Published in final edited form as:

Immunol Res. 2012 December ; 54(1-3): 4–13. doi:10.1007/s12026-012-8307-5.

Regulation of frontline antibody responses by innate immune signals

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Abstract

Mature B cells generate protective immunity by undergoing immunoglobulin (Ig) class switching and somatic hypermutation, two Ig gene-diversifying processes that usually require cognate interactions with T cells that express CD40 ligand. This T-cell-dependent pathway provides immunological memory but is relatively slow to occur. Thus, it must be integrated with a faster, T-cell-independent pathway for B-cell activation through CD40 ligand-like molecules that are released by innate immune cells in response to microbial products. Here, we discuss recent advances in our understanding of the interplay between the innate immune system and B cells, particularly “frontline” B cells located in the marginal zone of the spleen and in the intestine.

Keywords

B cells; Innate immune cells; Splenic marginal zone; Intestinal mucosa; Class switching

Introduction

The mammalian immune system is composed of innate and adaptive branches that mount integrated responses to combat invading pathogens while preserving homeostasis at mucosal sites colonized by commensal bacteria [1]. Dendritic cells (DCs), monocytes, macrophages, granulocytes, natural killer cells, and epithelial cells of the innate immune system mediate fast but nonspecific protective responses after recognizing generic microbial structures

through germ line gene-encoded receptors often referred to as pattern recognition receptors (PRRs), which include Toll-like receptor (TLR) family members [2, 3]. In contrast, T and B cells of the adaptive immune system mediate specific but temporally delayed responses after recognizing discrete antigenic epitopes through somatically recombined receptors. After sensing microbial signatures through PRRs, innate immune cells such as DCs undergo maturation and acquire the ability to present antigenic peptides to T cells, thereby initiating highly specific cellular and humoral responses [4–6]. The latter involve production of highly diversified antibody molecules that include immunoglobulin M (IgM), IgG, IgA, and IgE.

In addition to receiving stimulating signals from antigen-activated T cells, B cells can initiate Ig production after responding to activating signals from cells of the innate immune system. Unlike T-cell-dependent (TD) antibody responses, which predominantly involve follicular B cells, T-cell-independent (TI) antibody responses involve specialized subsets of extrafollicular B cells strategically located at the mucosal interface and in the marginal zone (MZ) of the spleen [7, 8]. These frontline environments are constantly exposed to external and blood-borne antigens, respectively, and therefore generate multiple TD and TI layers of antibody protection. In this review, we summarize recent data from our laboratory and other groups describing how innate immune signals regulate antibody diversification and production in splenic and intestinal B cells.

Antibody diversification

Diversification is essential for the immune system to mount protective responses. B cells diversify Ig-encoding genes through three major DNA-modifying processes known as V(D)J recombination, class switch recombination (CSR), and somatic hypermutation (SHM). Bone marrow B-cell precursors generate antigen recognition diversity through V(D)J recombination, an antigen-independent process mediated by recombination-activating gene (RAG) endonucleases that assemble antigen-binding Ig variable regions from individual V (variable), D (diversity), and J (joining) gene segments [9]. Mature B cells emerging from the bone marrow colonize peripheral lymphoid organs, where they undergo a second wave of Ig gene remodeling through SHM and CSR. These antigen-dependent processes require the DNA-editing enzyme activation-induced cytidine deaminase (AID) and mediate antibody affinity maturation and class (or isotype) switching, respectively [10, 11]. SHM introduces point mutations within V(D)J exons, thereby providing the structural correlate for selection of high-affinity Ig mutants by antigen [12, 13]. In contrast, CSR replaces constant μ (C_μ) and C_δ exons encoding IgM and IgD with C_γ , C_α , or C_e exons encoding IgG, IgA, or IgE, thereby providing antibodies with novel effector functions without changing their antigen-binding specificity [12, 13]. In humans, a non-canonical form of CSR from C_μ to C_δ also exists and generates B cells that are specialized in IgD production [14, 15].

