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New helping friends for B cells

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Abstract

Over the past decade, a growing recognition of the importance of neutralizing antibodies in host defense combined with the success of B-cell depletion therapies in treating autoimmune disorders has led to an increased focus on better understanding the pathways underpinning B-cell antibody production. In general, B cells require cognate interaction with T helper cells in the germinal center of lymphoid follicles to generate protective antibodies. However, recent evidence shows that B cells receive additional help from invariant natural killer T cells, dendritic cells, and various granulocytes, including neutrophils, eosinophils, and basophils. These innate immune cells enhance T-cell-dependent antibody responses by delivering B-cell helper signals both in the germinal center and at postgerminal center lymphoid sites such as the bone marrow. In addition to enhancing and complementing the B-cell helper activity of canonical T cells, invariant natural killer T cells, dendritic cells, and granulocytes can deliver T cell-independent B-cell helper signals at the mucosal interface and in the marginal zone of the spleen to initiate rapid innate-like antibody responses. Here, we discuss recent advances in the role of adaptive and innate B-cell helper signals in antibody diversification and production.

Keywords

Cytokines; Dendritic cells (DCs); Granulocytes; Immunoglobulins; Lymphocytes

Introduction

The mammalian immune system comprises of innate and adaptive branches that mount integrated protective responses against intruding microbes. The innate immune system includes dendritic cells (DCs), macrophages, granulocytes, and natural killer (NK) cells that mediate fast but nonspecific responses after recognizing generic microbial structures through invariant germline gene-encoded receptors often referred to as pattern recognition receptors, including Toll-like receptors (TLRs) (reviewed in [1]). In contrast, the adaptive immune system includes T and B cells that mediate specific but temporally delayed responses after recognizing discrete antigenic epitopes through highly diverse somatically recombined receptors (reviewed in [2]). The crosstalk between the innate and adaptive

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immune systems is exemplified by responses involving marginal zone (MZ) B cells or invariant NKT (iNKT) cells. Indeed, these lymphocyte subsets mount very early, innate-like adaptive responses after recognizing microbial carbohydrate and glycolipid antigens via both germline-encoded and somatically recombined receptors [3-5].

B cells confer immune protection by producing antibody molecules, also known as immunoglobulins (Igs), which can recognize antigen through either low- or high-affinity binding modes. Bone marrow B-cell precursors generate Ig recognition diversity by undergoing V(D)J gene recombination, an antigen-independent process that utilizes recombination activating gene (RAG) endonucleases to juxtapose noncontiguous variable (V), diversity (D) and joining (J) gene fragments into functional V(D)J genes encoding the antigen-binding V region of Ig molecules (reviewed in [6]). After further maturation events, multiple subsets of mature B cells co-expressing IgM and IgD emerge from the bone marrow and colonize different compartments of secondary lymphoid organs to initiate the antigen-dependent phase of B-cell development. In general, conventional follicular B cells, which are also called B-2 cells, predominantly participate in T-cell-dependent (TD) antibody responses to highly specific determinants usually associated with microbial proteins (reviewed in [7]). TD responses unfold in the germinal center of lymphoid follicles and generate high-affinity antibodies through a TD pathway that involves activation of B cells by follicular helper T (T_{FH}) cells. This germinal center-associated T-cell subset expresses the inducible T-cell costimulator (ICOS) receptor, the chemokine receptor CXCR5, the programmed cell death-1 (PD-1) inhibitory receptor and the transcription factor Bcl6 [8-15]. T_{FH} cells provide help to B cells via CD40 ligand (CD40L) and cytokines such as IL-21, IL-4, and IL-10 [16-19]. However, recent findings indicate that follicular antibody responses further involve additional T-cell subsets, including follicular regulatory T (T_{FR}) cells and iNKT cells [4,5,20-22].

Unlike follicular B cells, certain subsets of extrafollicular B cells such as B-1 cells, splenic MZ B cells (also referred to as IgM memory B cells in humans) and bone marrow perisinusoidal B cells predominantly give rise to rapid T-cell-independent (TI) antibody responses to highly conserved carbohydrate and glycolipid determinants associated with microbes [3,23-30]. TI antibody responses usually unfold at the mucosal interface or in the splenic MZ and generate polyspecific and low-affinity antibodies through a TI pathway involving the interaction of B cells with DCs, macrophages, and granulocytes [3,30-34]. These innate immune cells deliver antibody-inducing signals via CD40L-like cytokines known as B-cell-activating factor of the TNF family (BAFF, also known as BLyS) and a proliferation-inducing ligand (APRIL) [3,30,35-39]. However, it must be noted that TD and TI responses are not rigidly compartmentalized within the B-2 and MZ/B-1 cell subsets. For instance, MZ B cells also participate in TD antibody production owing to their ability to shuttle to the follicle and present antigen to T cells [40,41]. Conversely, B-2 cells can initiate TI antibody responses in the intestine [42]. Here, we discuss recent advances in our understanding of the mechanisms by which adaptive and innate immune cells provide help to B cells.

B-cell helper signals from T_H cells

Protein antigens initiate protective antibody responses in the follicles of secondary lymphoid organs, a microenvironment that favors the interaction of B and T cells with each other as well as with antigen presenting DCs and antigen exposing follicular dendritic cells (FDCs) (reviewed in [7]). After interacting with antigen through the B-cell receptor (BCR), which includes IgM and IgD (Fig. 1), naive B cells migrate to the boundary between the follicle and the outer T-cell zone [43]. At this location, B cells form dynamic conjugates with T_{FH} cells, which deliver cognate B-cell help through a mechanism involving the tumor necrosis

factor (TNF) family member CD40L and cytokines such as interferon-γ (IFN-γ, a cytokine also expressed by T_{H1} cells) and interleukin-4 (IL-4, a cytokine also expressed by T_{H2} cells) [13,14,43,44]. B cells thereafter differentiate along one of the two pathways. The follicular pathway generates Bcl6-positive germinal center B cells that further differentiate into long-lived memory B cells and plasma cells producing high-affinity antibodies, whereas the extrafollicular pathway generates Bcl6-negative blasts that further differentiate into short-lived plasma cells secreting low-affinity antibodies [14,45].

