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# The Shaping of a B Cell Pool Maximally Responsive to Infections

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## Keywords

antibodies, B cell subsets, B cell repertoire, extrafollicular responses, germinal centers, host-pathogen interaction, immunity, extrafollicular foci

## Abstract

B cell subsets differ in development, tissue distribution, and mechanisms of activation. In response to infections, however, all can differentiate into extrafollicular plasmablasts that rapidly provide highly protective antibodies, indicating that these plasmablasts are the main humoral immune response effectors. Yet, the effectiveness of this response type depends on the presence of antigen-specific precursors in the circulating mature B cell pool, a pool that is generated initially through the stochastic processes of B cell receptor assembly. Importantly, germinal centers then mold the repertoire of this B cell pool to be increasingly responsive to pathogens by generating a broad array of antimicrobial memory B cells that act as highly effective precursors of extrafollicular plasmablasts. Such B cell repertoire molding occurs in two ways: continuously via the chronic germinal centers of mucosal lymphoid tissues, driven by the presence of the microbiome, and via de novo generated germinal centers following acute infections. For effectively evaluating humoral immunity as a correlate of immune protection, it might be critical to measure memory B cell pools in addition to antibody titers.

## B CELLS ARE INTEGRAL COMPONENTS OF THE DEFENSE AGAINST PATHOGENS

**Germinal center (GC):** focus of proliferating B cells, CD4 Tfh cells, and FDCs in the center of lymphoid follicles; generates MBCs and plasma cells

**B-1 cell:** a B cell generated mostly during early B cell development in the fetus and neonate; maintained by self-renewal

**B-2 cell:** B cell developing after birth through de novo synthesis from bone marrow precursors; includes follicular and marginal zone B cells

**Transitional B cell:** B cell migrating from the bone marrow to the spleen prior to differentiation into follicular or marginal zone B cell

The immune system limits invasion of a host by microbes. When invasion cannot be avoided, the immune system integrates various cellular and humoral components to orchestrate a complex set of responses, both innate and adaptive. Successful immune responses result in the elimination of the pathogen and the development of long-lasting immunity that prevents reinfections. B cells are critical components of this orchestrated response, strengthening immune-mediated barriers to prevent infections, eliminating pathogens that have overcome these barriers, and providing immunological memory that either prevents another infection or reduces the impact of a repeat infection on the host. B cells contribute to immunity by continually generating antibodies, modulating the inflammatory response by secreting cytokines, and acting as antigen transporters in lymphoid tissues and/or as antigen-presenting cells to CD4 T cells.

Germinal center (GC) responses are considered the major drivers of B cell–mediated protective immunity. Their formation can result in the generation of antibodies with higher binding affinities for their cognate antigens than those of the original B cell clone entering the response, and they are considered critical for pathogen elimination. However, many infections are cleared even before GCs form, and evidence linking high-affinity interactions with better resolution of infection is surprisingly scant. This review discusses the development and distribution of B cell subsets and the events leading to their activation and responses to infections. I argue that the extrafollicular responses of B cells are the primary drivers of humoral immunity, while GCs shape the initially stochastically developed peripheral B cell pool into more appropriately focused and pathogen-responsive cells (**Figure 1**). This occurs continuously through interaction with the microbiome in GCs that persist in lymph tissues draining mucosal tissues, but it also occurs in response to acute infections. The infection signals provided to the existing B cell pool drive extrafollicular effector responses and induce GCs to further mold the B cell repertoire, using the invading pathogen as a blueprint.

## B CELL DEVELOPMENT AND DISTRIBUTION

B cells develop in multiple waves throughout ontogeny, beginning to form from extrahematopoietic precursors in the yolk sac as early as embryonic day E7 and then from hematopoietic precursors residing in the fetal aorta-gonad-mesonephros region (splanchnopleure), the fetal liver, and eventually the postnatal bone marrow (1). The earliest populations of fetus-derived B cells are mainly B-1 cells, which differ in repertoire and function from the later, predominantly postnatal-developing, B-2 cells (2–4). Some of the fetus-derived B-1 cells are maintained into adulthood, but whether the distinct waves of prenatal development result in B-1 cells of distinct functions is unknown.

While transfer of the bacterial microbiota or bacterial pathogens from mother to fetus is unlikely, given the strong maternofetal barriers (5), viral infections of a fetus can occur. Indeed, recent studies demonstrated a progressively diverse repertoire of fetal B and T cells during development, with B cells preceding T cell development. B cells are already circulating in the fetal blood by about week 12 of gestation in the human (6), and de novo fetus-derived IgM responses to viral infections have been measured in fetuses by week 24. Thus, the earliest developing fetal B cells can respond to external insults not prevented by the existing anatomical barriers.

The bone marrow takes over as the site of continued hematopoiesis beginning shortly after birth. Following the release of B cells that are selected against strong self-recognition, from the bone marrow into the blood, these transitional B cells enter the spleen. In the spleen, they undergo