Antibody production

Most antigens initiate Ig responses through a TD reaction that takes place in the germinal center of lymphoid follicles. This specialized microenvironment fosters the cognate interaction of follicular B cells (also known as B-2 cells) with antigen-activated CD4⁺ T helper (Th) cells, including T follicular helper (T_{FH}) cells. By activating B cells through cytokines and a membrane-bound tumor necrosis factor (TNF) family member known as CD40 ligand (CD40L), T cells promote B-cell clonal expansion, CSR, SHM, and selection of B cells expressing Ig receptors with high affinity for antigen [16, 17]. Ultimately, this TD pathway leads to the emergence of long-lived memory B cells and antibody-secreting plasma cells that produce protective IgM as well as class-switched IgG, IgA and IgE. Usually, TD antibody responses require 5–7 days, which can be too much of a delay to

control commensal bacteria inhabiting mucosal surfaces and highly replicating blood-borne pathogens.

To compensate for this limitation, mucosal B-1 cells and MZ B cells release low-affinity IgM but also IgG and IgA at earlier stages of the immune response through a TI pathway that involves production of soluble TNF family members known as B cell-activating factor of the TNF family (BAFF) and a proliferation-inducing ligand (APRIL). This TI pathway also involves sensing of conserved microbial molecular signatures by B cells through TLRs [18]. Indeed, B-1 and MZ B cells express elevated levels of TLRs, probably as a result of their constitutively high activation state [19–21]. In addition, B-1 and MZ B cells express poorly diversified (i.e., unmutated) Ig receptors that can bind multiple microbial determinants with low affinity, at least in mice [7, 22, 23]. Together with BAFF, APRIL, and other B cell-stimulating cytokines produced by innate immune cells, signals emanating from TLRs and Ig receptors are instrumental for MZ B cells and B-1 cells to generate an innate layer of antibody-mediated immune protection [24].

Marginal zone B-cell responses

The MZ is a splenic area proximal to sinusoidal vessels characterized by a slow blood flow rate, which enables local endothelial cells, macrophages, and DCs to efficiently capture circulating microbes and immune complexes [25]. In mice, MZ B cells are uniquely enriched in germ line-encoded Ig receptors that recognize microbial determinants collectively known as TI antigens [23]. These antigens include lipopolysaccharide, phospholipids, polysaccharides, and other highly conserved microbial structures [[26], [27]]. Unlike murine MZ B cells, human MZ B cells express hypermutated Ig receptors and yet can react against blood-borne TI antigens as murine B cells do [7]. Indeed, splenectomized individuals have an increased susceptibility to infections by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* [28, 29]. Similar infections are also more frequent in the first 2 years of life, an age in which the MZ is incompletely organized and functionally immature [7]. MZ B cells initiate rapid antibody responses by generating short-lived antibody-secreting plasmablasts after recognizing TI antigens captured by innate immune cells, including DCs, macrophages, and granulocytes.

Role of dendritic cells

DCs become activated and transport intact bacteria to the MZ of the spleen a few hours after capturing blood-borne antigens [30]. In addition to inducing TD antibody responses against microbial proteins in splenic follicles, bacteria-transporting DCs can interact with MZ B cells in the bridging channels of the spleen and at the border between T- and B-cell areas to initiate TI antibody responses against microbial carbohydrates [31]. Such responses would involve cross-linking of Ig receptors on MZ B cells by endocytosed TI antigen recycling to the surface of DCs as well as DC production of BAFF and APRIL. These CD40L-related cytokines elicit IgM production, class switching, and plasmablast differentiation by engaging the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptor on MZ B cells [30].

Role of macrophages

In mice, the spleen contains two subsets of macrophages known as MZ macrophages and metallophilic macrophages. Metallophilic macrophages form an inner ring between the MZ and the white pulp and express the sialoadhesin receptor MOMA-1 and the sialic-acid binding molecule SIGLEC1. In contrast, MZ macrophages form an outer ring between the MZ and the red pulp and express the type-A scavenger receptor MARCO and the C-type lectin receptor SIGNR1, which is the mouse homolog of human DC-SIGN. While SIGNR1

efficiently binds polysaccharides associated with bacteria and viruses, MARCO recognizes both LPS and non-LPS ligands on bacteria [32, 33]. Splenic macrophages facilitate antibody production by transferring antigen captured from the circulation to MZ B cells [32, 33]. Then, antigen-pulsed MZ B cells either initiate TI antibody responses by generating short-lived plasmablasts in the red pulp of the spleen or elicit TD antibody responses by presenting antigen to T cells in the follicles of the white pulp of the spleen [34, 35].