After receiving activating signals from T_{FH} cells at the border of the follicle with the T-cell zone, B cells upregulate the expression of the DNA-editing enzyme activation-induced cytidine deaminase (AID) and initiate somatic hypermutation (SHM) and class switch recombination (CSR), two Ig gene diversifying processes highly dependent on AID [46-49]. SHM introduces point mutations within V(D)J genes, thereby providing the structural correlate for selection of high-affinity Ig mutants by antigen (reviewed in [50]). By replacing constant (C) μ, and C_{δ} genes, which encode IgM and IgD, respectively, with C_{γ}, C, or C genes, which encode IgG, IgA, or IgE, respectively, CSR provides antibodies with novel effector functions without changing antigen specificity (reviewed in [51]). In humans, a noncanonical form of CSR from C_{μ} to C_{δ} has also been documented in lymphoid structures associated with the upper respiratory tract and generates B cells specialized in IgD production [52].

In addition to initiating CSR, the initial cognate interaction between B cells and T_{FH} cells leads to the differentiation of B cells into highly proliferating germinal center B cells known as centroblasts [53,54]. These cells further upregulate AID expression and complete the processes of CSR and SHM [53-55]. After exiting the cell cycle, centroblasts become centrocytes that screen antigens on the surface of FDCs using their newly hypermutated surface Ig receptors [56,57]. By binding antigen through high-affinity Igs, centrocytes become capable of processing and presenting antigen to T_{FH} cells [56,57]. These cells initiate their journey in the follicle after an initial cognate interaction with DCs in the T-cell zone [58]. Early T_{FH} cells migrate to the T-B cell border to interact with B cells and then move to the follicle after further upregulating the expression of CXCR5 ([16,59], and reviewed in [60]), a chemokine receptor that is also expressed by germinal center B cells and that senses CXCL13 produced by FDCs [9,61]. In the presence of additional follicular signals, including ICOS ligand-dependent signals provided by B cells, T_{FH} cell progenitors enter a Bcl6-dependent genetic program to become full-blown germinal center T_{FH} cells [10].

B-cell help from T_{FH} cells via CD40L, ICOS, and cytokines such as IL-21, IL-4, and IL-10 results in the survival and selection of high-affinity centrocytes, which stimulates the perpetuation of the germinal center reaction by inducing recycling of centrocytes into centroblasts, and provides signals for the differentiation of centrocytes into long-lived memory B cells and plasma cells expressing Igs with high affinity for antigen [15,17,57,62,63]. While T_{FH} cells are essential for the germinal center reaction, their number needs to be tightly controlled to avoid the emergence of low affinity and autoreactive B-cell clones. This control involves a recently identified T-cell subset named T_{FR} cells [20,21]. Although phenotypically similar to T_{FH} cells, T_{FR} cells originate from different precursors, express characteristics of regulatory T (Treg) cells such as the transcription factor Foxp3, and exert a suppressive activity on germinal center B cells and T_{FH} cells [20,21]. By controlling the number of T_{FH} cells, T_{FR} cells limit the outgrowth of nonantigen-specific germinal center B cells and optimize antibody affinity maturation. Additional control signals are provided to T_{FH} cells by plasma cells emerging from the germinal center reaction [64].

Memory B cells generated during the germinal center reaction enter the circulation and form extrafollicular aggregates in lymphoid organs [65,66]. Some of these memory B cells rapidly differentiate into extrafollicular IgG-secreting plasmablasts in response to recall antigens whereas others re-initiate the germinal center reaction [65]. Although cognate interaction of memory B cells with T_{FH} cells is likely to be required for anamnestic antibody responses, some evidence points to the existence of an alternative pathway involving antigen-independent polyclonal stimulation of memory B cells by microbial TLR ligands [67]. Unlike memory B cells, plasma cells generated during a germinal center response home to the bone marrow and populate survival niches that contain eosinophils and promote tonic release of high-affinity antibodies [68-70].

B-cell helper signals from iNKT cells

As mentioned earlier, the regulation of follicular B cells responses is not restricted to T_{FH} cells, but involves additional T-cell subsets, including iNKT cells. These cells express an invariant $V\alpha14^{+}$ T-cell receptor (TCR) that recognizes glycolipid antigens presented by the nonpolymorphic MHC-I-like molecule CD1d [71,72]. After recognizing the glycolipid α-galactosylceramide on CD1d-expressing paracortical DCs or subcapsular macrophages, iNKT cells can deliver noncognate help to B cells by inducing formation of efficient antigen presenting DCs and macrophages via CD40L and interferons [71,72]. Subsequent expansion of antigen-experienced T_{FH} cells leads to a germinal center reaction that induces moderate IgG production, affinity maturation via SHM, and immune memory [73].

More recent studies have shown that iNKT cells further help B cells in a cognate manner (Fig. 1). Indeed, a subpopulation of iNKT cells upregulates CXCR5 after interacting with glycolipids presented by B cells expressing CD1d [5]. Subsequent entry into the follicle stimulates these iNKT cells to activate the Bcl6 program and differentiate into NKT_{FH} cells that express CD40L, IL-21, and other typical T_{FH} cell-associated molecules, including ICOS and PD-1 [4,5]. The ensuing germinal center reaction induces strong primary IgG production but little affinity maturation and no immune memory [4,5]. A similar CD1d-dependent iNKT cell–B-cell interaction can occur in the extrafollicular area, but predominantly induces IgM and only some IgG production [74]. Similar to TI pathways, these iNKT cell-dependent pathways enable B cells to mount a rapid wave of IgG and IgM antibodies against pathogens.

