliev and M.R., unpublished data). However, the finding that mice with leukocytes lacking αvβ8 integrin, which is required for the activation of TGF-β (Travis et al., 2007), have increased serum IgA concentrations might argue against a prominent role of DCs in TGF-β-induced IgA CSR. Alternatively, TSLP-conditioned DCs may generate $CD4^+$ T cell subsets with both IgA-inducing and regulatory functions (Figure 2). Indeed, TSLP-conditioned DCs release IL-6 (Rimoldi et al., 2005), which cooperates with additional DC mediators, including TGF-β, retinoic acid, and IL-27, to induce $CD4^+CD25^+Foxp3^+$ T regulatory (Treg) cells (I.D. Iliev and M.R., unpublished data), $CD4^+CD25^-Foxp3^-$ T regulatory type 1 (Tr1) cells, and regulatory Th17 cells (Li and Flavell, 2008). By releasing TGF-β and IL-10, Treg, Tr1, and Th17 cells may not only promote intestinal homeostasis and tolerance, but also stimulate intestinal B cell production of IgA (Cerutti et al., 1998; Defrance et al., 1992; Fayette et al., 1997; Li and Flavell, 2008). Conversely, IgA-producing B cells and their precursors might enhance the generation of Treg, Tr1, and Th17 cells by releasing IL-6, IL-10, and TGF-β (Cerutti et al., 1998; Zan et al., 1998; Fillatreau et al., 2008). SIgA could amplify this process as a result of its ability to transport antigen from the lumen to DCs via M cells (Kadaoui and Corthesy, 2007). In the presence of TSLP and possibly other epithelial factors, these antigen-loaded DCs would initiate antigen-specific Treg, Tr1, and Th17 cell responses as described earlier. Although attractive, this model needs to be tested in cell-type-specific protein-deficient systems. In this regard, $CD4^+$ T cell-specific TGF-β-deficient mice showed increased IgA production, at least in the systemic compartment and under steady-state conditions (M.O. Li and R.A. Flavell, personal communication). Should this observation be extended to the intestinal compartment and to postimmunization conditions, one may conclude that intestinal IgA responses require a TGF-β-producing cell

type different from $CD4^+$ T cells for their induction. In agreement with this possibility, DCs, epithelial cells, stromal cells, mast cells, and B cells are good producers of TGF-β (Babyatsky et al., 1996; Fagarasan et al., 2001; Gonnella et al., 1998; Zan et al., 1998).

In addition to TGF-β, Peyer's patch DCs may utilize retinoic acid, IL-6, and inducible nitric-oxide synthase (iNOS) to enhance intestinal IgA responses (Figure 1). Retinoic acid drives intestinal IgA production through an elusive mechanism that might affect IgA CSR or, more likely, the differentiation of IgA class-switched B cells into IgA-secreting plasma cells. Furthermore, retinoic acid confers gut-homing properties to IgA class-switched B cells through its ability to upregulate CCR9 and α4β7 expression on these cells (Mora et al., 2006). As for IL-6, this cytokine enhances intestinal IgA production by promoting the differentiation of IgA-expressing B cells into plasma cells (Sato et al., 2003). Finally, iNOS enhances intestinal IgA class switching through a mechanism involving upregulation of the TGF-β receptor on Peyer's patch B cells (Tezuka et al., 2007).

In general, iNOS has a multifunctional role in the immune system, and therefore it may not be surprising that both systemic and intestinal IgA responses are decreased in iNOS-deficient mice (Nathan, 2006; Tezuka et al., 2007). Consistent with prior observations showing that innate immune cells express iNOS upon activation of Toll-like receptors (TLRs) by microbial ligands (Nathan, 2006), intestinal DCs require MyD88, a key TLR signaling molecule, to express iNOS (Tezuka et al., 2007). Interestingly, iNOS expression in the intestine is largely restricted to a discrete subset of $TNF\text{-}\alpha^+iNOS^+$ DCs. When adoptively transferred into iNOS-deficient mice, lamina propria $TNF\text{-}\alpha^+iNOS^+$ DCs from wild-type mice restore IgA production (Tezuka et al., 2007), confirming the central role of DCs in intestinal IgA responses. Nonetheless, the presence of $TNF\text{-}\alpha^+iNOS^+$ DCs in Peyer's patches and their relationship with known intestinal DC subsets remain unclear. In this regard, it must be noted that several populations of DCs have been described in Peyer's patches, each characterized by a distinctive CD11b, CD11c, CD8, CX3CR1, and CCR6 expression pattern and by different immune functions (Iwasaki, 2007; Rescigno, 2006).

Peyer's Patches in the Response to Pathogens

Peyer's patches are critical to initiate antigen-specific immune response to pathogens capable of penetrating M cells. One of these pathogens is *Salmonella typhimurium*, a bacterium equipped with a type-III secretion system that permits the invasion of nonphagocytic cells (Martinoli et al., 2007). Salmonella strains deficient for the expression of the *invA* gene, which is involved in the formation of a productive type III secretion system, neither enter Peyer's patches nor induce formation of fecal-antigen-specific IgA. However, these strains can still enter the lamina propria, presumably via a DC-mediated mechanism, and then reach the mesenteric lymph node and the spleen, where they induce IgG production (Martinoli et al., 2007). Notably, mice vaccinated with strains of Salmonella unable to elicit a fecal IgA response become infected if challenged with virulent Salmonella through the oral route, suggesting that antigen-specific IgA antibodies exert a protective role in the intestinal mucosa.

Together, these data tell us that protective IgA responses to pathogens are predominantly initiated in Peyer's patches. A similar scenario has been described for commensal bacteria. *Enterobacter cloacae* injected intragastrically in wild-type mice can be detected in DCs from Peyer's patches and mesenteric lymph nodes (Macpherson and Uhr, 2004). This localization is associated with induction of commensal-specific IgA responses. However, bacteria cannot be recovered from the spleen, suggesting that mesenteric lymph nodes are important to exclude commensals from the systemic immune system. It remains to be established how noninvasive commensal species gain access to Peyer's patches. One

possibility is that commensal bacteria first become opsonized by natural polyreactive IgA antibodies and then undergo IgA-mediated apical-to-basal transepithelial migration across M cells (Kadaoui and Corthesy, 2007; Mantis et al., 2002). Interestingly, IgA responses in mesenteric lymph nodes could also occur in response to transcutaneous immunization, suggesting the existence of a functional link between the skin and mucosal sites (Chang et al., 2008).

Payer's Patches as the Major Site for the Induction of Antigen-Specific Responses

IgA CSR can also take place in isolated lymphoid follicular structures that are characterized by a cellular composition similar to that of Peyer's patches (Hamada et al., 2002; Moghaddami et al., 1998). These isolated lymphoid follicles are lined by a specialized epithelium containing M cells and thus should mount IgA responses through pathways similar to those utilized by Peyer's patches. Mice treated postnatally with LTβR-Ig, a fusion protein of lymphotoxin-β receptor (LTβR) and IgG Fc, showed reduced size and numbers of Peyer's patches and lacked isolated lymphoid follicles but were still able to generate antigen-specific mucosal IgA responses after oral immunization, although to a lesser extent than control mice (Yamamoto et al., 2004). Mice treated in utero with both TNF receptor (TNF-R) of 55 kDa-Ig and LTβR-Ig lacked Peyer's patches and mesenteric lymph nodes but retained intact isolated lymphoid follicles (Yamamoto et al., 2004). These mice failed to induce antigen-specific IgA responses after oral immunization, although having unaltered intestinal IgA antibodies. Together, these findings demonstrate that Peyer's patches play a key role in the induction of specific IgA responses to orally administered antigens. They also indicate that isolated lymphoid follicles have a marginal role in these responses.