Role of granulocytes

Neutrophils constitute the major subset of granulocytes in our immune system and are the first immune cells to migrate to sites of infection [36]. After sensing conserved molecular signatures associated with microbes and tissue damage, neutrophils activate defensive programs that promote phagocytosis, intracellular degradation, extracellular discharge of antimicrobial factors, and the formation of antigen-trapping neutrophil extracellular traps (NETs) [37]. Neutrophils also release cytokines and chemokines that recruit monocytes to optimize antigen clearance. The long-held view that neutrophils function exclusively in the innate phase of the immune response has been challenged by studies showing that neutrophils also influence adaptive immunity by interacting with DCs and by releasing interleukin-12 (IL-12), which promotes the polarization of naive T cells into inflammatory T helper type 1 cells that release interferon- γ (IFN- γ) [37, 38]. In the presence of IFN- γ and other inflammatory cytokines, neutrophils also upregulate their expression of antigen-loading major histocompatibility class-II molecules to acquire DC-like antigen-presenting function. Moreover, neutrophils also produce the cytokine BAFF and APRIL [39]. Of note, granulocytes home to the MZ in response to blood-borne bacteria together with DCs [30]. Recently, we found that neutrophils colonize peri-MZ areas of the spleen in the absence of infection via a non-inflammatory pathway that becomes more prominent after post-natal colonization by commensal bacteria [40].

Compared to circulating neutrophils (N_C), splenic neutrophils (N_{BH}) express a distinct phenotype, form MZ B cell-interacting NET-like structures, and elicit CSR and SHM as well as IgM, IgG, and IgA production by activating MZ B cells through a mechanism involving BAFF and APRIL and the cytokine IL-21 (Fig. 1). N_{BH} cells activate MZ B cells as efficiently as splenic T cells via both contact-dependent and contact-independent mechanisms [40]. N_C cells can acquire B cell-helper function upon exposure to TLR-activated splenic sinusoidal endothelial cells releasing cytokines such as IL-10 [40]. Consequently, patients with congenital neutropenia have fewer and hypomutated MZ B cells, and their serum contain less pre-immune Igs to certain TI antigens [40]. Our data suggest that splenic filtration of microbial products originating from mucosal surfaces generates TLR signals that facilitate the recruitment of N_C cells and their reprogramming into N_{BH} cells. Consistent with this possibility, N_{BH} cells are less abundant in germ-free mice [40]. Thus, neutrophils may generate an innate layer of antimicrobial Ig defense by undergoing B-helper reprogramming in the spleen.

Mucosal B-cell responses

Mucosal membranes are colonized by large communities of commensal bacteria and represent the primary site of entry for pathogens [41]. A key component of this interface is the mucosal epithelium, which blocks microbial intruders by forming multiple layers of physical and immune protection [42]. Epithelial protection is particularly sophisticated in the intestine. A single layer of intestinal epithelial cells (IECs) separates the sterile milieu of our body from large communities of commensal bacteria that process otherwise indigestible polysaccharides, synthesize essential vitamins and isoprenoids, stimulate the maturation of the immune system, and form an ecological niche that prevents the growth of pathogenic species [43]. Conversely, the intestine provides commensals with a stable habitat rich in

energy derived from ingested food. To preserve homeostasis, the intestine has evolved several strategies to preserve the number and composition of commensals without causing life-threatening inflammatory reactions [44]. A key strategy involves the production of massive amounts of IgA, the most abundant antibody isotype produced in our body [45]. IgA works together with nonspecific protective factors such as mucus and antimicrobial peptides to block microbial adhesion to epithelial cells without causing inflammation [41]. By doing so, IgA establishes a state of armed peace in the homeostatic interaction between the host and bacteria. When microbes trespass the epithelial border, a state of open war breaks out and IgA receives help from IgG to repel invaders. In this life-threatening situation, IgG provides a second line of defense that controls microbial dissemination by eliciting a robust inflammatory reaction [46].