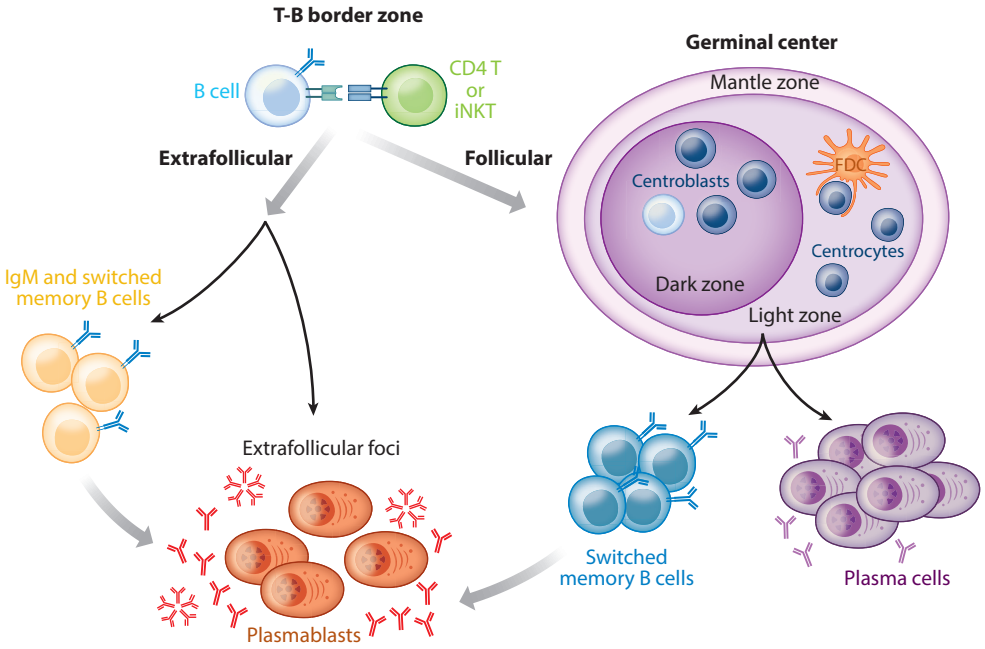



**Figure 1**

B cell responses to infections. Activation of antigen-specific B cells results in their accumulation in the T-B border zone of lymphoid tissue, where they receive costimulatory signals through interaction with CD4 T cells or iNKT cells via classical or nonclassical MHC interactions, respectively. Costimulation may also occur in a noncognate manner through secretion of cytokines. Based on the quality of these signals, B cells will remain outside the follicle or reenter the follicles to start GC responses. B cells can regain quiescence as switched or nonswitched MBCs, or they rapidly differentiate into antibody-secreting plasmablasts forming EFs, which are major sources of antibodies early in infection. GCs facilitate the shaping of the responding B cell clones through clonal expansion and introduction of high numbers of mutations in the antigen-binding sites of the B cell receptor and subsequent selection of effective antigen binders that interact productively with T cells. In contrast to extrafollicular MBCs, GC-derived MBCs provide a diversified source of responders that can feed into the EF response. Alternatively, B cells leave already programmed for terminal differentiation into antibody-secreting plasma cells. Abbreviations: EF, extrafollicular focus; GC, germinal center; iNKT, invariant natural killer T; MBC, memory B cell.

another selection process that results in the further elimination of autoreactive B cells (7). Selected B cells then mature into either spleen-resident marginal zone B (MZB) cells, a process requiring NOTCH and ADAM10 signaling, or mature follicular B (FOB) cells (8–10). The positioning of MZB cells adjacent to the splenic marginal sinus, where arterial blood enters the white pulp, places these cells into immediate contact with any circulating pathogens or their components (11). FOB cells instead home to the lymphoid follicles. B cell migration to and positioning within the follicles are guided by the chemokine receptor-ligand pair CXCR5/CXCL13 and the receptor EBI2 (GPR183) and its ligand, 7α,25-dihydroxycholesterol (12). The latter organizes the follicle into inner and outer zones. FOB cells and most MZB cells derive from the same bone marrow precursors postnatally and are thus considered the later-developing B-2 cells, although a subset of MZB cells appears to develop during early fetal development and to be maintained by self-renewal (13).

FOB cells recirculate via the blood between follicular regions of secondary lymphoid tissues, including those of the spleen and lymph nodes and Peyer's patches. The latter are located in the

**Marginal zone B (MZB) cell:** B cells residing in the spleen marginal zone adjacent to the marginal zone sinus; highly responsive to PAMPs and DAMPs

**Follicular B (FOB) cell:** B cell circulating between blood and B cell follicles of lymph tissues; FOB cells make up the majority of the peripheral B cell pool

small intestine and contain chronic GCs (14). While in circulation, they can also accumulate in the vasculature of a number of organs. There, the interaction of B cells with the endothelium may contribute to the regulation of leukocyte composition of the tissue and imprint onto the localized B cell population a distinct transcriptional profile (15). Alterations in the interaction of B cells with the endothelium can also contribute to the modulation of disease processes of the vasculature, such as observed in atherosclerosis (16). Remarkably little is known about the interaction of B cells with the endothelium at sites of infection-induced inflammation. However, B cells and perhaps plasmablasts and terminally differentiated plasma cells can migrate to these tissues, where they secrete large quantities of antibodies (17). Interestingly, a subset of plasma cells with features of B-1-derived plasma cells (B-1PCs) also acts as a source of IL-10 (18, 19). Depending on the organ, formation of tertiary lymphoid structures that support B cell activation and differentiation can lead to local differentiation to memory B cells (MBCs) or long-lived plasma cells (LLPCs), as has been reported for the lung (20–22). Little is known about the role of IL-10-producing regulatory B cells in infections, which have been studied mainly in the context of inflammation and autoimmunity. We refer to recent reviews on these cells (23–25).

Plasma cells are particularly numerous in the lamina propria of mucosal tissues that are exposed to and colonized by the microbiota. They regulate the microbiota, mostly through secretion of dimeric IgA that is transported by epithelial cells with the help of the polymeric immunoglobulin receptor to the luminal site of the mucosa (26). Indeed, colonization by the microbiota is a prerequisite for their presence (27, 28). Interestingly, the plasma cells in the skin are predominantly IgM-secreting cells, whose presence appears to be independent of microbial exposure (29), consistent with systemic natural IgM production (30). Enhanced plasma cell accumulation is also seen in instances of chronic tissue inflammation, such as in endometriosis, arthritis, myositis, and granulomatous skin inflammation (29, 31), as well as in classic granulomas forming in the lungs after infection with *Mycobacterium tuberculosis* (22), to name but a few. Thus, plasmablast and plasma cell responses provide a localized effector arm of humoral immunity.

B cells are also present in the pleural and peritoneal cavities, accumulating there in a process that requires CXCL13 (32). B-1 cells are the dominant B cell subset, although conventional B cells are present also (2). B-1 cells begin to accumulate in the cavities at about two weeks after birth, following their initial expansion in the spleen. B-1 cells are highly sensitive to innate stimuli and function as sentinels. In response to infection-induced innate stimuli, such as type I interferon or Toll-like receptor (TLR), they rapidly migrate from the cavities to the regional secondary lymphoid tissues, where they differentiate into antibody- or cytokine-secreting B-1 cells or B-1PCs (33–36). The role of the body cavity B-2 cells, which are imprinted to express a B cell receptor (BCR) repertoire and transcriptional profiles distinct from that of FOB cells in secondary lymphoid tissues, has not been sufficiently explored (37).

In addition to supporting the development of B cells from hematopoietic stem cells, the bone marrow harbors terminally differentiated LLPCs that develop from activated B cells in response to infections. Their migration to and retention in the bone marrow require their expression of the chemokine receptor CXCR4 and the secretion of the ligand CXCL12 (SDF-1) by bone marrow stromal cells. The stromal compartment of the bone marrow provides plasma cells with a survival niche in which LLPCs secrete antibodies for extended periods (38). Another site of plasma cell accumulation is the splenic red pulp. In contrast to bone marrow LLPCs, splenic plasma cells appear to be mostly short-lived. Despite intensive research, it remains unknown whether the difference between LLPCs and short-lived plasma cells (SLPCs) is due to the differences in the survival niches they occupy or due to any cell-intrinsic differences (39).