B-cell helper signals from DCs and epithelial cells

In mucosa-associated lymphoid follicles such as Peyer's patches, B cells are less dependent on cognate help from T_{FH} cells to generate protective antibodies, perhaps because B cells can receive alternative helper signals from FDCs [75,76]. These cells release BAFF, APRIL, and retinoic acid, a metabolite of vitamin A, upon "priming" by TLR signals from commensal bacteria [76]. Intestinal FDCs also release large amounts of active TGF-β, a cytokine critically involved in IgA CSR, and utilize their dendrites to organize antigens in "periodic" arrays to trigger BCR and TLR molecules on follicular B cells more efficiently [76]. By releasing TGF-β, BAFF, and APRIL, and by antigenically stimulating antigen receptors on B cells, intestinal FDCs dramatically enhance the IgA-inducing function of T_{FH} cells. Intestinal T_{FH} cells utilize CD40L, IL-21, and TGF-β to enhance the production of noninflammatory IgA and concomitantly inhibit the production of pro-inflammatory IgG [77]. Peyer's patches may also support some IgA production through a TI mechanism [78]. In addition to IgA-inducing FDCs, Peyer's patches include TipDCs, a TNF-inducible nitric oxide synthase (iNOS)-producing DC subset that usually occupies the intestinal lamina propria [79]. These TipDCs elicit IgA production by increasing the expression of the TGF-β receptor on B cells via nitric oxide, thereby rendering B cells more responsive to IgA-

inducing signals provided by TGF-β [79]. Of note, recent findings show that IgA-secreting plasma cells acquire TipDC-like phenotypic features in the intestinal microenvironment, including expression of the antimicrobial mediators, TNF and iNOS [80]. Thus, some of the functions previously ascribed to intestinal TipDCs also involve IgA-secreting plasma cells.

Follicular B cells from Peyer's patches and mesenteric lymph nodes further undergo IgA CSR and production in response to TI signals from plasmacytoid DCs (pDCs), which release large amounts of BAFF and APRIL upon being "primed" by type I interferon from intestinal stromal cells [81]. Together with Peyer's patches and mesenteric lymph nodes, isolated lymphoid follicles represent another intestinal site for IgA induction. Isolated lymphoid follicles contain lymphoid tissue-inducer cells that release the TNF family member lymphotoxin-β upon exposure to TLR signals from commensals [42]. The interaction of lymphotoxin-β with its cognate receptor stimulates local stromal cells to release TNF and DC-attracting chemokines such as CCL19 and CCL21 [42]. By inducing DC production of matrix metalloproteases 9 and 13, TNF stimulates DCs to process active TGF-β from a latent precursor protein [42]. In the presence of TLR signals, DCs further release BAFF and APRIL, which activate a TI pathway for IgA production by cooperating with TGF-β [42].

In addition to isolated lymphoid follicles, the intestinal lamina propria contains a diffuse lymphoid tissue comprised of scattered B cells that can undergo IgA class switching and production, although less efficiently and at a lower frequency than follicular B cells (reviewed in [82,83]). This IgA production is supported by multiple subsets of lamina propria DCs that can activate B cells in a TI manner. When exposed to microbial TLR signals, lamina propria TipDCs release nitric oxide, which in turn enhances the production of BAFF and APRIL [79]. Another lamina propria DC subset with IgA-licensing function is represented by DCs constitutively expressing the flagellin receptor TLR5 [84]. These DCs express little or no TLR4 and induce TI IgA class switching and production by releasing retinoic acid and IL-6 upon sensing flagellin from commensal bacteria [84]. Also, epithelial cells deliver IgA-inducing signals to lamina propria B cells by releasing BAFF and APRIL after recognizing bacteria via multiple TLRs [38,85]. This epithelial pathway contributes to the generation of IgA2 antibodies (that are resistant to bacterial degradation) by human IgM-expressing B cells or to the generation of IgA1 class-switched B cells that derive from Peyer's patches [38].

Epithelial cells further amplify the IgA-inducing function of local DCs by releasing thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine that enhances BAFF and APRIL production by TLR-stimulated DCs [38,85]. In addition to releasing B-cell helper factors, DCs may present intact TI antigens to B cells [34]. Indeed, a subset of mucosal DCs sample bacteria from the intestinal lumen by extending dendrites through epithelial cell junctions or across transcellular pores formed by specialized epithelial cells called M cells [86-88]. An additional subset of mucosal DCs captures small molecular weight antigens across passages formed by goblet cells [89]. All these mucosal DCs may recycle unprocessed TI antigens to the cell surface to present them to B cells [90]. Considering that BAFF and APRIL also provide survival signals to plasma cells [91], the combined B-cell helper function of epithelial cells and DCs may provide an alternative pathway for the continuous production of IgA antibodies against mucosal commensal bacteria.

B-cell helper signals from neutrophils

TI Ig responses also occur in the MZ of the spleen, a B-cell area positioned at the interface between the circulation and the immune system (reviewed in [92,93]). B cells lodged in the MZ are in a state of active readiness that enables them to mount very early Ig responses to blood-borne TI antigens from pathogenic or commensal bacteria (reviewed in [92,93]).

Remarkably, blood-borne antigens stimulate the homing of DCs, as well as neutrophils, to the MZ of the spleen [3]. While the role of DCs in the activation of MZ B cells is well documented [3], the role of neutrophils remains less understood, but clearly these cells have the ability to release large amounts of innate B-cell-stimulating factors, such as BAFF and APRIL, particularly after stimulation by cytokines or microbial ligands [37,94]. Consistent with this observation, recent findings show that neutrophils occupy peri-MZ areas of the spleen in the absence of infection, recruited via a noninflammatory pathway that starts during fetal life and accelerates after birth, a time that coincides with the colonization of mucosal surfaces by bacteria [30]. The splenic microenvironment stimulates conventional neutrophils to become B-cell helper neutrophils (N_{BH} cells) through a process that involves the delivery of neutrophil reprogramming signals from splenic sinusoidal endothelial cells and possibly other cell types, including macrophages (Fig. 2). These signals include the anti-inflammatory cytokine, IL-10 [30].