Antibody composition of mucosal sites

Different mucosal districts are characterized by distinct antibody signatures [41]. The proportion of different antibody types in distinct mucosal sites varies as a result of local factors that skew CSR toward one isotype or the other. In addition, epithelial cells from different mucosal sites express distinct antibody transporters and release distinct plasma cell-recruiting chemokines that further shape the isotype composition of a given mucosal site [41]. In general, IgA is the most abundant antibody isotype in mucosal secretions. Yet, IgA is somewhat less abundant than IgG in the urine, bile as well as genital and bronchoalveolar secretions. IgD can be detected in nasal, salivary, lacrimal, and bronchoalveolar secretions, whereas IgE is measurable in nasal, bronchoalveolar, and intestinal secretions, at least when allergens are present [41]. Unlike mouse B cells, human B cells produce two IgA subclasses, IgA1 and IgA2, which have a similar receptor-binding profile but different geographical distribution [47]. IgA1 is present in both systemic and mucosal districts, whereas IgA2 is mostly present in mucosal districts colonized by a large microbiota, including the distal intestinal tract and the urogenital tract [47]. This circumstance could reflect the fact that IgA2 is more resistant than IgA1 to degradation by bacterial proteases, because IgA2 has a shorter protease-sensitive hinge region than IgA1 does [48, 49].

IgA function

IgA produced at mucosal sites interacts with the polymeric Ig receptor (pIgR), an antibody transporter expressed on the basolateral surface of IECs. After binding to pIgR through a joining (J) chain, IgA dimers secreted by intestinal plasma cells translocate across epithelial cells onto the mucosal surface through a process known as transcytosis [50]. Transcytosis involves intracellular processing of pIgR into a secretory component (SC) that remains associated with the J chain of the IgA dimer to form a secretory IgA (SIgA) complex. SIgA and its dimeric IgA precursor bind to antigen without generating inflammatory products from the complement cascade and without stimulating the release of inflammatory mediators from immune cells. IgA excludes commensals from the mucosal surface by inducing bacterial agglutination, masking bacterial proteins involved in epithelial attachment and anchoring bacterial cells to mucus [50].

IgA also decreases the inflammatory tone of the intestine by maintaining appropriate bacterial communities within specific mucosal segments. Thus, the lack of IgA causes changes in the composition of the intestinal microbiota that can cause hyperactivation of the immune system and inflammation [51–53]. Moreover, recent findings show that, in the absence of IgA, commensal bacteria favor the expression of genes controlling immunity in IECs at the expense of genes regulating metabolism [54]. Thus, IECs from IgA-deficient mice upregulate the expression of IFN-dependent genes to compensate for the lack of adaptive humoral immunity. This upregulation leads to a downregulation of the expression

of metabolic genes controlled by the transcription factor Gata4. The resulting gene imbalance impairs the absorption of lipids, which may explain why individuals with immunodeficiencies causing impaired IgA production show defective lipid absorption [54, 55].

Mucosal IgA comprises antibodies that recognize antigen with high- and low-affinity binding modes [45]. In general, high-affinity IgA neutralizes microbial toxins and invasive pathogens, whereas low-affinity IgA confines commensals in the intestinal lumen. Yet, this distinction is not absolute. Indeed, growing evidence indicates an important role for high-affinity IgA in the control and regulation of the commensal microbiota [56]. On the other hand, additional evidence shows that low-affinity IgA can protect against some pathogens [57, 58]. High-affinity IgA is thought to emerge from follicular B cells stimulated via TD pathways, whereas low-affinity IgA likely emerges from extrafollicular B cells stimulated via TI pathways [59]. However, this view is rapidly changing, as recent findings document the existence of TI pathways for IgA production in follicular B cells [60].

IgD function

The function of IgD has puzzled immunologists over the past several decades. Originally thought to be a recently evolved isotype, IgD is now recognized to be an evolutionarily ancient molecule that has been conserved throughout evolution to complement the functions of IgM [14, 61]. IgD would afford protection to the respiratory mucosa by binding to pathogenic bacteria such as *Moraxella catarrhalis* and *H. influenzae* as well as their virulence factors [15, 62]. We recently found that, in addition to crossing epithelial cells, IgD binds to circulating basophils, monocytes, and neutrophils as well as mucosal mast cells through an unknown receptor [14, 63]. Consistent with recently published data showing the important role of basophils in T helper type 2 (Th2) cell responses and antibody production [64–67], we also found that IgD cross-linking induces basophil release of B cell-activating cytokines such as IL-4 and IL-13, which in turn facilitate IgM as well as IgG and IgA production [15].