B cells are most numerous in secondary lymphoid tissues, but they circulate continuously throughout the vasculature and even through tissues and are broadly distributed throughout the

**Plasmablast:** rapidly proliferating, antibody-secreting cell expressing Blimp-1 and high levels of IRF4; can develop from extrafollicular or germinal center responses

**Plasma cell:** terminally differentiated short-lived or long-lived B cell secreting large quantities of antibody; most of the latter reside in the bone marrow

**Memory B cell (MBC):** clonally expanded, antigen-experienced, non-immunoglobulin-secreting, class-switched or nonswitched B cells; develop from extrafollicular or germinal center responses

**Polymeric immunoglobulin receptor:** surface receptor of mucosal epithelial cells that binds to and transports multimeric IgA and IgM onto mucosal surfaces

body. Their migration into secondary lymphoid tissues is controlled through chemokine and integrin-mediated processes, while their migration from lymph tissues into efferent lymphatics and blood is critically regulated by signaling through the sphingosine-1-phosphate receptor S1PR in processes that are similar between B and T cells (40–42). The presence of B cells in the afferent lymphatics, albeit fewer in number than T cells, further suggests their continuous entry and exit also from solid tissues, even in the steady state (43, 44). Physiological triggers, such as microbiota colonization on mucosal surfaces, as well as pathological triggers of chronic inflammation result in the local accumulation of B cells and plasma cells. Overall, these findings indicate that B cells contribute to immunity against pathogens not only through the systemic secretion of antibodies but also as active participants of local tissue surveillance.

**Subcapsular sinus (SCS) macrophage:** $CD169^+$ macrophage in SCS of lymph nodes; captures antigen for presentation to B cells in SCS underlying outer follicular areas

**Follicular dendritic cell (FDC):** differentiated lymph epithelial cell in the follicles of lymph tissue; critical for antigen presentation to B cells in germinal centers

## CANONICAL B CELL RESPONSES TO INFECTIONS

### Antigen Delivery to the B Cell Follicles

Natural infections occur mostly via the large mucosal surfaces of the gastrointestinal and respiratory tracts and less frequently through the reproductive tract or via breaches of the skin barrier. What follows infection is a rapid orchestration of local immune responses that initially involve mostly innate cells but can involve tissue-resident memory B cells (MBCs) and memory T cells when they are present due to a prior insult. The presence of local MBCs has been associated with increased protection (45, 46), as seen previously for tissue-resident T cells (47). In addition, and critical for the initiation of a strong immune response, dendritic cells (DCs) and macrophages carry pathogen-derived antigens via the afferent lymphatics to the local draining lymph nodes. Pathogens, whole or in part, can also arrive in the lymph nodes as free antigens. Lymph nodes are designed to filter these antigens, preventing pathogens from spreading beyond the area of the locally affected tissue. When local lymph node filter functions are insufficient, antigen will enter the blood and reach the spleen. The white pulp of the spleen is structured similarly to lymph nodes but filters blood-borne antigens and pathogens.

Conventional cells, or FOB cells, are the most numerous B cell subset in lymph nodes and in the spleen. The phenotype of FOB cells is characterized by high expression of the IgD-BCR, varied expression of the IgM-BCR, intermediate expression of the complement receptor CD21, and expression of CD23 (48). B cells are antigen-presenting cells equipped with antigen-binding BCRs. The unique structure of the lymph tissue follicles strongly supports B cell antigen encounter. Antigen delivery can occur through afferent lymphatics that shunt small antigens into the porous conduit system that emanates from the sinuses and traverses the follicles (49). In lymph nodes, afferent lymphatics drain into the subcapsular sinus (SCS), where $CD169^+$ F4/80- SCS macrophages are located at the floor and onto which antigens larger than those traveling through the conduit system (>70 kDa), or antigen-antibody complexes, can adhere (50). SCS macrophages are critical for displaying nonprocessed antigens to B cells in the follicular outer areas, which are rich in 7α,25-dihydroxycholesterol and underlie the SCS floor, and into which the SCS macrophages stretch their antigen-covered processes (40, 51). FOB cells do not have to be antigen-specific to acquire antigen. They can bind complement-tagged antigens and/or antigen-antibody complexes via their complement receptors and then transport and deliver the antigen to lymph tissue stromal cells termed follicular dendritic cells (FDCs) (51). FDCs in turn can then present the antigen to antigen-specific FOB cells located in the center of follicles, supporting the establishment and maintenance of GCs.

Similarly, arteriolar blood–derived antigens pool in the splenic MZ sinus adjacent to the white pulp of the spleen. Here, antigen uptake is facilitated in part by resident MZB cells, which can shuffle between the MZ and the follicle, transporting nonprocessed antigens to FDCs, which then

present those antigens to FOB cells (52–54). FDCs are critical participants of antigen-specific B cell responses, as their presence in the follicle and their ability to display antigen-antibody complexes for extended periods are required for successful initiation and maintenance of GC responses, considered hallmark T-dependent B cell responses (55–58). FDCs are part of the stromal cell network of secondary lymphoid tissues and are derived from perivascular endothelial cell precursors (59). Interestingly, FDC precursors are present throughout the vasculature, and upon signals from inflammatory cytokines such as lymphotoxin and TNF, they can differentiate into FDCs, explaining the establishment of tertiary lymphoid tissues at local sites of chronic inflammation or infection (59).

Some infections result in the dissolution of the normal lymphoid tissue organization and structure, disrupting the proper functioning of these organs, including the appropriate positioning of cells for antigen capture, antigen presentation, and antigen-specific CD4 T cell–B cell interactions. Following infection with *Salmonella enterica* Typhimurium, such changes depend on lipopolysaccharide (LPS)-mediated stimulation via TLR4, which results in reduced production of CCL21, the chemokine responsible for the organization of the lymph tissue T cell zone (60). Similar disruption of the lymph node structures with dissolution of T cell zones and B cell zones was also observed in response to infection of mice with *Borrelia burgdorferi*, although these alterations were independent of MyD88 and TRIF, and thus of TLR signaling (61, 62), as well as following infection with *Toxoplasma gondii* (63).