In general, neutrophils are the first immune cells that migrate to sites of infection and inflammation to eliminate microbes and necrotic cells and initiate adaptive immune responses (reviewed in [95]). Remarkably, N_{BH} cells occupy peri-MZ areas of the spleen under homeostatic conditions, that is, in the absence of infection or inflammation [30]. The colonization of the spleen by N_{BH} cells correlates with postnatal deposition of microbial products that likely originate from mucosal surfaces, including lipopolysaccharide [30]. Compared with circulating neutrophils, N_{BH} cells are more activated as they express increased amounts of B-cell-stimulating molecules such as BAFF, APRIL, CD40L, and IL-21, as well as increased levels of immunostimulatory cytokines such as IL-12 and TNF [30]. However, this activation is counterbalanced by an increased expression of immune regulatory molecules, including protease inhibitors and T-cell suppressor factors such as arginase and iNOS [30].

Consistent with this phenotype, N_{BH} cells induce IgM secretion, as well as IgG and IgA CSR, by stimulating MZ B cells via BAFF, APRIL, IL-21, and possibly CD40L, at least in humans [30]. On the other hand, N_{BH} cells express T-cell-suppressive factors such as arginase and iNOS and suppress T-cell proliferation in a contact-independent manner [30]. By exerting this dual B-cell helper/T-cell suppressor function, N_{BH} cells may maximize extrafollicular B-cell responses to TI antigens while minimizing follicular B-cell responses to TD antigens and inflammation. Accordingly, N_{BH} cells are excluded from splenic follicles under homeostatic conditions, but then infiltrate follicles under inflammatory conditions, perhaps to activate T cells (Fig. 2; [30]). Remarkably, N_{BH} cells can induce SHM through a mechanism that could involve exposure of microbial TI antigens such as TLR ligands to MZ B cells [30]. This possibility is consistent with studies suggesting that MZ B cells activate the SHM machinery through a TI pathway activated by TLR ligation [27,96-100]. Additional evidence indicates that MZ B cells also undergo SHM through a typical TD pathway, which may reflect the ability of MZ B cells to deposit antigen in the follicle and activate T cells [41,101]. In mice, MZ B cells express unmutated Ig genes under steady-state conditions, but other B-cell subsets have been shown to induce SHM via a TI pathway involving TLR signaling [100,102,103].

The mechanism by which N_{BH} cells activate MZ B cells likely involves mucosal colonization by bacteria [30]. Discrete amounts of microbial products such as lipopolysaccharide undergo peri-MZ deposition soon after birth [30]. The resulting activation of TLR4 on sinusoidal endothelial cells would then cause the release of neutrophil-attracting chemokines, such as CXCL8, as well as perifollicular accumulation and activation of N_{BH} cells, some of which form postapoptotic DNA-containing cellular projections similar to neutrophil traps (NETs) [30]. In addition to exposing trapped TI antigens to MZ B cells, N_{BH} cell-derived NETs might “inject” apoptotic CpG DNA into the

peri-MZ microenvironment, thereby delivering adjuvant-like TLR signals to MZ B cells, as has been postulated for the autoimmune disease SLE [104,105]. The interaction of CpG DNA with TLR9 could then trigger survival, activation, SHM, as well as CSR, signals in MZ B cells [67,98,106,107].

In general, the crosstalk of MZ B cells with N_{BH} cells may be instrumental to enhance the generation of a second line of innate (or natural) antibody defense against systemic invasion by commensal antigens and microbes that breach first line defenses at the mucosal barrier. An insufficiency of N_{BH} cells may contribute to the pathogenesis of systemic infections by mucosal bacteria in patients with neutropenia. Conversely, harnessing N_{BH} cells may enhance vaccine-induced Ig responses to poorly immunogenic TI antigens and mucosal pathogens in healthy individuals.

B-cell helper signals from eosinophils, basophils, and mast cells

Plasma cells emerging from the germinal center reaction home to the bone marrow, a highly vascularized lymphoid compartment containing a specialized niche that promotes long-term plasma cell survival, as well as continuous plasma cell release of high-affinity antibodies into the circulation (reviewed in [108]). Although it is known to be different from the bone marrow niche sustaining early B-cell precursors, the bone marrow niche supporting plasma cells has remained poorly defined. Recent evidence shows that this niche contains eosinophils (Fig. 3), a granulocyte subset that produces APRIL and is in close contact with stromal cells that release CXCL12, a chemokine that binds to a CXCR4 receptor highly expressed by plasma cells [70]. Engagement of CXCR4 on plasma cells by CXCL12 from stromal cells stimulates plasma cells to navigate toward and colonize eosinophil-containing niches [70]. Of interest, eosinophils also express CXCR4, which would explain their ability to colocalize with stromal cells and plasma cells in the bone marrow [70]. By releasing large amounts of APRIL and the cytokine IL-6, bone marrow eosinophils facilitate the long-term survival of plasma cells [70]. This effect may be further enhanced by megakaryocytes, a platelet-generating hematopoietic cell that also releases APRIL [109].

Similar to eosinophils, mast cells have long been known for their participation in pathological allergic reactions characterized by dysregulated production of the inflammatory antibody isotype IgE (reviewed in [110]). However, a number of studies have also implicated mast cells in the development of adaptive immune responses, including antibody production by B cells [111-116]. By releasing the regulatory cytokines, IL-10 and TGF-β, mast cells also contribute to the modulation and possibly formation of Treg cells expressing the transcription factor Foxp3 [117]. In the intestine, Treg cells express CD40L, IL-10, and TGF-β and thereby promote homeostatic IgA responses by B cells while inhibiting inflammatory IFN-γ and IL-17 responses by T_{H1} and T_{H17} cells, respectively [118-120]. Furthermore, intestinal Treg cells differentiate into T_{FH} cells, which are critical for the induction of germinal centers, as well as IgA CSR and production in intestinal Peyer's patches [119]. Some Treg cells also infiltrate germinal centers to negatively regulate T_{FH} cells and this process would lead to higher affinity B-cell responses [20,21]. Finally, mast cells also directly activate B cells to induce IgA production via CD40L, IL-6, and IL-10 [121]. This activation may contribute to TI IgA responses in the intestinal lamina propria.