Furthermore, IgD cross-linking triggers basophil release of antimicrobial peptides that kill pathogenic respiratory bacteria and cytokines that enhance inflammation [15, 63]. Therefore, IgD may contribute to mucosal immunity not only by neutralizing pathogens and excluding commensals but also by recruiting circulating innate immune cells with antimicrobial and immune-augmenting functions. Of note, mucosal IgD increases in some primary immunodeficiencies impairing IgA production, including common variable immunodeficiency [14]. One possibility is that IgD production increases to compensate for the lack of IgA.

Innate antibody-inducing factors

Gut follicular IgA

Peyer's patches (PPs) are the major portal of entry of bacteria and together with mesenteric lymph nodes (MLNs), and isolated lymphoid follicles (ILFs) constitute the major follicular IgA inductive sites in the intestine. PPs develop during fetal life independently of gut colonization by bacteria and consist of large structures built on a stromal scaffold composed of several B-cell follicles separated by areas containing T cells and DCs [16]. In PPs, there is an ongoing germinal center reaction that continuously drives IgA diversification and production. This germinal center reaction is optimized by microbial signals, as mice depleted of intestinal bacteria have PPs with fewer and smaller germinal centers. In both PPs and MLNs, germinal center B cells produce IgA through a TD pathway involving activation of CD4⁺ T cells by multiple subsets of antigen-presenting DCs, including migratory DCs that originate from circulating pre-DC precursors and express the integrin CD103 [16].

Remarkably, PPs have a less stringent requirement for cognate T cell–B cell interaction than systemic lymphoid follicles [68–70]. Instead, mucosal follicles are highly dependent on microbial signals, as lack of the TLR-associated adaptor protein myeloid differentiation primary response gene 88 (MyD88) alters intestinal IgA responses [60, 71, 72]. Recent evidence shows that microbial signals stimulate IgA production in PPs through a mechanism involving follicular dendritic cells (FDCs), a key structural component of lymphoid follicles. FDCs express large amounts of TLRs such as TLR2 and TLR4, which allows FDCs to respond to LPS and lipopeptides derived from gut microbes [60]. FDCs from PPs also express nuclear retinoic acid receptor- β (RAR- β), which prepares FDCs to respond to retinoic acid (RA) produced in the gut environment. Coordinated signaling through TLR2, TLR4, and RAR- β synergistically up-regulates the expression of CXCL13 and BAFF, two molecules that support the recruitment and survival of B cells. Similar signals trigger FDC expression of metalloproteases associated with the secretion and activation of TGF- β , a key IgA-inducing cytokine [60]. In this manner, intestinal FDCs from PPs skew class switching toward IgA.

DCs expressing TNF and inducible nitric oxide synthase (TipDCs) may further enhance IgA class switching and production in PPs [71]. When activated by TLR ligands, TipDCs release BAFF and APRIL as well as nitric oxide, a compound that up-regulates the expression of the TGF- β receptor on follicular B cells [71]. This up-regulation causes further skewing of IgA class switching toward IgA. Of note, DCs from PPs also produce RA, a metabolite of vitamin A that up-regulates $\alpha 4\beta 7$ and CCR9 gut-homing receptors on B cells [73]. This up-regulation facilitates the migration of IgA class-switched from the inductive site of PPs to the effector site of the lamina propria (LP).

Similar to PPs, MLNs have IgA inductive pathways that function in a TI manner. Indeed, recent studies show that plasmacytoid DCs induce IgA production in MLNs by releasing APRIL and BAFF in response to IFN- β produced by TLR-activated stromal cells [74]. TI pathways may be even more prominent in ILFs [16]. These lymphoid structures are scattered throughout the intestine and consist of solitary B-cell clusters built on a scaffold of stromal cells with interspersed T cells and abundant perifollicular DCs [75]. In ILFs, lymphotoxin β (LT β) from TLR-activated lymphoid tissue-inducer cells stimulates local stromal cells to release TNF as well as DC-attracting chemokines such as CCL19 and CCL21 [76]. In these DCs, TNF promotes production of active TGF- β as well as BAFF and APRIL, which cooperatively induce TI IgA CSR and production in follicular B cells [76].