Remarkably, Peyer's patches do not absolutely require germinal centers to initiate antigen-specific antibody responses. Indeed, mice lacking CD28, a B7-binding T cell costimulatory molecule necessary for germinal-center formation, not only retain IgA-producing plasma cells in the intestinal lamina propria but can also mount high-affinity IgA antibodies to an orally administered T cell-dependent antigen (Gardby et al., 2003). In contrast, CD28-deficient mice cannot mount specific antibody responses when challenged with a T cell-dependent antigen through a systemic route (Gardby et al., 2003). This evidence indicates that Peyer's patches can generate high-affinity IgA antibodies in the absence of canonical cognate T-DC or T-B cell interactions in the germinal center. The unique nature of Peyer's patches is further emphasized by studies showing that Peyer's patch B cells do not need to express surface Ig receptors (also known as B cell antigen receptor, BCR) to produce antigen-specific IgA antibodies (Casola et al., 2004). This production, rather, requires antigen signaling via TLRs as well as help from $CD4^+$ T cells (Casola et al., 2004). Thus, it is tempting to speculate that Peyer's patches utilize both canonical and noncanonical pathways for the generation of IgA antibodies to specific T cell-dependent antigens.

Extrafollicular Inductive Sites for Intestinal IgA Production

Although important, Peyer's patches are not essential for intestinal IgA production. Indeed, mice treated during gestation with an LTβR-Ig fusion protein do not develop Peyer's patches and yet retain IgA-producing plasma cells in the intestinal lamina propria (Yamamoto et al., 2004). These mice probably utilize mesenteric lymph nodes and isolated lymphoid follicles to produce IgA, because these follicular structures are not affected by LTβR-Ig (Yamamoto et al., 2004). Consistent with this possibility, IgA-producing plasma cells are profoundly reduced in the intestinal lamina propria of LT-α-deficient mice and double-LT-α-TNF-deficient mice, which lack mesenteric lymph nodes and isolated lymphoid follicles in addition to Peyer's patches (Kang et al., 2002; Ryffel et al., 1998). However, mesenteric

lymph nodes and isolated lymphoid follicles are also not absolutely required for the initiation of antigen-specific IgA responses. Indeed, reconstitution of LT-α-deficient mice and double-LT-α-TNF-deficient mice with bone marrow from normal animals restores the intestinal IgA response of these animals to a variable degree (Kang et al., 2002; Ryffel et al., 1998).

The nonessential role of intestinal follicular lymphoid structures for the production of IgA is further indicated by studies with mice lacking inhibitor of DNA binding 2 (Id2), an inhibitor of helix-loop-helix transcription factors, or retinoic-acid-related orphan receptor γt (RORγt), a member of the nuclear-receptor family of transcription factors (Eberl and Littman, 2004). These proteins are instrumental for the generation of lymphoid-tissue-inducing cells, a cell type that mediates the formation of organized intestinal lymphoid tissue through LT-α. Similarly to bone-marrow-reconstituted LT-α-deficient mice (Kang et al., 2002), Id2-deficient mice and RORγt-deficient mice have no Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles and yet retain some antigen-specific IgA-producing plasma cells in the lamina propria (Eberl and Littman, 2004). It must be noted that in all of these mice, the number of IgA-producing plasma cells varies considerably, depending on the background and rearing conditions. Nonetheless, these models support the notion that the gut-associated lymphoid tissue can generate IgA antibodies outside the organized environment of lymphoid follicles.

IgA Class Switching in the Lamina Propria

The presence of IgA-producing plasma cells in the intestinal lamina propria of mice lacking Peyer's patches, mesenteric lymph nodes, and isolated lymphoid follicles points to the lamina propria as an extrafollicular inductive site for IgA antibodies. Indeed, the intestinal lamina propria contains IgM^+ B cells that may function as a local precursor of IgA-producing plasma cells (Fagarasan et al., 2001). These IgM^+ precursors comprise naive B cells that migrate from the bone marrow to the intestine in response to chemotactic signals generated by intestinal stromal cells through an LT-mediated NF-κB-inducing kinase (NIK)-dependent pathway (Suzuki et al., 2005). Another subset of IgM^+ precursors is that of gut-experienced IgM^+ B cells, which migrate from Peyer's patches to the intestinal lamina propria independently of stromal signals (Suzuki et al., 2005).

Of note, the intestinal lamina propria of normal but not AID-deficient mice also contains IgA^+ B cells, indicating that resident IgM^+ B cells may switch to IgA-producing plasma cells in situ (Fagarasan et al., 2001). Although still debated (Cerutti, 2008a), the presence of locally induced IgA class switching is consistent with the identification of AID transcripts in both IgM^+ and IgA^+ B cells from the intestinal lamina propria of an AID-GFP (green fluorescent protein) reporter mouse capable of recapitulating physiological immune responses (Crouch et al., 2007). Active IgA class switching is also present in the human intestinal lamina propria. Indeed, this site includes B cells that express AID transcripts and protein and contain extrachromosomal S_α-S_μ switch circles, an episomal DNA byproduct of ongoing IgA CSR (He et al., 2007).

Another strong indication of the IgA class-switch-inducing capability of the intestinal lamina propria comes from studies showing abundant production of IgA class-switch-inducing factors by various cell types dwelling at this site. For instance, intestinal lamina propria $CD4^+$ T cells were recently shown to produce large amounts of IL-10, a cytokine involved in IgA class switching and production (Defrance et al., 1992; Fayette et al., 1997; He et al., 2007; Kamanaka et al., 2006; Xu et al., 2007). Of note, $CD4^+$ T cells from the intestinal lamina propria express an activated phenotype, which possibly results from local activation by antigen-presenting DCs (Benson et al., 2007). In this regard, growing evidence

indicates that M cell-mediated antigen entry is not restricted to the follicle-associated epithelium but also occurs in the conventional epithelium in proximity of isolated lymphoid follicles (Hamada et al., 2002). In addition to containing scattered M cells, the conventional epithelium is extensively infiltrated by DCs, which form transepithelial projections while capturing antigen in the intestinal lumen (Chieppa et al., 2006; Rescigno et al., 2001). Uptake of antigen by these DCs may be followed by its presentation to lamina propria $CD4^+$ T cells, including antigen-specific Treg and Tr1 cells, which may thereafter initiate local IgA responses through CD40L and cytokines, including IL-10 and TGF-β (Cerutti et al., 1998; Defrance et al., 1992; Fayette et al., 1997; Li and Flavell, 2008).

Lamina Propria T Independent IgA Responses

Intestinal lamina propria DCs may also present antigen to B cells (Bergtold et al., 2005), thereby inducing their activation via both somatically recombined and germline gene-encoded antigen receptors, including BCR and TLRs. These DCs may further activate B cells through B cell-activating factor of the TNF family (BAFF, also known as BLyS) and a proliferation-inducing ligand (APRIL) (Figure 1), two B cell-stimulating factors structurally and functionally related to CD40L (He et al., 2007; Litinskiy et al., 2002; Schneider, 2005; Xu et al., 2007). In both mice and humans, BAFF and APRIL deliver CD40-independent IgA CSR-inducing signals via transmembrane activator and calcium-modulating cyclophilin-ligand interactor (TACI), a receptor that is preferentially expressed by B cells (Castigli et al., 2005b; Chiu et al., 2007; He et al., 2003, 2007; Litinskiy et al., 2002; von Bulow et al., 2001; Xu et al., 2007; Cerutti, 2008b). Growing evidence indicates that this pathway may support intestinal IgA production in a T cell-independent fashion. Indeed, mice lacking CD40 or T cells retain intestinal IgA responses to both commensal bacteria and pathogens, although these responses are decreased compared to those occurring in wild-type animals (Bergqvist et al., 2006; Macpherson et al., 2000). Similarly, intestinal IgA responses are partially conserved in humans lacking $CD4^+$ T cells or CD40 as a result of HIV infection and hyper-IgM syndrome, respectively (He et al., 2007). Conversely, mice lacking APRIL or TACI and humans expressing mutant TACI molecules exhibit impaired IgA responses (Castigli et al., 2004, 2005a; von Bulow et al., 2001).

Recent data indicate that recognition of bacterial signatures by TLRs at the intestinal epithelial barrier is essential for the production of BAFF and APRIL by lamina propria DCs. Indeed, TLR signaling not only stimulates DC production of BAFF and APRIL (He et al., 2007; Xu et al., 2007) but also elicits DC expression of iNOS (Figure 1), an enzyme that augments BAFF and APRIL synthesis through the generation of nitric oxide (Tezuka et al., 2007). Recognition of bacteria through TLRs would also account for the production of BAFF and APRIL by intestinal epithelial cells (He et al., 2007; Kato et al., 2006; Xu et al., 2007). Intriguingly, epithelial cells further amplify BAFF and APRIL production by stimulating DCs via TSLP (Figure 1), at least in humans (He et al., 2007; Xu et al., 2007). Ultimately, BAFF and APRIL would induce IgA class switching by activating B cells in cooperation with cytokines released by DCs or other cell types, including IL-10 and TGF-β1 (He et al., 2007; Kaminski and Stavnezer, 2006; Litinskiy et al., 2002; Xu et al., 2007; Cerutti, 2008b). In humans, this process appears to be negatively regulated by secretory leukocyte protease inhibitor (SLPI), a TLR-inducible epithelial factor endowed with both antimicrobial and anti-inflammatory functions (Xu et al., 2007). These observations indicate that epithelial cells orchestrate mucosal IgA responses through both positive and negative regulatory pathways.