Basophils, an innate cell type closely related to mast cells, also deliver helper signals to B cells via both direct and indirect mechanisms (Fig. 4). Firstly, under certain circumstances, basophils can migrate to draining lymph nodes where they release IL-4 to induce the formation of T_{H2} cells, an IL-4-producing T-cell subset critically involved in the induction of protective IgG1 and IgE responses against various allergens and pathogens, including helminths [122-125]. Secondly, after secondary immunization, basophils recognize antigen

through prebound antigen-specific IgE generated during a primary immune response [126]. Antigen recognition via IgE causes upregulation of CD40L and release of IL-4 and IL-6, which provide antibody-inducing signals to B cells not only directly, but also indirectly via enhancement of IL-4, IL-6, IL-10, and IL-13 production by T_{H2} cells [112,126]. Presumably, the antigen-IgE interaction does not trigger pathological release of preformed highly inflammatory compounds, such as histamine, from basophils owing to the low affinity of IgE for antigen. It must be also noted that IgE can also bind DCs, which raises the possibility that DCs could account for at least part of the Th2-inducing activity ascribed to basophils [127].

Basophils may deliver similar B-cell helper signals by interacting with IgD (Fig. 4), an enigmatic antibody isotype released by IgD class-switched plasmablasts originating in the human upper respiratory mucosa [52,128]. In spite of being heavily hypermutated, these IgD antibodies are largely polyreactive and may afford mucosal protection by binding not only to commensals and pathogens but also to their virulence factors [52,83,129,130]. In addition to crossing the epithelial barrier to reach the surface of upper respiratory mucosal surfaces, IgD binds to circulating basophils, monocytes, and neutrophils, as well as mucosal mast cells, via an unknown receptor [52]. Crosslinking of prebound IgD induces basophil release of BAFF, IL-4, and IL-13, which in turn stimulate B cells to undergo IgM production, as well as CSR to IgG and IgA, in a TI manner [52]. CD40L and APRIL further help the activation of B cells by IgD-activated basophils [52]. Thus, basophils may utilize both prebound IgE and IgD as immune amplifiers of both systemic and mucosal B-cell responses.

Conclusions

T_{FH} cells, T_{FR} cells, NKT_{FH} cells, and Treg cells play a pivotal role in TD antibody responses against microbial proteins. A finely tuned division of labor between these T-cell subsets regulates the activation, expansion, diversification, selection, and survival of B cells engaged in TD antibody responses at different lymphoid sites and at different times after immunization or infection. Thus, while T_{FH} and NKT_{FH} cells are clearly essential to support IgG responses in systemic lymphoid follicles, other T-cell subsets such as Treg cells are crucial to initiate IgA responses in mucosal lymphoid follicles. The stimulating signals provided by T_{FH} cells and NKT_{FH} cells to germinal center B cells are counterbalanced by inhibitory signals provided by T_{FR} cells. These cells are critical to select germinal center B cells with optimal affinity for antigen and may also influence the decision of germinal center B cells to differentiate along either plasma cell or memory B-cell pathways. Plasma cells and memory B cells generated by the germinal center reaction require additional helper signals from eosinophils and possibly basophils to extend their lifespan in postgerminal center niches. Finally, the generation of short-lived plasmablasts during natural or postimmune B-cell responses to TI antigens such as microbial carbohydrates and glycolipids involves multiple subsets of myeloid and plasmacytoid DCs, FDCs, epithelial cells, neutrophils, basophils, and mast cells, particularly in the MZ of the spleen and at mucosal sites.

The identification of novel helping partners for B cells opens up novel avenues for therapeutic intervention. In addition to harnessing the power of DCs and T_{FH} cells, vaccines may need to target NKT_{FH} cells, T_{FR} cells, granulocytes, and mast cells to optimize the quantity, quality, and lifespan of antibodies produced by systemic and mucosal B cells. Conversely, inhibiting helper signals from DCs, T_{FH} cells, NKT_{FH} cells, granulocytes, and mast cells may be useful to dampen the production of pathogenic antibodies by autoreactive B cells and plasma cells that appear in autoimmune disorders.

Abbreviations

AID	activation-induced cytidine deaminase
CSR	class switch recombination
MZ	marginal zone
NK	natural killer
SHM	somatic hypermutation
TI	T-cell-independent
TD	T-cell-dependent