Gut extrafollicular IgA

Although most mucosal IgA derives from follicular B cells residing in PPs, MLNs and ILFs, some mucosal IgA also derives from scattered extrafollicular B cells residing in the intestinal LP [41, 77]. Consistent with this notion, genetically engineered mice lacking PPs, MLNs and ILFs retain some antigen-specific IgA plasma cells, which are mostly located in the LP [78, 79]. In both mice and humans, a fraction of B cells from the intestinal LP contain molecular hallmarks of ongoing IgA CSR, including AID, H2AX protein (a nuclear protein associated with double-strand DNA breaks generated by AID within S regions), excised S α -S μ switch circles, and switch circle I α -C μ transcripts [80–83]. Growing evidence demonstrates that multiple subsets of DCs can activate B cells in a TI fashion to induce IgA CSR and production in the LP (Fig. 2) [30, 84–89]. One of these subsets includes TipDCs, which elicit IgA CSR by releasing BAFF and APRIL through a mechanism involving TLR-mediated iNOS-dependent nitric oxide production [71]. The LP also contains a subset of DC that expresses large amounts of the flagellin receptor TLR5 and elicit IgA production through a mechanism that requires RA and IL-6 [90].

In addition to DCs, IECs may further contribute to the induction of IgA in subepithelial areas of the intestine. By sensing microbial signatures via PRRs such as TLRs, IECs instruct mucosal immune cells as to the microbial composition of the intestinal lumen to generate a state of tolerance or immune activation [91]. Thus, while IEC recognition of commensals is crucial to maintain mucosal homeostasis [92–94], IEC recognition of pathogens causes strong defensive inflammatory responses [95]. Remarkably, numerous mediators produced by IECs can modulate the immune system to promote IgA production in B cells. These IgA-inducing factors can either directly signal to B cells or condition DCs, macrophages and T cells to enhance IgA responses (Fig. 2) [96].

IECs can deliver IgA-inducing signals to LP B cells by releasing BAFF, APRIL, and IL-10 in response to TLR signals [80, 81, 97, 98]. In humans, APRIL is particularly effective for the induction of IgA2, an IgA subclass particularly abundant in the distal intestine [80]. In addition to triggering direct IgM-to-IgA1 CSR [80], APRIL elicits sequential IgA1-to-IgA2 CSR in the LP of the distal intestine, which would allow B cells arriving from PPs to acquire an IgA2 subclass more resistant than IgA1 to degradation by bacterial proteases [49]. Accordingly, the human colonic lamina propria of immunodeficient patients lacking functional T cells, CD40 signals, and germinal centers retains B cells with active IgA1 and IgA2 CSR and production. In addition, IECs can amplify DC production of BAFF, APRIL, and IL-10 by stimulating DCs through an IL-7-like cytokine known as thymic stromal lymphopoietin [80, 97].

Respiratory IgD

IgD constitutes a significant fraction of antibodies produced in the upper segments of the human respiratory tract. We found that mucosal IgD originates from plasmablasts that delete the C μ gene encoding IgM after undergoing CSR from C μ to C δ [41]. This recombinatorial process involves a rudimentary switch-like intronic DNA region known as $\sigma\delta$ that is present upstream of the C δ gene in the Ig heavy chain locus of humans and other higher mammals but not rodents [14]. Like canonical switch regions positioned upstream of C μ , C γ , C α , and C ϵ genes, $\sigma\delta$ contains guanosine–cytosine repeats and serves as an acceptor DNA region for donor S μ to mediate CSR from C μ to C δ . We found that this process requires AID, because patients with a deficient or nonfunctional AID protein show a lack of IgD class-switched plasmablasts [15]. In addition, B cells from AID-deficient patients are unable to undergo CSR from C μ to C δ when exposed to appropriate stimuli in vitro [15]. Of note, IgD class-switched plasmablasts are also decreased in patients with deficient or nonfunctional CD40L, CD40, and TACI proteins, suggesting that IgD CSR and production involve both TD and TI pathways [15]. Consistent with this possibility, CD40L, BAFF, or APRIL can induce IgD CSR when combined with appropriate cytokines [15].