B cells undergoing T cell-independent IgA class switching in the lamina propria would further differentiate into IgA-secreting plasma cells upon receiving additional signals from BCR ligands, TLR ligands, and cytokines, including IL-6 and IL-10 (Fagarasan et al., 2001;

Groom et al., 2007; He et al., 2007; Kaminski and Stavnezer, 2006; Katsenelson et al., 2007; Litinskiy et al., 2002; Ng et al., 2006; Cerutti, 2008b). In this regard, it must be noted that IL-6 and IL-10 are produced not only by mucosal DCs but also by mucosal macrophages, stromal cells, and epithelial cells (Denning et al., 2007; Fagarasan et al., 2001; He et al., 2007; Jarry et al., 2008; Xu et al., 2007). Sustained IgA secretion may also require DC and epithelial cell production of BAFF and APRIL given that these factors have been shown to deliver plasma cell survival and differentiation signals via BCMA (B cell maturation antigen) and TACI (Castigli et al., 2007; O'Connor et al., 2004). This pathway is likely to be important for the survival of intestinal IgA-secreting plasma cells generated in the context of both T cell-independent and T cell-dependent responses.

In mice, T cell-independent IgA responses predominantly involve B-1 cells, a peritoneal IgM^+ B cell subset with phenotypic and functional features distinct from those of conventional B cells (or B-2) (Hayakawa and Hardy, 1988; Macpherson et al., 2000; Macpherson and Uhr, 2004). B-1 cells migrate from the peritoneum to intestinal sites, including the lamina propria, in response to microbial TLR ligands (Ha et al., 2006). Consistent with this possibility, the peritoneal cavity of germ-free mice contains more B-1 cells that the peritoneal cavity of pathogen-free mice harboring a diverse intestinal microbiota. In addition to secreting IgM antibodies in a seemingly natural fashion, B-1 cells produce IgA antibodies to commensal bacteria upon exposure to antigen. Indeed, studies in TCR-deficient animals show that B-1 cells initiate T cell-independent IgA responses upon exposure to DCs loaded with commensal bacteria (Macpherson and Uhr, 2004). Whether this response is highly dependent on engagement of TACI on B-1 cells by BAFF and APRIL remains to be established.

As for humans, the origin, phenotype, and functions of IgM^+ B cells undergoing T cell-independent IgA class switching in the intestinal lamina propria are not known. Of note, the intestinal lamina propria from the human colon may also foster sequential IgA2 class switching and production in IgA1-expressing B cells originating from colonic lymphoid aggregates (He et al., 2007). Compared to IgA1, IgA2 may be more appropriate to cope with the dense flora of the distal intestine, possibly because of its increased resistance to bacterial proteases (Brandtzaeg et al., 1999; Mestecky et al., 1999).

Homing of IgA-Producing B Cells to the Intestine

In mice, B cells activated in Peyer's patches derived from the bone marrow are distinct from B-1 cells, which originate in the peritoneal cavity (Hayakawa and Hardy, 1988). B-1 and B-2 cells express distinct phenotypes and carry different Ig receptor repertoires but contribute equally to IgA production (Kroese et al., 1989; Stoel et al., 2005). It is becoming clear that IgA antibodies to T cell-dependent antigens derive mostly from B-2 cells, whereas IgA antibodies to T cell-independent antigens derive predominantly from B-1 cells (Fagarasan and Honjo, 2003; Macpherson et al., 2008). This probably reflects different homing properties of B-1 and B-2 cells, their different thresholds of activation, and their distinct sites for IgA CSR. Naive B-2 cells express higher amounts of the intestinal homing receptor α4β7 and slightly lower amounts than T cells of L-selectin, which is required for homing to peripheral lymph nodes (Andrew et al., 1996). Interestingly, B and T cells undergo firm adhesion to specific regions of Peyer's patches, adhesion being more prominent in or near follicles for B cells and at interfollicular regions for T cells (Warnock et al., 2000). This probably contributes to a greater homing of B cells to Peyer's patches.

Once activated in Peyer's patches, B cells that have undergone IgA CSR become IgA^+ effector B cells, including memory B cells and plasmablasts (Macpherson et al., 2008). These cells upregulate the expression of the gut-homing receptors α4β7, CCR9, and/or

CCR10 (Figure 1), recirculate via the thoracic duct, and home to the intestinal lamina propria (Mora et al., 2006). Here, α4β7 binds to mucosal addressin cell-adhesion molecule 1 (MadCAM-1) on endothelial cells, whereas CCR9 and CCR10 respond to TECK (also known as CCL25) and MEC (CCL2), respectively, two chemokines released by epithelial cells (Hieshima et al., 2004; Wagner et al., 1996). In the lamina propria, IgA^+ plasmablasts terminally differentiate into IgA-secreting plasma cells (Brandtzaeg et al., 1999). These plasma cells synthesize the joining (J) chain, which allows the formation of stable IgA oligomers with increased avidity for antigen (Brandtzaeg, 1974; Mestecky et al., 1971). IgA oligomers bind the pIgR on the basolateral membrane of epithelial cells through the J chain and thereafter translocate into the lumen as an SIgA complex (Figure 1), which comprises the secretory component (Brandtzaeg and Prydz, 1984; Mostov and Deitcher, 1986). This polypeptide originates from intracellular cleavage of pIgR and mediates binding of SIgA to the mucus layer (Phalipon et al., 2002). The development of an antigen-specific SIgA response is quite a long event; 3 to 4 weeks are needed to detect an appreciable amount of SIgA antibodies in the feces. This could reflect the long time needed for B cells to get activated, undergo affinity maturation, leave the Peyer's patches, recirculate through the thoracic duct, and reach the final gut destination.

A faster activation of a more primitive IgA response requires B-1 cells. This mouse B cell subset is characterized by the expression of CD9, a surface tetraspanin that associates with surface integrins to regulate cell motility (Won and Kearney, 2002). B-1 cells primarily reside in pleural and peritoneal cavities and are retained in situ by a concerted action of integrins and CD9 (Ha et al., 2006). After TLR signaling, B-1 cells transiently down-regulate CD9 and integrins and move in response to chemokines (Ha et al., 2006). This event provides a first innate immune defense to invading microorganisms through the generation of a fast wave of TLR-activated B-1 cells migrating to infection sites, including the gut. Of note, B-1 cells can undergo CSR in situ in the intestinal lamina propria, which can give rise to IgA-secreting cells in a T cell-independent fashion (Crouch et al., 2007; Fagarasan et al., 2001). Naive bone-marrow-derived B cells can also migrate to the lamina propria, but this migration requires the presence of stromal cells expressing NIK (Suzuki et al., 2005).

Role of IgA in Intestinal Homeostasis and Immune Protection

Intestinal IgA antibodies serve a variety of functions. In general, high-affinity IgA antibodies emerging from T cell-dependent pathways are thought to protect intestinal mucosal surfaces against colonization and invasion by pathogenic microorganisms (Macpherson et al., 2008; Martinoli et al., 2007). Conversely, low-affinity IgA antibodies emerging from T cell-independent pathways are important to confine commensal bacteria in the intestinal lumen through a process known as "immune exclusion" (Macpherson et al., 2008). This functional dichotomy is not absolute. Indeed, T cell-independent IgA (and IgM) responses provide some degree of immune protection against certain intestinal pathogens, such as rotavirus (Franco and Greenberg, 1997). Conversely, strong evidence points to an important role of T cell-dependent IgA responses in the control of commensal bacteria (Casola et al., 2004). In addition to controlling pathogens and commensals, IgA antibodies neutralize microbial products with proinflammatory activity, such as lipopolysaccharide, in intestinal epithelial cells (Fernandez et al., 2003). Hence, IgA can play a role both during steady-state (unperturbed) conditions and infection.