## Follicular B Cell Activation

The frequency of antigen-specific FOB cells prior to a primary infection has been estimated to be in the order of 1 cell in $2 \times 10^5 - 1 \times 10^6$ cells (64). The efficient and varied modes of antigen delivery to secondary lymphoid B cell follicles outlined above are critical, as they increase the likelihood that these rare antigen-specific B cells will rapidly encounter and bind their cognate antigen. Important for the understanding of B cell response regulation, cognate antigen recognition initially occurs in the inflammatory milieu generated in response to an infection. For example, direct type I interferon signaling strongly affects B cells early during viral infections, prior to cognate T cell–B cell interaction (65–67). This cytokine induced the upregulation of many interferon-regulated genes in B cells. For example, type I interferon signaling enhances expression of CD69, which can trap B cells in the draining lymph nodes (68); induces the upregulation of the endosomal TLR3 and TLR7, thereby enhancing responsiveness of B cells to internalized pathogen-associated molecular pattern (PAMP)-containing antigens; and increases surface expression of the costimulatory molecule CD86, driving the activation and differentiation of B cells following cognate interaction with T cells (65, 66, 69). Lack of type I interferon–dependent direct signals reduces B cell activation, IgG production, and plasma cell differentiation following influenza virus infection (65–67). Type I interferon, as well as other inflammatory stimuli, also induces various cells, including epithelial cells, monocytes, DCs, and neutrophils, to secrete B cell–activating factor (BAFF, or Tnfsf13b) (70, 71). BAFF is a critical B cell survival factor required for the maintenance of B cells beyond the transitional stage 1 of development (72). Enhanced secretion of BAFF by innate leukocytes supports the development of neutralizing antigen-specific B cell responses during infection, as recently shown for infection with West Nile virus (73).

These findings are significant, as they indicate that in vivo B cell activation is achieved through a diverse array of signals that include but are not limited to BCR signaling and costimulation by T cells. While T cell responses have long been appreciated to require polarizing signals for differentiation into appropriate effector CD4 T cell subsets (Th1, Th2, etc.), much less is known about how innate signals may drive distinct differentiation pathways in B cells. Yet, class-switch

recombination (CSR) is determined by the cytokine milieu in which B cells are placed, and polarization of B cells similar to that observed in CD4 T cells can similarly be achieved (74). This was further demonstrated by the identification of B cells expressing the Th1-polarizing transcriptional regulator T-bet in various infections (see the section titled Extrafollicular Effector and Memory B Cells).

**T-B border zone:** the area between the T cell zone and B cell follicle in which T and B cells move after priming

Recognition, i.e., binding of cognate antigens to the BCRs of FOB cells, triggers classic adaptive B cell responses by inducing a complex BCR signaling cascade that results in (*a*) BCR signalosome reorganization and antigen internalization, (*b*) endosomal reorganization causing the loading of internalized antigen into MHC-II, (*c*) transcriptional changes associated with enhanced B cell survival and B cell entry into the cell cycle for clonal expansion, (*d*) relocation of FOB cells from follicles to the T-B border region, and (*e*) upregulation of MHC-II, costimulatory molecules, and chemokines that support productive interaction of B cells with CD4 T cells (75). At the same time, CD4 T cells are activated by antigen-presenting DCs in the T cell zones of the same secondary lymphoid tissues. Their activation results in the upregulation of CXCR5, supporting their migration toward the B cell zone and into the T-B border. Their expression of EBI2, the receptor for 7α,25-dihydroxycholesterol, further helps to position activated CD4 T cells into the outer T cell area in the vicinity of CD25-expressing DCs (76). DC-expressed CD25, the high-affinity IL-2 receptor, is thought to compete for access to IL-2, a cytokine known to inhibit T follicular helper (Tfh) development. Subsequent interaction of these T cells with B cells via ICOSL and CD40 together with antigen-specific activation via TCR-peptide MHC-II complexes of B cells supports Tfh differentiation as well as initiates T cell–dependent B cell responses.

T and B cells may recognize distinct peptides derived from the same pathogen, due to the linked recognition of conjugate antigens by the B cell and then subsequently by CD4 T cells following presentation of another epitope of that protein within MHC-II. Interestingly, a recent study on the HIV glycoprotein gp120 demonstrated that CD4 T cells may not only recognize the peptide backbone of a protein but also engage with an MHC-II-presented glycosylated peptide, where the nature of the glycosylation determines antigen recognition (77). The data thus expand the universe of potential pathogen-derived antigens that can generate T cell–dependent B cell responses to include glycoproteins. Small viruses may engage and be internalized in toto by B cells through their BCRs, which could lead to antigen presentation of many distinct viral antigens to T cells, independent of the epitope specificity of the B cell. Indeed, studies on the small, enveloped, and negative-strand RNA virus influenza A demonstrated that IgG responses to the surface hemagglutinin (HA)-spike protein are dependent on CD4 T cells, but support was similarly provided by CD4 T cells specific for the intraviral nuclear capsid or matrix protein (78). However, larger viruses as well as most bacteria and protozoa may not be taken up intact by B cells, unless they are the targets of pathogen infection. In a series of elegant studies, Sette and colleagues (79) defined parameters of epitope recognition and antigen immune prevalence and immunodominance by CD4 and CD8 T cells by studying immunogenic peptides and antigens of vaccinia virus, a relatively large pathogen that contains over 200 open reading frames. They demonstrated that the generation of antibodies to a vaccinia virus antigen correlates strongly with the presence of CD4 T cells of that same specificity (80). Furthermore, enhanced presence of antigen-specific CD4 T cells does not boost a specific B cell response, unless the CD4 T cells are specific for the same viral proteins as the B cells (80). The strong correlation between B cell and CD4 T cell specificity is further underscored by findings that B cells selectively expand CD4 T cells of the same specificity (81 and references therein).

Following antigen uptake, FOB cells upregulate CCR7 and migrate to the T-B border zone, where they secrete CCL4, a chemoattractant for CD4 T cells (82). CD4 T cells migrate to the same region following their upregulation of CXCR5 in response to priming by DCs in the T cell

zone (83). The initial CD4 T cell–B cell interactions in the border region are critical. They induce further expansion of B cells through cell-cell interaction via MHC-II–TCR, CD86-CD28, ICOSL-ICOS, and CD40-CD40L. The latter supports B cell survival and proliferation and induces expression of the enzyme activation-induced cytidine deaminase (AID), encoded by the gene *aicda* and critical for CSR (84). Induction of AID further supported by secretion of cytokines such as IL-4 and IFN-γ provides early signals directing the isotype profile of the antibody response (85, 86). Similarly, the interaction of CD4 T cells with B cells drives the polarization of the T cells toward a Tfh cell fate (87). Through continued engagement of CD4 Tfh cells with B cells, a process that requires expression of signaling lymphocyte activation molecule–associated protein (SAP) (88), the further fate of the B cells is determined.