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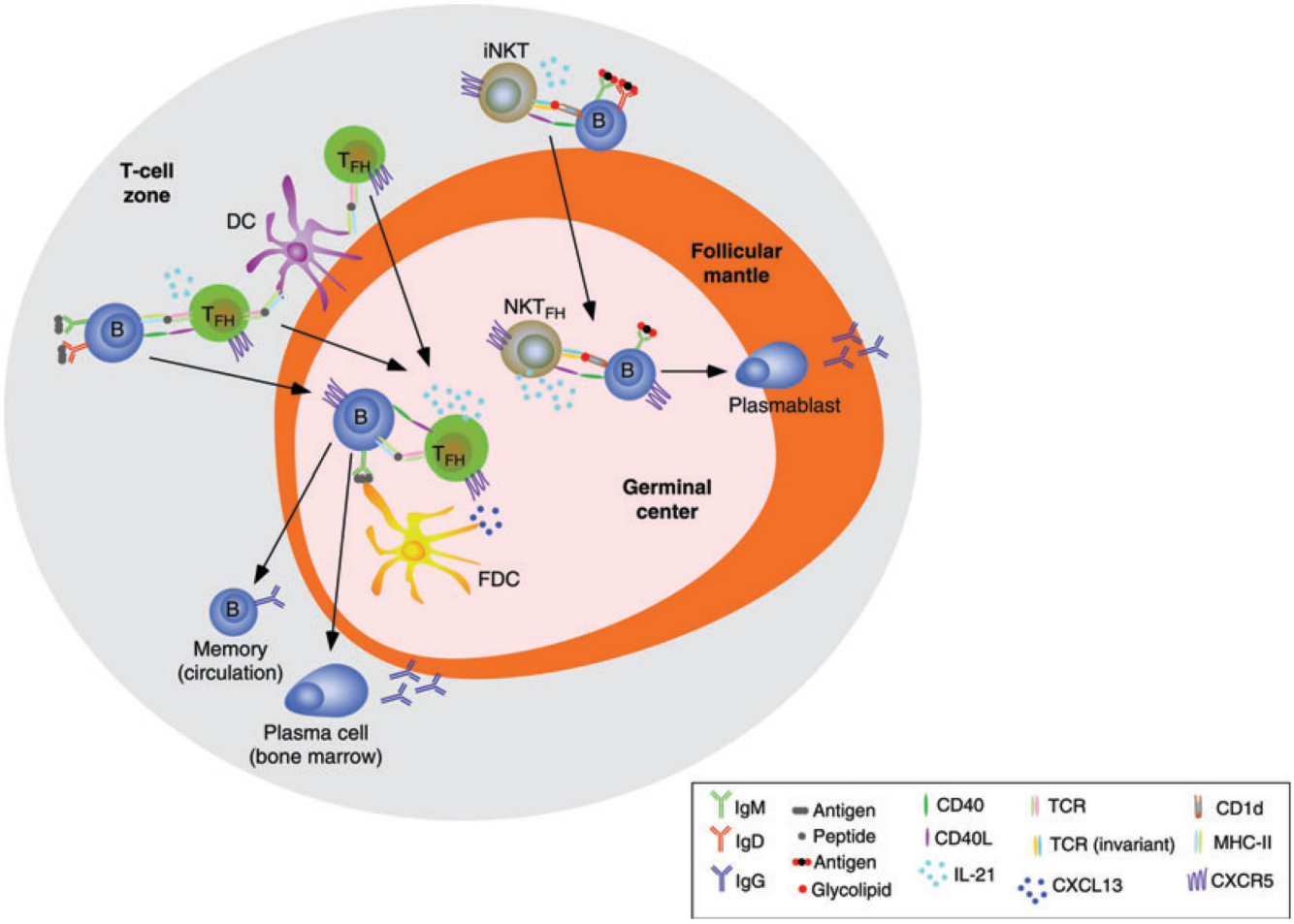

Figure 1.

T_{FH} cells and NKT_{FH} cells provide help to germinal center B cells. Cognate interaction of T_{FH} cells with DCs and B cells induces migration of T_{FH} cells and B cells to the germinal center of the follicle under the influence of CXCL13, a CXCR5 ligand released by from FDCs. Cognate interaction of iNKT cells with B cells induces a similar effect, leading to the differentiation of iNKT cells into NKT_{FH} cells. Interaction of B cells with T_{FH} cells involves internalization and processing of a protein antigen via the BCR (IgM or IgD), followed by presentation of a peptide–MHC class II complex to the TCR on T_{FH} cells. Interaction of B cells with iNKT cells involves presentation of a CD1d-bound soluble glycolipid such as α-galactosylceramide to an invariant TCR on iNKT cells. In this interaction, B cells also recognize an α-galactosylceramide-containing antigen via the BCR. The ensuing activation of a Bcl6-dependent maturation program causes upregulation of IL-21 expression in both T_{FH} cells and NKT_{FH} cells. By expressing CD40L, IL-21, and other B-cell-stimulating cytokines, T_{FH} cells sustain a germinal center reaction that involves induction of CSR from IgM to IgG as well as elicitation of SHM in B cells, followed by generation of high-affinity and long-lived memory B cells and plasma cells. Memory B cells enter the circulation, whereas IgG-secreting plasma cells are home to the bone marrow. Unlike T_{FH} cells, NKT_{FH} cells trigger a germinal center reaction characterized by induction of IgG CSR with little or no affinity maturation and generation of memory B cells. Instead, NKT_{FH} cells elicit the formation of short-lived IgG-secreting plasmablasts.