IgA can also mediate apical-to-basolateral transcytosis of antigens across M cells via an unknown receptor or across duodenal epithelial cells via the transferrin receptor, also known as CD71 (Favre et al., 2005; Kadaoui and Corthesy, 2007; Mantis et al., 2002; Matysiak-Budnik et al., 2008). By promoting "controlled" antigen entry, binding of IgA-antigen

immune complexes by M cells could be critical for the initiation or amplification of intestinal immune responses, including IgA production (Favre et al., 2005). The same pathway could favor neutralization of bacteria in a cytosolic compartment. Consistent with this possibility, *Shigella flexneri*, a Gram-negative bacterium unable to spontaneously enter the mouse epithelium, was rapidly detected in Peyer's patches and mesenteric lymph nodes if coated with specific SIgA antibodies before its injection in intestinal loops (Kadaoui and Corthesy, 2007). Yet, under these conditions, the epithelial barrier was preserved and the bacterium was unable to spread to other nonmucosal tissues. It would be interesting to test whether entrance of SIgA-coated bacteria also leads to IgA production or development of tolerance toward the introduced bacteria.

IgA-mediated reverse transcytosis across M cells could target bacteria to intra- and subepithelial DCs. These DCs may induce tolerogenic immune responses, including IgA production, without delivering inflammatory signals (Kelsall and Rescigno, 2004), a circumstance that could cause recruitment of immunogenic DCs. Unlike intestinal epithelial cells, intestinal DCs express an IgA receptor complex comprising FcαRI and its signaling subunit FcγR (Monteiro and Van De Winkel, 2003). Triggering of FcαRI can lead to either inflammatory or noninflammatory responses, depending on the monovalent or multivalent nature of the IgA ligand (Pasquier et al., 2005). Binding of monomeric IgA to FcαRI leads to reduced phosphorylation of an immunotyrosine activating motif (ITAM) embedded within the FcRγ chain and elicits recruitment of src homology 2 domain-containing protein-tyrosine phosphatase-1 (SHP-1), a signal inhibitor that prevents inflammation by interfering with the activation of multiple signaling pathways (Kanamaru et al., 2008; Pasquier et al., 2005). Conversely, crosslinking of FcαRI by polymeric IgA causes inflammation by triggering full phosphorylation of FcγR and subsequent recruitment of Syk, a protein tyrosine kinase linked to multiple proinflammatory signaling pathways. Thus, IgA-containing immune complexes retrotranscytosed across epithelial cells may initiate noninflammatory or inflammatory immune responses depending on the monomeric or polymeric nature of the IgA ligand.

In general, monomeric IgA antibodies are particularly abundant in systemic districts, at least in humans (Macpherson et al., 2008). These IgA monomers may initiate FcαRI-mediated noninflammatory responses against bacteria that breach the mucosal barrier (Pasquier et al., 2005; van Egmond et al., 2000). On the contrary, IgA polymers may trigger FcαRI-mediated inflammatory responses, particularly when these antibodies are present in large excess in a nonmucosal context. Indeed, IgA polymers are frequently found in several autoimmune conditions and might be an aggravating factor of IgA nephropathy, as recently shown in a spontaneous model of this disease (Kanamaru et al., 2007). In any case, the Janus-like nature of FcαRI might explain prior contradictory reports on the ability of IgA to activate DCs (Geissmann et al., 2001; Heystek et al., 2002).

Of note, IgA-dependent retrotranscytosis can deliver intact antigen to the basolateral side of epithelial cells (Phalipon and Corthesy, 2003). This process may be particularly relevant to the pathogenesis of celiac disease, an intestinal autoimmune disorder caused by a dysregulated immune response to the gluten protein gliadin. Indeed, CD71-mediated retrotranscytosis of immunocomplexes comprising intact gliadin peptides and antigliadin IgA antibodies might trigger inflammation as a result of a progressive accumulation of toxic gliadin peptides in subepithelial districts (Matysiak-Budnik et al., 2008). These peptides would be completely degraded if transported via fluid-phase transcytosis, indicating that epithelial cells must tightly control retrotranscytosis to avoid tissue damage. Such control might be lost in celiac disease, given that intestinal epithelial cells from celiac patients display an increased expression of CD71 (Matysiak-Budnik et al., 2008). In addition to gliadin, IgA antibodies from celiac patients target tissue transglutaminase and connective

tissue. However, it must be remarked that IgA deficiency is more frequent among celiac patients (1 in 40) than in the general population (1 in 400), suggesting a secondary rather than a primary involvement of IgA in the pathogenesis of this intestinal disease (Green and Cellier, 2007).

IgA can further participate in intestinal immune homeostasis by interacting with the local microbiota. It is estimated that the number of intestinal bacteria is close to 10^{14} and is one log higher than that of human cells (Macpherson and Harris, 2004). Mice kept under germ-free conditions that lack the intestinal microflora have highly reduced intestinal IgA, suggesting a direct correlation between IgA and commensals. But what is the role of IgA antibodies? Do they protect the host from commensals? Or do they shape the composition of the microbiota? IgA could be implicated in both functions. Indeed, mice lacking the pIgR have no fecal IgA or IgM and display an increased penetration of commensals as well as a systemic antibody response to commensals (Johansen et al., 1999). In this regard, it is important to note that IgA usually limits the penetration of intestinal bacteria to mesenteric lymph nodes (Macpherson and Uhr, 2004). In addition, AID-deficient mice lacking somatically mutated SIgA have an aberrant expansion of anaerobic bacteria in the small intestine, whereas mice lacking the pIgR show no changes in their microbiota (Fagarasan et al., 2002; Johansen et al., 1999).

IgA antibodies to commensal bacteria can also limit the inflammatory response of intestinal immune cells. This conclusion was suggested by results generated in the following experimental system. Germ-free mice on a RAG-deficient background (i.e., with no B and T cells) were monoassociated with *Bacteroides betaiotaomicron* in the presence of absence of a hybridoma backpack releasing bacteria-specific SIgA in the intestinal lumen (Peterson et al., 2007). The effect was dramatic in both the host and the bacteria. In the host, SIgA significantly decreased the oxidative burst. In bacteria, SIgA downregulated the expression of the targeted epitope and decreased the expression of genes involved in nitric-oxide metabolism, without inducing cell death or growth arrest. Thus, IgA to a specific bacterial epitope may have a profound effect not only on the expression of that epitope, but also and on the oxidative response elicited by that epitope.

In principle, a dysregulation of intestinal antibody responses to commensal bacteria might result in an excessive innate immune response, which in turn could precipitate or aggravate intestinal inflammation. For instance, in patients with Crohn's disease, IgG and IgA antibodies to *Saccharomyce Cerevisiae* or microbial flagellin could play a role in shaping the microbiota (Lodes et al., 2004; Zholudev et al., 2004), with effects on both the host and the microorganisms, including excessive activation of the innate immune response. Altogether, the available evidence suggests that IgA is important not only to confine bacteria in the intestinal lumen, but also to shape the overall composition of the intestinal microbiota. A dysregulation of these processes may trigger inflammatory disorders like celiac disease, IgA nephropathy, and Crohn's disease.

Conclusions

Growing evidence indicates that intestinal IgA antibodies provide immune protection by functioning through both high-affinity and low-affinity modes. It is also becoming increasingly clear that the intestinal mucosa utilizes multiple follicular and extrafollicular sites as well as multiple T cell-dependent and T cell-independent pathways to generate protective IgA responses. More studies are needed to better define the relative contribution of these pathways to the induction of protective IgA responses to pathogens, commensals, and dietary antigens. It is also of paramount importance to better understand the mechanisms through which IgA antibodies exert their protective role in a noninflammatory manner. In

this regard, intestinal IgA are thought to lack complement-fixing activity, and intestinal macrophages seemingly lack proinflammatory IgA receptors (Macpherson et al., 2008). Although these factors are certainly important to limit inflammation, the mechanisms by which IgA strikes the balance between immune protection and immune tolerance at intestinal sites remain unclear.