**Activation-induced cytidine deaminase (AID):** enzyme required for immunoglobulin class-switch recombination and somatic hyperaffinity maturation; encoded by the gene *aicda*

**Invariant natural killer T (iNKT) cell:** $CD4^+$ αβ T cell expressing a highly limited TCR repertoire binding to lipids presented in CD1d; recognizes α-galactosylceramide

**Extrafollicular focus (EF):** cluster of rapidly developing and short-lived extrafollicular plasmablasts; development is T cell dependent or independent

In addition to harboring activated CD4 T cells and B cells, the T-B border zone also contains innate-like lymphocytes such as innate lymphoid cells (ILCs) and invariant natural killer T (iNKT) cells that can interact with B cells. iNKT cells express an invariant αβ TCR that recognizes the canonical glycolipid α-galactosylceramide presented within the nonclassical MHC-I molecule CD1d, expressed by B cells and other antigen-presenting cells (89). While mice only express one CD1 allotype (CD1d), humans harbor additional allotypes (CD1a–CD1e) that can present various glycolipids to a more diverse repertoire of NKT cells (90). Many bacterial pathogens express glycolipids. Studies on *Streptococcus pneumoniae* and *B. burgdorferi* have demonstrated the importance of iNKT cells in supporting B cell responses to these pathogens through antigen-specific FOB cells interacting with iNKT cells via antigen presentation through the CD1d complex (91, 92). These interactions appear very similar to interactions between classical peptide-restricted CD4 T cells, in that $Bcl6^+$ iNKT cells required expression of CD40L for upregulation of AID and SAP and supported B cell expansion and differentiation via secretion of IL-21, although the induced B cell responses appeared more short-lived (91–94). iNKT cells can also provide critical noncognate support for B cell responses through secretion of cytokines, as has been shown following infection with influenza virus, which does not express glycolipids (95). Thus, although the original view of T cell–B cell interaction was restricted to that involving protein antigens, there is now support for T cell–dependent B cell responses to pathogen-derived glycan, lipid, and protein antigens, greatly expanding the number of antigens that can trigger a T cell–dependent humoral response to natural infection or vaccination.

Taken together, these findings indicate that initial clonal expansion of antigen-activated FOB cells occurs at the time of antigen encounter and is enhanced through costimulatory and cytokine signals provided at the T-B border zone (83, 96). This process supplies an increased number of antigen-specific and often, but not always, class-switched B cells (97–99).

## Outcomes of FOB Cell Activation

The further fate of the B cells is determined by signals provided during their initial activation. They return to the follicles, where they initiate GC responses that give rise to MBCs and LLPCs (55), or they remain in the extrafollicular space, as antigen-experienced B cells or MBCs, or they differentiate into plasmablasts. The latter congregate in so-called extrafollicular foci (EFs) in the T-B border and the medullary cord area of lymph nodes or red pulp of the spleen (97). As outlined below, extrafollicular responses rapidly amplify preexisting antibody responses to eliminate acute infections and, I would argue, are the main effector responses to infections. GC responses, on the other hand, use the infections to alter the existing B cell repertoire through expansion of a more diverse and adapted set of B cell clones that develop into MBCs, which can enhance EF responses during an ongoing infection or during reinfection with the same or a related pathogen (100, 101). In addition, the provision of LLPCs by GCs is a layer of immune protection aimed at preventing subsequent infections (**Figure 1**).

**Extrafollicular effector and memory B cells.** Despite earlier work suggesting that MBC development depends on GCs, more recent work, enabled by the use of fluorescent antigen-baits for identification of antigen-specific B cells, suggested GC-independent formation of nonswitched $IgM^+$ as well as class-switched $IgG^+$ effectors or MBCs (64, 102–104). Although their specific developmental paths remain to be more firmly established, it appears likely that they derive following (T cell–dependent and –independent) B cell activation at the T-B border. They may form from FOB cell clones that do not receive sufficiently strong BCR signals to become plasmablasts, or signals of a different quality than required for EF plasmablast formation. $IgM^+$ nonswitched MBCs, which seem to separate into B cells that are $IgM^+IgD^-$ and those that have a naive, $IgD^+IgM^+$ phenotype (105), can respond to reinfection with rapid seeding of either EF or GC responses; thus, in this regard they behave similarly to naive B cells and are not a priori precluded from EF responses (106). The data are significant, as they suggest that quiescent, antigen-experienced, and clonally expanded nonswitched B cell populations, including populations that by phenotype resemble naive B cells, shape the repertoire of the circulating B cell pool, thus skewing the B cell pool toward expanded numbers of B cells with BCRs that recognize pathogens. MBCs' apparent potential for self-renewal (106, 107) further suggests that these cells remain in the peripheral circulating B cell pool in the long term. By virtue of their increased frequencies alone, they can support more rapid responses to recall infections.

The data may also explain how MBCs can respond to pathogens that the host has not encountered previously. By retaining a naive-like ($IgM^+$ $IgD^+$ or $IgM^+$ $IgD^-$) state, these cells can provide an initial wave of pathogen-specific antibodies of an appropriate quality, i.e., isotype and glycan profile, in response to infections with distinct pathogens that share epitopes, perhaps conformational in nature. The quality of the humoral response is then shaped by the inflammatory milieu of the newly encountered pathogen, rather than being dependent on the legacy of the previous infection that led to their initial induction. It may also support the development of cross-reactive humoral immune responses to broader classes of pathogens, as recently shown for cross-reactive B cell responses to LPS O antigen in humans (108) and to flavivirus envelope epitopes (100).