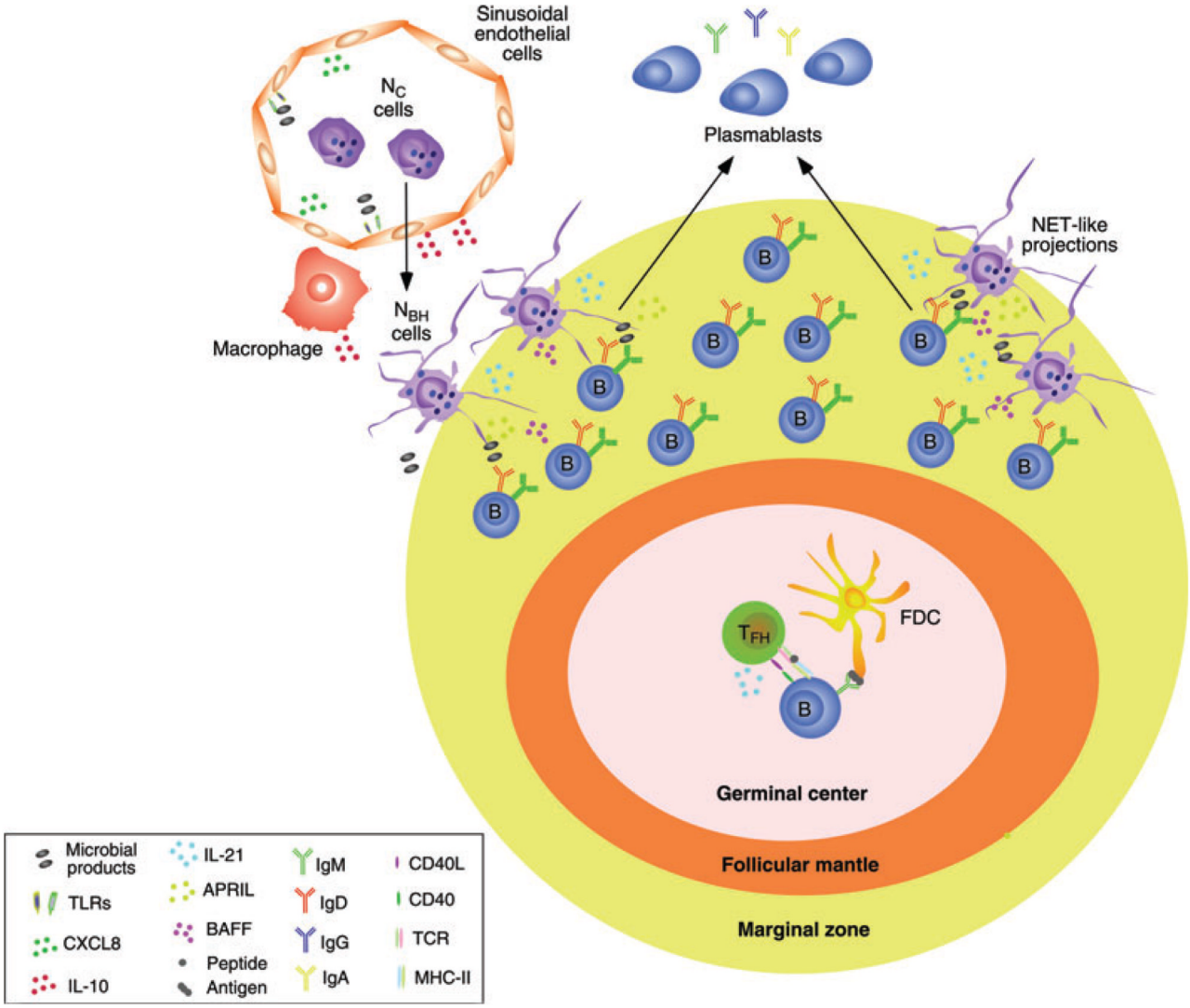

Figure 2.

Neutrophils provide help to splenic MZ B cells. Splenic sinusoidal endothelial cells sense microbial products, including commensal antigens from mucosal surfaces, via TLRs. The ensuing release of chemokines such as CXCL8 (IL-8) enhances the migration of conventional circulating neutrophils (N_C cells) to perifollicular areas of the spleen. Further release of cytokines such as IL-10 by perifollicular sinusoidal endothelial cells and macrophages stimulates the reprogramming of N_C cells into B-cell-helper neutrophils (N_{BH} cells). N_{BH} cells trigger CSR from IgM to IgG or IgA as well as moderate levels of SHM (at least in humans) and differentiation of plasmablasts by activating a subset of MZ B cells through BAFF, APRIL, and IL-21. Antigen trapped on the surface of NET-like structures emanating from N_{BH} cells might further increase the activation of MZ B cells by binding to the BCR (IgM or IgD) and TLRs. The interaction of N_{BH} cells with MZ B cells facilitates the formation of an innate repertoire of IgM, IgG, and IgA antibodies to provide a fast second line of defense against systemic invasion by microbes, including bacteria breaching the mucosal barrier.

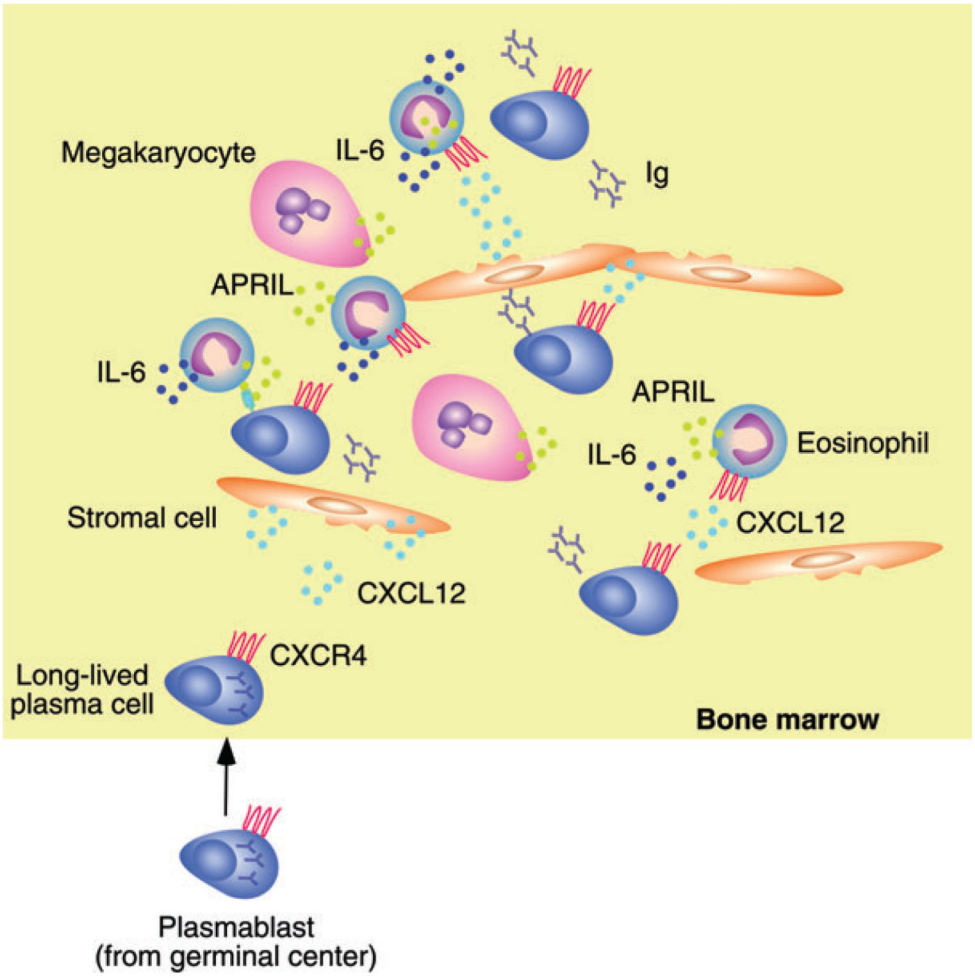

Figure 3.