Remarkably, a substantial proportion of patients affected with IgA deficiency develop intestinal inflammation as well as autoimmune, allergic, and mucosal B cell lymphoproliferative disorders in addition to mucosal infections (Cunningham-Rundles and Knight, 2007; Daniels et al., 2007). This evidence indicates that IgA is important not only for the establishment of intestinal immune homeostasis and immune protection, but also for the control of autoreactive, proinflammatory, and neoplastic B cell clones present in both intestinal and systemic districts. Such control might involve a crosstalk between Treg, Tr1, and Th17 cells and IgA-producing B cells or their precursors. A better understanding of this crosstalk may help develop novel mucosal vaccines as well as more effective therapies for the treatment of intestinal inflammatory disorders.

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REFERENCES

Andrew DP, Rott LS, Kilshaw PJ, Butcher EC. Distribution of alpha 4 beta 7 and alpha E beta 7 integrins on thymocytes, intestinal epithelial lymphocytes and peripheral lymphocytes. Eur. J. Immunol 1996;26:897–905. [PubMed: 8625986]

Babyatsky MW, Rossiter G, Podolsky DK. Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease. Gastroenterology 1996;110:975–984. [PubMed: 8613031]

Benson MJ, Pino-Lagos K, Rosemblatt M, Noelle RJ. All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. J. Exp. Med 2007;204:1765–1774. [PubMed: 17620363]

Bergqvist P, Gardby E, Stensson A, Bemark M, Lycke NY. Gut IgA class switch recombination in the absence of CD40 does not occur in the lamina propria and is independent of germinal centers. J. Immunol 2006;177:7772–7783. [PubMed: 17114448]

Bergtold A, Desai DD, Gavhane A, Clynes R. Cell surface recycling of internalized antigen permits dendritic cell priming of B cells. Immunity 2005;23:503–514. [PubMed: 16286018]

Brandtzaeg P. Presence of J chain in human immunocytes containing various immunoglobulin classes. Nature 1974;252:418–420. [PubMed: 4215033]

Brandtzaeg P, Farstad IN, Johansen FE, Morton HC, Norderhaug IN, Yamanaka T. The B-cell system of human mucosae and exocrine glands. Immunol. Rev 1999;171:45–87. [PubMed: 10582165]

Brandtzaeg P, Prydz H. Direct evidence for an integrated function of J chain and secretory component in epithelial transport of immunoglobulins. Nature 1984;311:71–73. [PubMed: 6433206]

Butcher EC, Rouse RV, Coffman RL, Nottenburg CN, Hardy RR, Weissman IL. Surface phenotype of Peyer's patch germinal center cells: Implications for the role of germinal centers in B cell differentiation. J. Immunol 1982;129:2698–2707. [PubMed: 6982940]

Casola S, Otipoby KL, Alimzhanov M, Humme S, Uyttersprot N, Kutok JL, Carroll MC, Rajewsky K. B cell receptor signal strength determines B cell fate. Nat. Immunol 2004;5:317–327. [PubMed: 14758357]

Castigli E, Scott S, Dedeoglu F, Bryce P, Jabara H, Bhan AK, Mizoguchi E, Geha RS. Impaired IgA class switching in APRIL-deficient mice. Proc. Natl. Acad. Sci. USA 2004;101:3903–3908. [PubMed: 14988498]

Castigli E, Wilson SA, Elkhal A, Ozcan E, Garibyan L, Geha RS. Transmembrane activator and calcium modulator and cyclophilin ligand interactor enhances CD40-driven plasma cell differentiation. J. Allergy Clin. Immunol 2007;120:885–891. [PubMed: 17689597]

Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS. TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat. Genet 2005a;37:829–834. [PubMed: 16007086]

Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS. TACI and BAFF-R mediate isotype switching in B cells. J. Exp. Med 2005b;201:35–39. [PubMed: 15630136]

Cazac BB, Roes J. TGF-β receptor controls B cell responsiveness and induction of IgA in vivo. Immunity 2000;13:443–451. [PubMed: 11070163]

Cerutti A. Location, location, location: B-cell differentiation in the gut lamina propria. Mucosal Immunology 2008a;1:8–10. [PubMed: 19079155]

Cerutti A. The regulation of IgA class switching. Nat. Rev. Immunol 2008b;8:421–434. [PubMed: 18483500]

Cerutti A, Zan H, Schaffer A, Bergsagel L, Harindranath N, Max EE, Casali P. CD40 ligand and appropriate cytokines induce switching to IgG, IgA, and IgE and coordinated germinal center-like phenotype differentiation in a human monoclonal $IgM^{+}IgD^{+}$ B cell line. J. Immunol 1998;160:2145–2157. [PubMed: 9498752]

Chang SY, Cha HR, Uematsu S, Akira S, Igarashi O, Kiyono H, Kweon MN. Colonic patches direct the cross-talk between systemic compartments and large intestine independently of innate immunity. J. Immunol 2008;180:1609–1618. [PubMed: 18209057]

Chieppa M, Rescigno M, Huang AY, Germain RN. Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement. J. Exp. Med 2006;203:2841–2852. [PubMed: 17145958]

Chiu A, Xu W, He B, Dillon SR, Gross JA, Sievers E, Qiao X, Santini P, Hyjek E, Lee JW, et al. Hodgkin lymphoma cells express TACI and BCMA receptors and generate survival and proliferation signals in response to BAFF and APRIL. Blood 2007;109:729–739. [PubMed: 16960154]

Coffman RL, Lebman DA, Shrader B. Transforming growth factor beta specifically enhances IgA production by lipopolysaccharide-stimulated murine B lymphocytes. J. Exp. Med 1989;170:1039–1044. [PubMed: 2788703]

Craig SW, Cebra JJ. Peyer's patches: An enriched source of precursors for IgA-producing immunocytes in the rabbit. J. Exp. Med 1971;134:188–200. [PubMed: 4934147]

Crouch EE, Li Z, Takizawa M, Fichtner-Feigl S, Gourzi P, Montano C, Feigenbaum L, Wilson P, Janz S, Papavasiliou FN, Casellas R. Regulation of AID expression in the immune response. J. Exp. Med 2007;204:1145–1156. [PubMed: 17452520]

Cunningham-Rundles C, Knight AK. Common variable immune deficiency: Reviews, continued puzzles, and a new registry. Immunol. Res 2007;38:78–86. [PubMed: 17917013]

Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): A clinicopathologic study and review. Am. J. Surg. Pathol 2007;31:1800–1812. [PubMed: 18043034]

Defrance T, Vanbervliet B, Briere F, Durand I, Rousset F, Banchereau J. Interleukin 10 and transforming growth factor beta cooperate to induce anti-CD40-activated naive human B cells to secrete immunoglobulin A. J. Exp. Med 1992;175:671–682. [PubMed: 1371300]

Denning TL, Wang YC, Patel SR, Williams IR, Pulendran B. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. Nat. Immunol 2007;8:1086–1094. [PubMed: 17873879]

Eberl G, Littman DR. Thymic origin of intestinal αβ T cells revealed by fate mapping of $ROR\gamma t^{+}$ cells. Science 2004;305:248–251. [PubMed: 15247480]

Fagarasan S, Honjo T. Intestinal IgA synthesis: Regulation of front-line body defences. Nat. Rev. Immunol 2003;3:63–72. [PubMed: 12511876]

Fagarasan S, Kinoshita K, Muramatsu M, Ikuta K, Honjo T. In situ class switching and differentiation to IgA-producing cells in the gut lamina propria. Nature 2001;413:639–643. [PubMed: 11675788]

Fagarasan S, Muramatsu M, Suzuki K, Nagaoka H, Hiai H, Honjo T. Critical roles of activation-induced cytidine deaminase in the homeostasis of gut flora. Science 2002;298:1424–1427. [PubMed: 12434060]

Favre L, Spertini F, Corthesy B. Secretory IgA possesses intrinsic modulatory properties stimulating mucosal and systemic immune responses. J. Immunol 2005;175:2793–2800. [PubMed: 16116164]

Fayette J, Dubois B, Vandenabeele S, Bridon JM, Vanbervliet B, Durand I, Banchereau J, Caux C, Briere F. Human dendritic cells skew isotype switching of CD40-activated naive B cells towards IgA1 and IgA2. J. Exp. Med 1997;185:1909–1918. [PubMed: 9166420]