Recent studies have shown that engagement of TLR9 following BCR-mediated antigen stimulation in the presence of T cells contributes to the development of a $CD11c^+$ B cell subset that expresses the transcription factor T-bet (109, 110). The first description of B cells with this phenotype was by Winslow and colleagues (111), who noted that a population of IgM-secreting extrafollicular $CD11c^+$ plasmablasts emerged rapidly and independently of T cell help following infection with the intracellular bacterium *Ehrlichia muris*. A population of $CD11c^+$ $CD19^+$ MBCs developed somewhat later in the response (112). Collectively, additional studies have revealed that this $CD11c^+$ B cell subset harbors a transcriptional profile dominated by expression of the transcription factor T-bet (113–115), a well-known transcriptional regulator of CD4 Th1 differentiation (116). Plasmablasts and MBCs with this phenotype emerge in IFN-γ-driven infections of both humans and mice, such as following chronic infection with HIV (117, 118) and repeat infections with *Plasmodium falciparum* in malaria-endemic areas (119), as well as during acute influenza virus infection (86). Initial reports of MBCs with this phenotype in patients with chronic HIV infection (118) as well as in those with autoimmune diseases (120) suggested that these cells were atypical MBCs showing signs of exhaustion and dysfunction. Subsequent studies, however, have demonstrated that they represent a population of B cells poised to develop into plasmablasts and that their emergence is related to the inflammatory milieu in which they develop. Elegant studies by Lund and colleagues (86) recently defined the transcriptional control of these cells, demonstrating that B cell–intrinsic signaling via IFN-γ induces T-bet during influenza infection. T-bet expression then orchestrates transcriptional changes that suppress the initial IFN-γ-driven inflammatory

signaling profile in favor of one that enables these cells to respond to BCR signaling with rapid upregulation of Blimp1$^+$ and IRF4 and thus to initiate differentiation into plasma cells (86).

EFs are generated by antigen-specific B cells that undergo rapid rounds of proliferation followed by their differentiation into CD138$^+$ Blimp-1–expressing plasmablasts that secrete either IgM or class-switched immunoglobulin. This response type is induced by all mature peripheral B cell populations—B-1 cells, MZB cells and FOB cells—underscoring its significance for the survival of the host. While many EF responses require initial interaction of B cells with CD4 T cells, EF responses can form in response to T cell–independent antigens. Here, in addition to strong antigen-BCR interaction, TLR signals and sufficient availability of BAFF and other cytokines supplied by innate immune cells, such as ILCs, NK cells, and even neutrophils, can replace the need for T cell–derived costimulation of FOB cells. In addition, however, and as discussed below (see the section titled Innate-Like B Cell Subsets in Infection), splenic MZB cells and B-1 cells respond more rapidly and more strongly to such signals compared to the FOB cells and may be responsible for an early wave of T cell–independent plasmablast responses.

Class-switch recombination of EF-bound FOB cells is likely induced following CD40-CD40L interaction with CD4 T cells in the T-B border zone (97–99). During primary infections, EF-derived antibodies show only limited signs of affinity maturation. This may be due to the fact that continued engagement of these cells with CD4 T cells via CD40 is not required in the EF and thus CD40-induced AID expression, responsible for both class-switch recombination and somatic affinity hypermutation, may not be sustained (84, 97). Furthermore, recent studies showed that the transcriptional regulator Pax-5 supports AID expression, suggesting that the downregulation of Pax-5 during plasmablast differentiation further represses AID expression (85). This is in contrast to ongoing interactions of B cells with CD4 Tfh cells in the GCs, which continue to drive expression of AID, explaining the difference in the levels of affinity maturation seen between EF and GC B cell responses.

Importantly, this does not mean that all EF responses are of low affinity. Indeed, development of EF responses requires a relatively high-affinity BCR for cognate antigen binding (121), presumably because high-affinity interactions induce strong expression of IRF4 (122), a key transcriptional regulator of plasma cell development (123). For example, Gerhard and colleagues (124) noted high-affinity early antibody responses consisting of germ line–encoded IgG of the C12 idiotype specific for the Cb site of HA1 following primary influenza A/Puerto Rico/8/34 vaccination of BALB/c mice. These responses did not generate MBCs and did not participate in later antibody responses. We subsequently identified B cells expressing this idiotype to form EF but not GC responses following primary influenza infections (125). Thus, when available in the existing repertoire, high-affinity B cell clones are favored for EF development. This is also the case during recall responses, or during infections with related pathogens that induce cross-reactive responses, and can explain the appearance of highly mutated plasmablasts in the blood of patients within a few days of acute infection during recall responses (100, 126, 127).

In summary, EF responses are rapidly induced and can provide critical, early, and protective antibody responses of a variety of affinities. Given the need for strong BCR signaling to initiate B cell differentiation (122), the notion that FOB cell–derived EF responses generate mostly low-affinity antibodies seems inconsistent with available evidence, and it wrongfully diminishes the strong impact and importance of these B cell immune effector mechanisms for host survival. Such a notion might have arisen from studies with model antigens in mice, in which the preimmune repertoire simply does not contain clones able to mount a strong EF response. Indeed, during recall responses, extrafollicular or GC-derived MBCs preferentially feed into the EF pathway for enhanced immune responses (100, 128) (**Figure 1**). Based on these data, the EF response appears