Secreted IgD would exert its protective function not only by binding to antigen, but also by interacting with cells of the innate immune system such as basophils [15]. By arming basophils with IgD highly reactive against respiratory bacteria, mucosal IgD-producing plasmablasts may educate our immune system as to the antigenic composition of the upper respiratory tract [14]. Upon sensing respiratory antigen, IgD-activated basophils would initiate or enhance innate and adaptive immune responses both systemically and at mucosal sites of entry. This possibility is consistent with recent evidence showing that activated basophils can migrate to secondary lymphoid organs to initiate T-cell and B-cell responses [64, 66, 67, 99].

Innate B-cell signaling pathways

BAFF and APRIL are CD40L-related TNF family members derived from cells of the innate immune system and trigger CSR and antibody production by engaging the TACI receptor on

B cells [96]. BAFF and APRIL also deliver survival signals by engaging the BAFF receptor (BAFF-R; this receptor binds only BAFF) and the B-cell maturation antigen (BCMA; this receptor binds both BAFF and APRIL) receptor on mature B cells and plasma cells, respectively [47]. We found that, in the presence of co-signals from cytokine receptors and TLRs, TACI induces AID expression via NF- κ B, followed by CSR, antibody production, and plasma cell differentiation. Of note, TACI establishes a close functional cooperation with B cell-intrinsic TLR signals [21, 80, 97], which involves up-regulation of TACI expression by TLR-activated B cells [19, 100]. Consistent with these studies, we found that TACI utilizes the adaptor protein myeloid differentiation primary response gene 88 (MyD88) and TRAF6 to activate NF- κ B, as TLRs do. However, TLRs recruit MyD88 and downstream kinases such as IL-1 receptor-associated kinase 1 (IRAK-1) and IRAK4 through a cytoplasmic Toll-interleukin-1 receptor (TIR) motif, whereas TACI utilizes a cytoplasmic motif different from TIR. Given that TLR signals are also important to generate the production of BAFF and APRIL by innate immune cells, these findings highlight the intimate cooperation between the innate and adaptive immune systems at both cellular and signaling levels and provide an additional mechanistic explanation for studies linking intestinal IgA responses to MyD88 [41, 96].

Acknowledgments

Supported by US National Institutes of Health grants R01 AI074378, P01 AI61093, U01 AI95613, and P01 096187 to A. Cerutti, Ministerio de Ciencia e Innovación grant SAF 2008-02725 to A. Cerutti, EUROPADnet HEALTH-F2-2008-201549 to A. Cerutti, a Sara Borrell post-doctoral fellowship to A. Chorny, and a Juan de la Cierva post-doctoral fellowships to I. Puga.

Biography

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Fig. 1.

Innate B cell-stimulating signals in the spleen. Canonical neutrophils (N_C cells) colonize peri-MZ areas of the spleen under homeostatic conditions via a non-inflammatory pathway. N_C cells acquire a distinct phenotype and B cell-helper function in response to splenic signals such as IL-10 from sinusoidal endothelial cells and macrophages. The resulting N_{BH} cells form MZ B cell-interacting NET-like structures to elicit CSR, SHM as well as IgM, IgG, and IgA production via a mechanism involving the cytokines BAFF, APRIL, and IL-21

Fig. 2.

Innate B cell-stimulating signals in the intestine. IECs release APRIL and trigger direct IgM-to-IgA1 CSR in LP IgM⁺ B cells and sequential IgA1-to-IgA2 CSR in LP IgA1⁺ B cells after sensing microorganisms through TLRs. iNOS⁺TNF⁺ DCs (TipDCs) and TLR5⁺ DCs cooperate with stromal cells and macrophages to further enhance local IgA CSR and production through a mechanism involving BAFF, APRIL, IL-6, IL-10, and TGF-β1. Similar signals promote the differentiation of IgA class-switched B cells into IgA-secreting plasma cells and facilitate plasma cell survival