Fernandez MI, Pedron T, Tournebize R, Olivo-Marin JC, Sansonetti PJ, Phalipon A. Anti-inflammatory role for intracellular dimeric immunoglobulin a by neutralization of lipopolysaccharide in epithelial cells. Immunity 2003;18:739–749. [PubMed: 12818156]

Fillatreau S, Gray D, Anderton SM. Not always the bad guys: B cells as regulators of autoimmune pathology. Nat. Rev. Immunol 2008;8:391–397. [PubMed: 18437156]

Franco MA, Greenberg HB. Immunity to rotavirus in T cell deficient mice. Virology 1997;238:169–179. [PubMed: 9400590]

Frey A, Giannasca KT, Weltzin R, Giannasca PJ, Reggio H, Lencer WI, Neutra MR. Role of the glycocalyx in regulating access of microparticles to apical plasma membranes of intestinal epithelial cells: Implications for microbial attachment and oral vaccine targeting. J. Exp. Med 1996;184:1045–1059. [PubMed: 9064322]

Gardby E, Wrammert J, Schon K, Ekman L, Leanderson T, Lycke N. Strong differential regulation of serum and mucosal IgA responses as revealed in CD28-deficient mice using cholera toxin adjuvant. J. Immunol 2003;170:55–63. [PubMed: 12496383]

Geissmann F, Launay P, Pasquier B, Lepelletier Y, Leborgne M, Lehuen A, Brousse N, Monteiro RC. A subset of human dendritic cells expresses IgA Fc receptor (CD89), which mediates internalization and activation upon cross-linking by IgA complexes. J. Immunol 2001;166:346–352. [PubMed: 11123311]

Gonnella PA, Chen Y, Inobe J, Komagata Y, Quartulli M, Weiner HL. In situ immune response in gut-associated lymphoid tissue (GALT) following oral antigen in TCR-transgenic mice. J. Immunol 1998;160:4708–4718. [PubMed: 9590216]

Green PH, Cellier C. Celiac disease. N. Engl. J. Med 2007;357:1731–1743. [PubMed: 17960014]

Groom JR, Fletcher CA, Walters SN, Grey ST, Watt SV, Sweet MJ, Smyth MJ, Mackay CR, Mackay F. BAFF and MyD88 signals promote a lupuslike disease independent of T cells. J. Exp. Med 2007;204:1959–1971. [PubMed: 17664289]

Ha SA, Tsuji M, Suzuki K, Meek B, Yasuda N, Kaisho T, Fagarasan S. Regulation of B1 cell migration by signals through Toll-like receptors. J. Exp. Med 2006;203:2541–2550. [PubMed: 17060475]

Hamada H, Hiroi T, Nishiyama Y, Takahashi H, Masunaga Y, Hachimura S, Kaminogawa S, Takahashi-Iwanaga H, Iwanaga T, Kiyono H, et al. Identification of multiple isolated lymphoid follicles on the antimesenteric wall of the mouse small intestine. J. Immunol 2002;168:57–64. [PubMed: 11751946]

Hayakawa K, Hardy RR. Normal, autoimmune, and malignant $CD5^+$ B cells: The Ly-1 B lineage? Annu. Rev. Immunol 1988;6:197–218. [PubMed: 3289567]

He B, Raab-Traub N, Casali P, Cerutti A. EBV-encoded latent membrane protein 1 cooperates with BAFF/BLyS and APRIL to induce T cell-independent Ig heavy chain class switching. J. Immunol 2003;171:5215–5224. [PubMed: 14607922]

He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, Shan M, Chadburn A, Villanacci V, Plebani A, et al. Intestinal bacteria trigger T cell-independent immunoglobulin A2 class switching by inducing epithelial-cell secretion of the cytokine APRIL. Immunity 2007;26:812–826. [PubMed: 17570691]

Heystek HC, Moulon C, Woltman AM, Garonne P, van Kooten C. Human immature dendritic cells efficiently bind and take up secretory IgA without the induction of maturation. J. Immunol 2002;168:102–107. [PubMed: 11751952]

Hieshima K, Kawasaki Y, Hanamoto H, Nakayama T, Nagakubo D, Kanamaru A, Yoshie O. CC chemokine ligands 25 and 28 play essential roles in intestinal extravasation of IgA antibody-secreting cells. J. Immunol 2004;173:3668–3675. [PubMed: 15356112]

Holmgren J, Czerkinsky C. Mucosal immunity and vaccines. Nat. Med 2005;11:S45–S53. [PubMed: 15812489]

Huang YT, Wright A, Gao X, Kulick L, Yan H, Lamm ME. Intraepithelial cell neutralization of HIV-1 replication by IgA. J. Immunol 2005;174:4828–4835. [PubMed: 15814709]

Islam KB, Nilsson L, Sideras P, Hammarstrom L, Smith CI. TGF-β1 induces germ-line transcripts of both IgA subclasses in human B lymphocytes. Int. Immunol 1991;3:1099–1106. [PubMed: 1760405]

Iwasaki A. Mucosal dendritic cells. Annu. Rev. Immunol 2007;25:381–418. [PubMed: 17378762]

Jarry A, Bossard C, Bou-Hanna C, Masson D, Espaze E, Denis MG, Laboisse CL. Mucosal IL-10 and TGF-beta play crucial roles in preventing LPS-driven, IFN-gamma-mediated epithelial damage in human colon explants. J. Clin. Invest 2008;118:1132–1142. [PubMed: 18259614]

Johansen FE, Pekna M, Norderhaug IN, Haneberg B, Hietala MA, Krajci P, Betsholtz C, Brandtzaeg P. Absence of epithelial immunoglobulin A transport, with increased mucosal leakiness, in polymeric immunoglobulin receptor/secretory component-deficient mice. J. Exp. Med 1999;190:915–922. [PubMed: 10510081]

Kadaoui KA, Corthesy B. Secretory IgA mediates bacterial translocation to dendritic cells in mouse Peyer's patches with restriction to mucosal compartment. J. Immunol 2007;179:7751–7757. [PubMed: 18025221]

Kamanaka M, Kim ST, Wan YY, Sutterwala FS, Lara-Tejero M, Galan JE, Harhaj E, Flavell RA. Expression of interleukin-10 in intestinal lymphocytes detected by an interleukin-10 reporter knockin tiger mouse. Immunity 2006;25:941–952. [PubMed: 17137799]

Kaminski DA, Stavnezer J. Enhanced IgA class switching in marginal zone and B1 B cells relative to follicular/B2 B cells. J. Immunol 2006;177:6025–6029. [PubMed: 17056527]

Kanamaru Y, Arcos-Fajardo M, Moura IC, Tsuge T, Cohen H, Essig M, Vrtovsnik F, Loirat C, Peuchmaur M, Beaudoin L, et al. Fcα receptor I activation induces leukocyte recruitment and promotes aggravation of glomerulonephritis through the FcRγ adaptor. Eur.J. Immunol 2007;37:1116–1128. [PubMed: 17393381]

Kanamaru Y, Pfirsch S, Aloulou M, Vrtovsnik F, Essig M, Loirat C, Deschenes G, Guerin-Marchand C, Blank U, Monteiro RC. Inhibitory ITAM signaling by FcαRI-FcRγ chain controls multiple activating responses and prevents renal inflammation. J. Immunol 2008;180:2669–2678. [PubMed: 18250479]

Kang HS, Chin RK, Wang Y, Yu P, Wang J, Newell KA, Fu YX. Signaling via LTβR on the lamina propria stromal cells of the gut is required for IgA production. Nat. Immunol 2002;3:576–582. [PubMed: 12006975]

Kato A, Truong-Tran AQ, Scott AL, Matsumoto K, Schleimer RP. Airway epithelial cells produce B cell-activating factor of TNF family by an IFN-β-dependent mechanism. J. Immunol 2006;177:7164–7172. [PubMed: 17082634]

Katsenelson N, Kanswal S, Puig M, Mostowski H, Verthelyi D, Akkoyunlu M. Synthetic CpG oligodeoxynucleotides augment BAFF- and APRIL-mediated immunoglobulin secretion. Eur. J. Immunol 2007;37:1785–1795. [PubMed: 17557373]

Kelsall BL, Rescigno M. Mucosal dendritic cells in immunity and inflammation. Nat. Immunol 2004;5:1091–1095. [PubMed: 15496943]