Eosinophils provide help to bone marrow plasma cells. Plasma cells emerging from the germinal center reaction upregulate the expression of the chemokine receptor CXCR4 and home to the bone marrow in response to CXCL12, a chemokine released by bone marrow stromal cells. By expressing CXCR4, eosinophils home to the same bone marrow niche occupied by plasma cells. APRIL and IL-6 release by eosinophils enhances the survival of Ig-secreting plasma cells. A similar effect is induced by megakaryocytes through the release of APRIL.

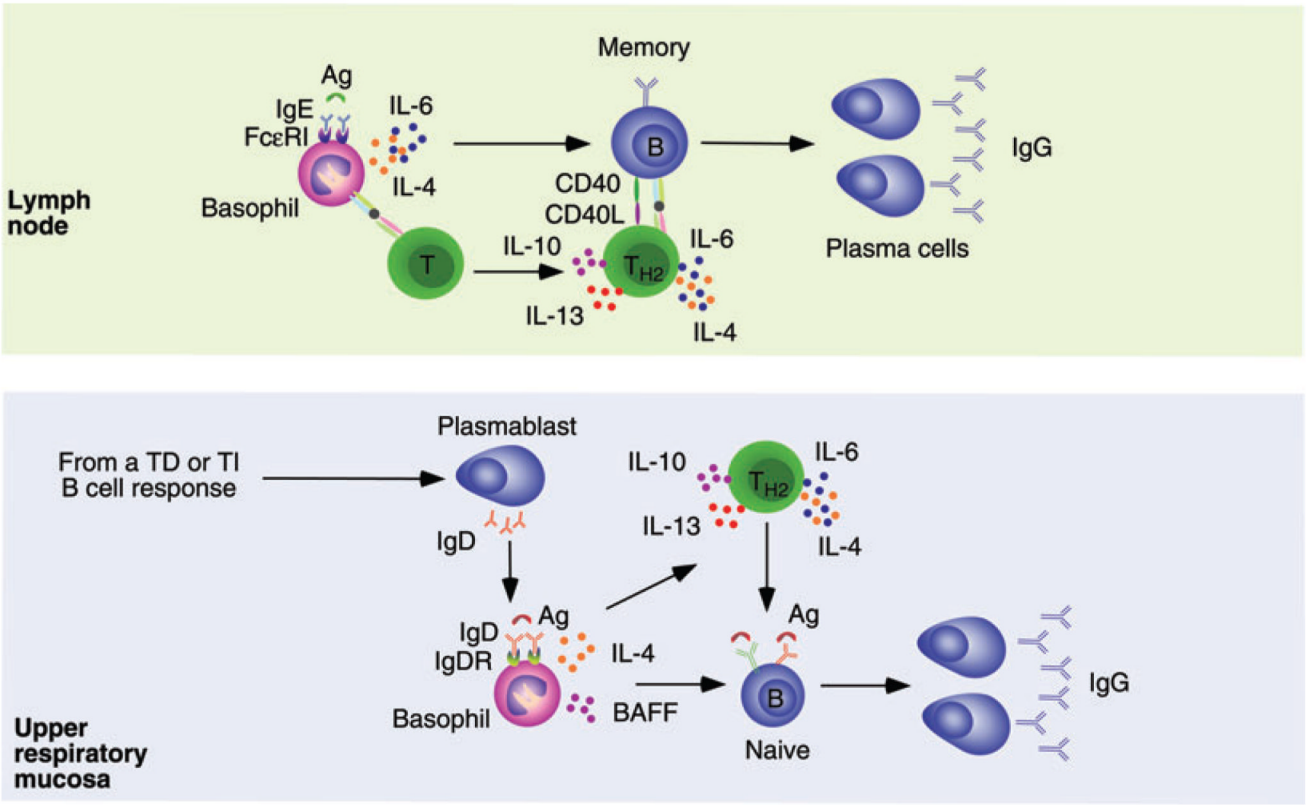

Figure 4.

Basophils provide help to lymph node and mucosal B cells. *Upper panel.* Basophils bind to IgE generated during a primary immune response through a high-affinity receptor named FcRI. In a secondary immune response, binding of recall antigen to IgE via either conventional or unconventional mechanisms triggers basophil release of IL-4 and IL-6, which enhances the conversion of naïve T cells into T_{H2} cells secreting IL-4, IL-6, IL-10, and IL-13. Together with CD40L, these cytokines enhance the activation and expansion of IgG-expressing memory B cells in the context of a cognate interaction that leads to the generation of IgG-secreting plasma cells. Basophils may further enhance the activation of memory B cells by delivering helper signals independently of T cells. *Bottom panel.* B cells from the human upper respiratory mucosa undergo noncanonical CSR from IgM to IgD by following either TD or TI pathways. This process leads to the formation of mucosal and circulating plasmablasts that secrete IgD antibodies reactive against respiratory bacteria. Mucosal IgD would enhance local immunity and homeostasis after translocating across epithelial cells, whereas circulating IgD binds to basophils via an unknown receptor (IgDR). In addition to delivering rapid innate responses and alerting the immune system as to the presence of invading bacteria, basophils exposed to IgD-reactive antigens may enhance immune responses in both systemic and mucosal lymphoid organs. These basophils enhance IgG (but also IgA) CSR and antibody production by activating B cells via BAFF, IL-4, and other B-cell-activating factors, including CD40L and APRIL (not shown). Similar to IgE-stimulated basophils, IgD-stimulated basophils might further enhance the local antibody response by promoting the formation of T_{H2} cells via IL-4.