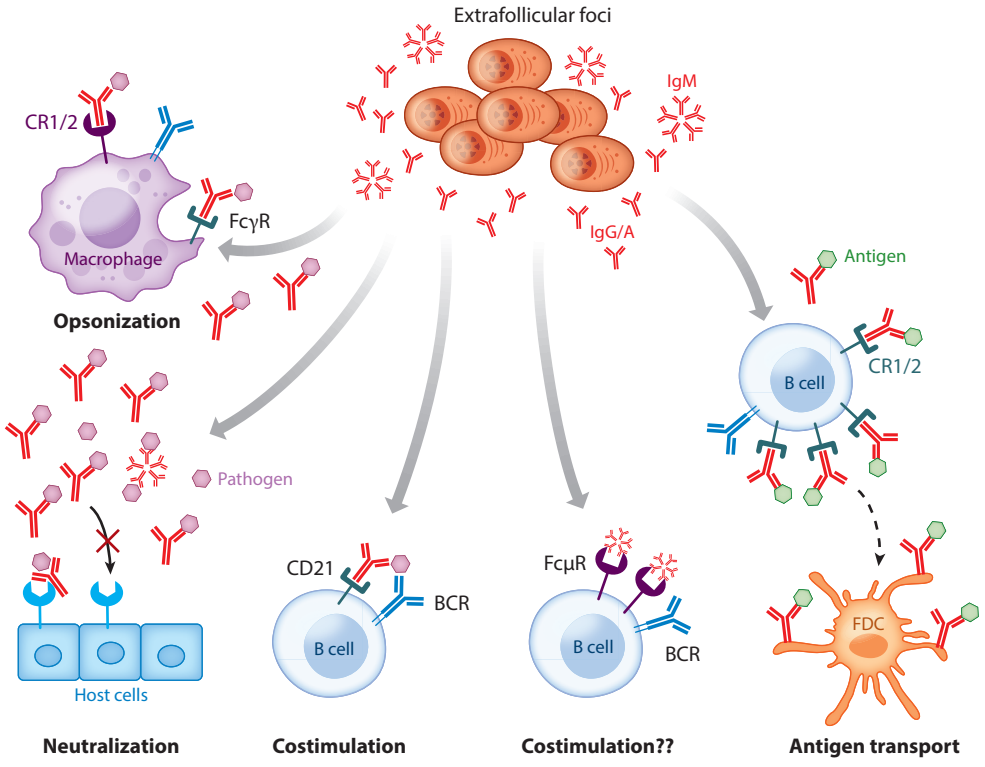



**Figure 2**

Rapidly generated, extrafollicularly derived antibodies provide immune protection and regulate pathogen-specific B cell responses. Extrafollicular foci rapidly form after infection and secrete both IgM and class-switched antibodies. IgG and IgM provide rapid protection by opsonizing the pathogen for uptake by macrophages and neutrophils. Antibody-antigen complexes bind to activating FcγR, or when tagged with complement they bind to complement receptors CR1/2 (CD35/21). They may also directly bind to and neutralize pathogens. Support for B cell activation is provided through costimulatory signals via binding to CD21, which can deposit antigen onto the B cell surface, which may support binding to the BCR. Secreted IgM and the B cell–expressed FcμR may also activate B cells, albeit the mechanisms underlying their effects are unknown. Finally, immune complexes bound to follicular B cells can be transported and deposited onto the surface of FDCs situated inside the follicles, thereby supporting germinal center responses.
Abbreviations: BCR, B cell receptor; FDC, follicular dendritic cell.

to be a central and critical effector response of the humoral immune system, not simply a short-lived, low-affinity response preceding a more important and effective GC response.

**Functions of extrafollicular focus–derived antibodies.** The outcome of EF development is the rapid generation of antibodies that critically support host defenses (**Figure 2**). Current evidence suggests that the developing plasmablasts are relatively short-lived, with antibody secretion usually occurring a few days prior to the establishment of GC B cell responses in the same lymph tissue (97, 125). Yet, given that the half-life of IgG is in the order of three to five weeks, these responses nonetheless will outlast typical infections. Indeed, during acute infections with influenza virus, the kinetics of the EF response strongly correlates with that of virus clearance, while the slower-developing GCs do not form until the virus is already cleared (56, 125). The early presence of antibodies can limit pathogen spread and thereby reduce the risk of overshooting cellular

immune responses, which often engender higher levels of tissue destruction. The antibodies can also facilitate provision of costimulatory signals to FOB cells by forming complement-tagged antigen-IgG immune complexes that bind to CD21 (129). Via that same route, they can also help transport antigen to FDCs (50, 51), thereby strongly supporting GC B cell responses. Tethering the immune complexes to the surface of FOB cells may also enhance even low-affinity BCR engagement with antigen. Coligation of BCRs and immune complexes bound to the inhibitory FcγRIIb, the only type I IgG-FcR expressed by B cells, would also override any FcγRIIb-mediated inhibitory effects on the B cell response and instead provide support for GCs (130, 131).

IgM-antigen complexes may fulfill similar functions as IgG immune complexes, given that IgM strongly binds to complement (132). Indeed, the absence of secreted IgM has been associated with strong reductions in the ensuing IgG responses to infections and immunizations (132). FOB cells also express an Fc receptor for IgM (FcμR) (133). Its absence was shown to lead to reduced IgG responses to influenza virus infection similar to those seen in secreted IgM–deficient mice, suggesting that IgM binding to the FcμR is important for IgM enhancement of the subsequent IgG response (134). Thus, EF-derived antibody responses are critical for both direct neutralization and opsonization of pathogens, as well as for optimal GC B cell responses.

Few studies have documented mechanisms by which pathogens may exploit the EF response as an immune evasion strategy. One example is secondary dengue virus infections in individuals living in dengue-endemic regions. Dengue repeat infections induce very strong MBC-driven plasmablast responses, which in cases of heterotypic infections can be directed against nonneutralizing, cross-reactive epitopes. These nonneutralizing antibodies opsonize the virus, which perversely enhances disease severity in some patients, due to enhanced virus infection of macrophages and other FcR-bearing cells (135–137). Host cell infection via IgG- but not IgA-mediated opsonization of plasmablast-derived antibodies was also reported for patients infected with *M. tuberculosis* (138). Most recently, a study on infections with *Plasmodium yoelii* in mice suggested that rapidly proliferating plasmablasts can compete with GC B cells for nutrients, starving activated B cells and abrogating the establishment of GC responses. Interestingly, the inhibitory effects of EF plasmablasts on GC responses were overcome by supplementation of drinking water with L-glutamate (139). These are remarkable observations providing mechanistic explanations for clinical observations of malnutrition and insufficient development of pathogen-specific immunity (140). Driving EF responses, while diminishing GC responses that provide MBCs that can feed into future EF responses, as well as strong antibody-mediated protection via formation of LLPCs makes evolutionary sense in that *Plasmodium* requires frequent reinfections of a host in malaria-endemic areas. But it also suggests that strong EF responses have an associated cost that is usually balanced through their rapid involution.

## Intrafollicular Germinal Center B Cell Responses

In response to infections or immunization, the de novo formation of GCs is delayed by a few days compared to that of extrafollicular responses, taking upward of 10–14 days. Multiple excellent recent reviews have discussed the regulation of GC B cell responses to both model antigens and infectious agents, and the reader is referred to these for an in-depth discussion (55, 141–143). Briefly, GCs contain two histologically distinct compartments: the dark zone and the light zone. The dark zone encompasses a recently discovered subarea, the gray zone (144), in which rapidly proliferating B cells incorporate frequent point mutations into the hypervariable antigen-binding region of the Ig locus. B cells with missense mutations undergo apoptosis and are eliminated by tangible body macrophages. Successfully mutated B cells will enter the major dark zone compartment, differentiate, and re-express their BCRs, and then they will move to the light zone, which

contains antigen-presenting FDCs and CD4 Tfh cells. Light zone B cells undergo selection, and only those that compete successfully for antigen binding, and thus can present antigen for subsequent engagement with CD4 Tfh cells, are selected for further rounds of proliferation. Continued competition for antigen and interaction with CD4 T cells selects for BCRs with increasing binding strengths to the selecting antigen. While much emphasis has been placed on the increasing affinity of individual GC-derived B cell clones, there is scant evidence that enhanced affinity is responsible for the development of protective B cell responses to pathogens (56, 145–147).