Kroese FG, Butcher EC, Stall AM, Lalor PA, Adams S, Herzenberg LA. Many of the IgA producing plasma cells in murine gut are derived from self-replenishing precursors in the peritoneal cavity. Int. Immunol 1989;1:75–84. [PubMed: 2487677]

Li MO, Flavell RA. Contextual regulation of inflammation: A duet by transforming growth factor-beta and interleukin-10. Immunity 2008;28:468–476. [PubMed: 18400189]

Litinskiy MB, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, Cerutti A. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat. Immunol 2002;3:822–829. [PubMed: 12154359]

Lodes MJ, Cong Y, Elson CO, Mohamath R, Landers CJ, Targan SR, Fort M, Hershberg RM. Bacterial flagellin is a dominant antigen in Crohn disease. J. Clin. Invest 2004;113:1296–1306. [PubMed: 15124021]

Macpherson AJ. IgA adaptation to the presence of commensal bacteria in the intestine. Curr. Top. Microbiol. Immunol 2006;308:117–136. [PubMed: 16922088]

Macpherson AJ, Gatto D, Sainsbury E, Harriman GR, Hengartner H, Zinkernagel RM. A primitive T cell-independent mechanism of intestinal mucosal IgA responses to commensal bacteria. Science 2000;288:2222–2226. [PubMed: 10864873]

Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. Nat. Rev. Immunol 2004;4:478–485. [PubMed: 15173836]

Macpherson AJ, McKoy KD, Johansen FE, Brandtzaeg P. The immune geography of IgA induction and function. Mucosal Immunolgy 2008;1:11–22.

Macpherson AJ, Uhr T. Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. Science 2004;303:1662–1665. [PubMed: 15016999]

Mantis NJ, Cheung MC, Chintalacharuvu KR, Rey J, Corthesy B, Neutra MR. Selective adherence of IgA to murine Peyer's patch M cells: Evidence for a novel IgA receptor. J. Immunol 2002;169:1844–1851. [PubMed: 12165508]

Martinoli C, Chiavelli A, Rescigno M. Entry route of Salmonella typhimurium directs the type of induced immune response. Immunity 2007;27:975–984. [PubMed: 18083577]

Matysiak-Budnik T, Moura IC, Arcos-Fajardo M, Lebreton C, Menard S, Candalh C, Ben-Khalifa K, Dugave C, Tamouza H, van Niel G, et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. J. Exp. Med 2008;205:143–154. [PubMed: 18166587]

McIntyre TM, Kehry MR, Snapper CM. Novel in vitro model for high-rate IgA class switching. J. Immunol 1995;154:3156–3161. [PubMed: 7897205]

Mestecky J, Russell MW, Elson CO. Intestinal IgA: Novel views on its function in the defence of the largest mucosal surface. Gut 1999;44:2–5. [PubMed: 9862815]

Mestecky J, Zikan J, Butler WT. Immunoglobulin M and secretory immunoglobulin A: Presence of a common polypeptide chain different from light chains. Science 1971;171:1163–1165. [PubMed: 5544873]

Moghaddami M, Cummins A, Mayrhofer G. Lymphocyte-filled villi: Comparison with other lymphoid aggregations in the mucosa of the human small intestine. Gastroenterology 1998;115:1414–1425. [PubMed: 9834269]

Monteiro RC, Van De Winkel JG. IgA Fc receptors. Annu. Rev. Immunol 2003;21:177–204. [PubMed: 12524384]

Mora JR, Iwata M, Eksteen B, Song SY, Junt T, Senman B, Otipoby KL, Yokota A, Takeuchi H, Ricciardi-Castagnoli P, et al. Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells. Science 2006;314:1157–1160. [PubMed: 17110582]

Mostov KE, Deitcher DL. Polymeric immunoglobulin receptor expressed in MDCK cells transcytoses IgA. Cell 1986;46:613–621. [PubMed: 3524859]

Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T. Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. Cell 2000;102:553–563. [PubMed: 11007474]

Nathan C. Role of iNOS in human host defense. Science 2006;312:1874–1875. [PubMed: 16809512]

Neutra MR. M cells in antigen sampling in mucosal tissues. Curr. Top. Microbiol. Immunol 1999;236:17–32. [PubMed: 9893353]

Neutra MR, Kozlowski PA. Mucosal vaccines: The promise and the challenge. Nat. Rev. Immunol 2006;6:148–158. [PubMed: 16491139]

Ng LG, Ng CH, Woehl B, Sutherland AP, Huo J, Xu S, Mackay F, Lam KP. BAFF costimulation of Toll-like receptor-activated B-1 cells. Eur. J. Immunol 2006;36:1837–1846. [PubMed: 16791880]

O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, Lin LL, Mantchev GT, Bram RJ, Noelle RJ. BCMA is essential for the survival of long-lived bone marrow plasma cells. J. Exp. Med 2004;199:91–98. [PubMed: 14707116]

Okahashi N, Yamamoto M, Vancott JL, Chatfield SN, Roberts M, Bluethmann H, Hiroi T, Kiyono H, McGhee JR. Oral immunization of interleukin-4 (IL-4) knockout mice with a recombinant Salmonella strain or cholera toxin reveals that $CD4^+$ Th2 cells producing IL-6 and IL-10 are associated with mucosal immunoglobulin A responses. Infect. Immun 1996;64:1516–1525. [PubMed: 8613355]

Pasquier B, Launay P, Kanamaru Y, Moura IC, Pfirsch S, Ruffie C, Henin D, Benhamou M, Pretolani M, Blank U, Monteiro RC. Identification of FcαRI as an inhibitory receptor that controls inflammation: Dual role of FcRγ ITAM. Immunity 2005;22:31–42. [PubMed: 15664157]

Peterson DA, McNulty NP, Guruge JL, Gordon JI. IgA response to symbiotic bacteria as a mediator of gut homeostasis. Cell Host Microbe 2007;2:328–339. [PubMed: 18005754]

Phalipon A, Cardona A, Kraehenbuhl JP, Edelman L, Sansonetti PJ, Corthesy B. Secretory component: A new role in secretory IgA-mediated immune exclusion in vivo. Immunity 2002;17:107–115. [PubMed: 12150896]

Phalipon A, Corthesy B. Novel functions of the polymeric Ig receptor: Well beyond transport of immunoglobulins. Trends Immunol 2003;24:55–58. [PubMed: 12547499]

Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 2004;118:229–241. [PubMed: 15260992]

Rescigno M. $CCR6^+$ dendritic cells: The gut tactical-response unit. Immunity 2006;24:508–510. [PubMed: 16713968]

Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R, Granucci F, Kraehenbuhl JP, Ricciardi-Castagnoli P. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. Nat. Immunol 2001;2:361–367. [PubMed: 11276208]

Rhee KJ, Sethupathi P, Driks A, Lanning DK, Knight KL. Role of commensal bacteria in development of gut-associated lymphoid tissues and preimmune antibody repertoire. J. Immunol 2004;172:1118–1124. [PubMed: 14707086]

Rimoldi M, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM, Nespoli A, Viale G, Allavena P, Rescigno M. Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. Nat. Immunol 2005;6:507–514. [PubMed: 15821737]

Ryffel B, Le Hir M, Muller M, Eugster HP. Correction of the TNF-LTα-deficient phenotype by bone marrow transplantation. Dev. Immunol 1998;6:253–260. [PubMed: 9814599]

Sato A, Hashiguchi M, Toda E, Iwasaki A, Hachimura S, Kaminogawa S. $CD11b^+$ Peyer's patch dendritic cells secrete IL-6 and induce IgA secretion from naive B cells. J. Immunol 2003;171:3684–3690. [PubMed: 14500666]

Schneider P. The role of APRIL and BAFF in lymphocyte activation. Curr. Opin. Immunol 2005;17:282–289. [PubMed: 15886118]

Shockett P, Stavnezer J. Effect of cytokines on switching to IgA and alpha germline transcripts in the B lymphoma I.29 mu. Transforming growth factor-beta activates transcription of the unrearranged C alpha gene. J. Immunol 1991;147:4374–4383. [PubMed: 1753105]

Stevens SK, Weissman IL, Butcher EC. Differences in the migration of B and T lymphocytes: Organ-selective localization in vivo and the role of lymphocyte-endothelial cell recognition. J. Immunol 1982;128:844–851. [PubMed: 6976385]

Stoel M, Jiang HQ, van Diemen CC, Bun JC, Dammers PM, Thurnheer MC, Kroese FG, Cebra JJ, Bos NA. Restricted IgA repertoire in both B-1 and B-2 cell-derived gut plasmablasts. J. Immunol 2005;174:1046–1054. [PubMed: 15634929]

Suzuki K, Meek B, Doi Y, Honjo T, Fagarasan S. Two distinctive pathways for recruitment of naive and primed IgM^+ B cells to the gut lamina propria. Proc. Natl. Acad. Sci. USA 2005;102:2482–2486. [PubMed: 15695334]

Tezuka H, Abe Y, Iwata M, Takeuchi H, Ishikawa H, Matsushita M, Shiohara T, Akira S, Ohteki T. Regulation of IgA production by naturally occurring TNF/iNOS-producing dendritic cells. Nature 2007;448:929–933. [PubMed: 17713535]

Travis MA, Reizis B, Melton AC, Masteller E, Tang Q, Proctor JM, Wang Y, Bernstein X, Huang X, Reichardt LF, et al. Loss of integrin αvβ8 on dendritic cells causes autoimmunity and colitis in mice. Nature 2007;449:361–365. [PubMed: 17694047]

van Egmond M, van Garderen E, van Spriel AB, Damen CA, van Amersfoort ES, van Zandbergen G, van Hattum J, Kuiper J, van de Winkel JG. FcαRI-positive liver Kupffer cells: Reappraisal of the function of immunoglobulin A in immunity. Nat. Med 2000;6:680–685. [PubMed: 10835685]

von Bulow GU, van Deursen JM, Bram RJ. Regulation of the T-independent humoral response by TACI. Immunity 2001;14:573–582. [PubMed: 11371359]

Wagner N, Lohler J, Kunkel EJ, Ley K, Leung E, Krissansen G, Rajewsky K, Muller W. Critical role for β7 integrins in formation of the gut-associated lymphoid tissue. Nature 1996;382:366–370. [PubMed: 8684468]

Warnock RA, Campbell JJ, Dorf ME, Matsuzawa A, McEvoy LM, Butcher EC. The role of chemokines in the microenvironmental control of T versus B cell arrest in Peyer's patch high endothelial venules. J. Exp. Med 2000;191:77–88. [PubMed: 10620606]

Won WJ, Kearney JF. CD9 is a unique marker for marginal zone B cells, B1 cells, and plasma cells in mice. J. Immunol 2002;168:5605–5611. [PubMed: 12023357]

Xu W, He B, Chiu A, Chadburn A, Shan M, Buldys M, Ding A, Knowles DM, Santini PA, Cerutti A. Epithelial cells trigger frontline immunoglobulin class switching through a pathway regulated by the inhibitor SLPI. Nat. Immunol 2007;8:294–303. [PubMed: 17259987]

Xu-Amano J, Kiyono H, Jackson RJ, Staats HF, Fujihashi K, Burrows PD, Elson CO, Pillai S, McGhee JR. Helper T cell subsets for immunoglobulin A responses: Oral immunization with tetanus toxoid and cholera toxin as adjuvant selectively induces Th2 cells in mucosa associated tissues. J. Exp. Med 1993;178:1309–1320. [PubMed: 8376936]

Yamamoto M, Kweon MN, Rennert PD, Hiroi T, Fujihashi K, McGhee JR, Kiyono H. Role of gut-associated lymphoreticular tissues in antigen-specific intestinal IgA immunity. J. Immunol 2004;173:762–769. [PubMed: 15240662]

Zan H, Cerutti A, Schaffer A, Dramitinos P, Casali P. CD40 engagement triggers switching to IgA1 and IgA2 in human B cells through induction of endogenous TGF-βμ. Evidence for TGF-β but not IL-10-dependent direct Sμ->Sα and sequential Sμ->Sγ, Sγ->Sα DNA recombination. J. Immunol 1998;162:5217–5225. [PubMed: 9820493]

Zholudev A, Zurakowski D, Young W, Leichtner A, Bousvaros A. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: Diagnostic value and correlation with disease phenotype. Am. J. Gastroenterol 2004;99:2235–2241. [PubMed: 15555007]

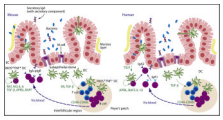

Figure 1. Intestinal IgA Responses in Mice and Humans

In mice (left model), DCs lodged in the subepithelial dome of Peyer's patches capture bacteria or antigen internalized by M cells or by epithelial cells (ECs) via receptor-mediated endocytosis. These DCs migrate to the interfollicular region (IFR) of Peyer's patches, where they present antigen to $CD4^+$ T cells. Antigen-activated $CD4^+$ T cells elicit IgA class switching by stimulating IgM^+IgD^+ B cells through CD40L and TGF. A subset of Peyer's patch DCs, TNF-α^+iNOS$^+$ DCs, enhance IgA class switching by upregulating the expression of the TGF-β receptor on B cells through nitric oxide (NO). In the presence of retinoic acid (RA), IgA^+ B cells upregulate the expression of CCR9 and α4β7 and thereafter migrate to the lamina propria, where they differentiate into plasma cells that release dimeric IgA antibodies. This T cell-dependent pathway yields high-affinity, monoreactive IgA antibodies that preferentially target pathogens and toxins. IgA class switching can also take place in the lamina propria via a T independent mechanism that involves activation of B-1 cells and possibly other IgM^+IgD^+ B cell subsets by DCs, including TNF-α^+iNOS$^+$ DCs. These DCs release innate IgA class-switch-inducing factors, such as BAFF, APRIL, TGF-β, and NO, as well as IgA secretion-inducing factors, such as IL-6 and RA, after sensing bacteria through TLRs. NO amplifies IgA class switching by enhancing BAFF and APRIL production by DCs. This T cell-independent pathway preferentially yields low-affinity, polyreactive IgA antibodies to commensal bacteria.

In humans (right model), $CD4^+$ T cells elicit IgA1 class switching by activating Peyer's patch IgM^+IgD^+ B cells through CD40L and TGF-β. The resulting $IgA1^+$ B cells migrate to the lamina propria through a mechanism presumably similar to that utilized by mouse IgA^+ B cells. In the lamina propria, $IgA1^+$ B cells sequentially switch to IgA2 in response to APRIL and IL-10 released by TLR-activated ECs. Also, DCs can release these cytokines in response to TSLP produced by ECs. In the lamina propria, additional IgM^+IgD^+ B cells can undergo direct class switching from IgM to IgA1 or IgA2 in response to BAFF or APRIL and IL-10. In general, IgA2 is more resistant to bacterial proteases than IgA1 and may therefore have a longer half-life in the lumen of the distal intestinal tract.

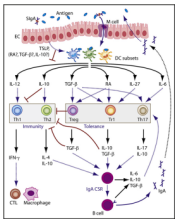

Figure 2. Putative Role of IgA in Intestinal Tolerance and Homeostasis

Intestinal M cells transfer IgA-bound antigen from the lumen to DCs. In the presence of TSLP and other epithelial cell (EC) products, possibly including retinoic acid (RA), TGF-β, and IL-10, multiple subsets of Peyer's patch DCs initiate noninflammatory $CD4^+$ T cell responses. By blocking DC production of IL-12 and inducing DC production of IL-10, TSLP prevents intestinal DCs from initiating proinflammatory Th1 responses, including IFN-γ-dependent activation of macrophages and cytotoxic T lymphocytes (CTLs). The resulting Th2 response triggers IgA (and IgG) class switching and production by activating B cells via CD40L (not shown) as well as IL-4 and IL-10. By upregulating DC release of TGF-β, IL-6, IL-27, and RA, TSLP alone or combined with other epithelial factors might also initiate Treg, Tr1, and Th17 cell responses. Treg cells dampen Th1-Th2 immunity through contact-dependent mechanisms and TGF-β, whereas Tr1 cells and regulatory-stage Th17 cells attenuate Th1-Th2 immunity via IL-10. Treg, Tr1, and Th17 cells might also trigger IgA (but not IgG) class switching and production by activating B cells via CD40L (not shown) as well as TGF-β and IL-10. Intestinal Treg, Tr1, and Th17 cell responses might be further amplified by TGF-β, IL-10, IL-6, and IgA derived from B cells.