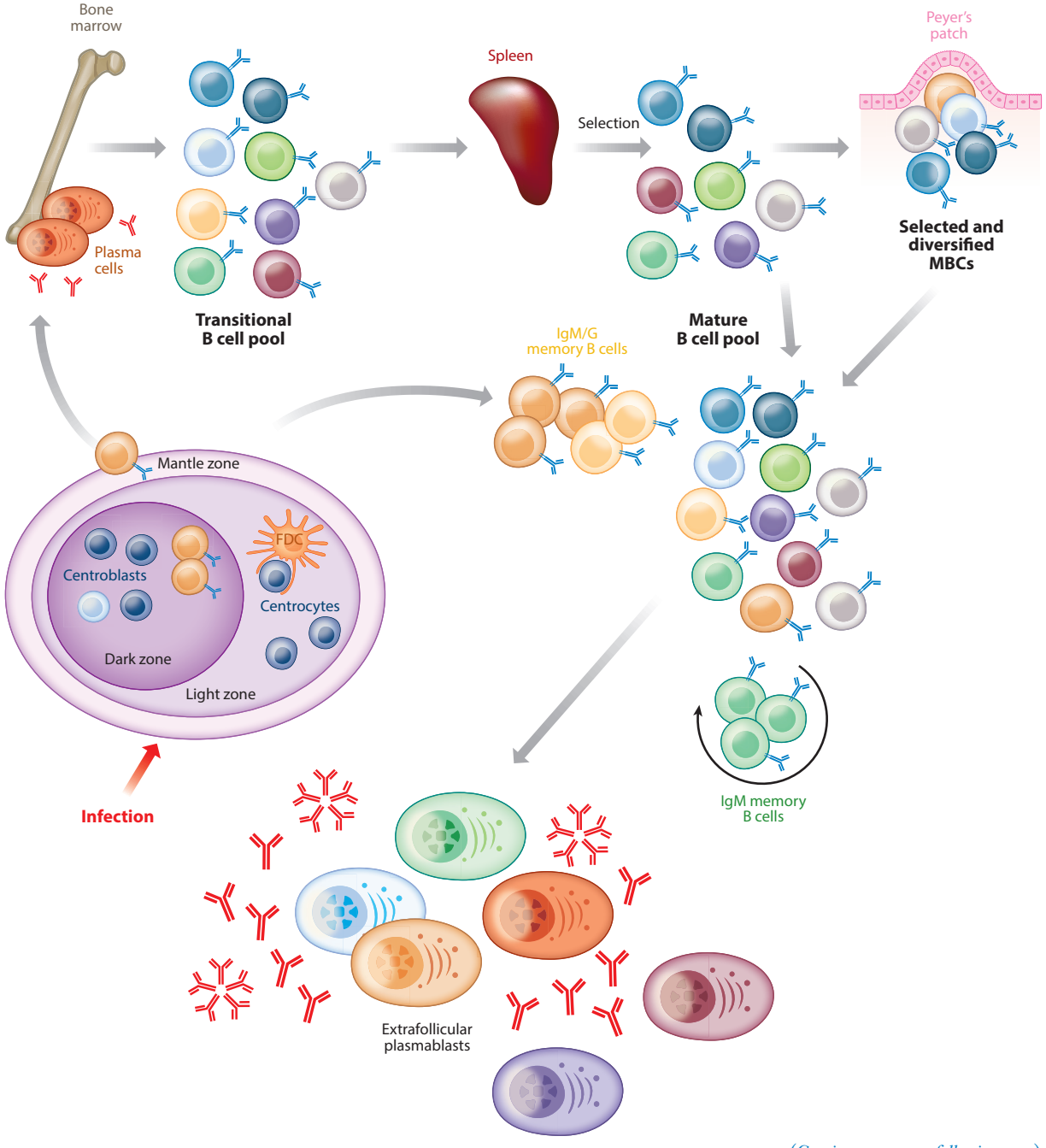
Importantly, however, and in contrast to the EF response that relies on the available B cell repertoire, the GC response actively shapes the B cell repertoire, driving diversity by selecting BCRs that strongly bind to antigens from pathogens that could infect the host. While EFs usually rapidly resolve within a few days after their formation, GCs can persist for extended periods, even after the infection is cleared. Following influenza infection of mice that is cleared within 7–10 days, mediastinal lymph nodes contain GCs for up to five months, although their total number diminishes as the lymph node involutes. This is consistent with the long retention of antigen on the surface of FDCs, which act as the main antigen-presenting cells for B cells in the follicles (88). Chronic GCs are also found in the mesenteric lymph nodes draining the gastrointestinal tract and in Peyer's patches of the small intestine, in response to microbial stimuli, suggesting that these structures are repurposed for differing antigens over time. Recent data show that the chronic Peyer's patch GCs expand somatically mutated public clones, i.e., clones that occur in many individuals, further supporting the idea of these structures driving diversification of a repertoire of specificities to common antigenic structures (148). The long-lived GCs are reminiscent of the processes of B cell diversification observed in the appendixes of rabbit and sheep, among other species, that rely on gene conversion for generating a diversified repertoire upon interaction with microbiota-derived antigens (149).

I argue that these findings further support the idea (56) that the primary goal of GC responses must be not only the removal of an ongoing infection, but also the use of antigens from the infection as a means to shape the repertoire of the B cell compartment on important antigens. Important antigens would be those that are derived from an intruding pathogen and, in the gastrointestinal tract, antigens that provide a blueprint of common bacterial structures, sampled through M cell uptake from the luminal site for presentation to GC B cells within the Peyer's patches. Consistent with this interpretation is the recent observation that GC-derived MBCs do not usually return to the GC in a recall response (100, 150). Thus, generation of MBCs supports primarily a more effective and more diverse EF response upon rechallenge. Such repertoire reshaping overcomes the inherent limitations of a stochastic process of B cell development in many mammalian species, including humans and mice. Most B cells are initially selected by this process only for the functionality of their BCRs and for their lack of self-recognition, but not for usefulness.

De novo GC responses are established in the follicles when B cells activated in the T-B border return to these sites, where they are further stimulated by antigens trapped on FDCs, as well as by CD4 Tfh cells that are recruited by B cells to the GCs, causing further extensive clonal expansion (88). Similar to extrafollicular responses, GC responses result in the formation of antibody-secreting plasmablasts and plasma cells, as well as MBCs. In contrast to the EF response, however, GC-derived plasmablasts migrate to the bone marrow, where they differentiate into LLPCs and can remain for extended periods (151, 152). The output of GC switches over time from an early wave of MBCs to a wave of later-developing plasma cells (103, 153). The determinants of B cell development toward MBCs or plasma cells have not been identified, but MBC fate may require lower BCR affinity compared to plasma cells (102, 154), as they show lower rates of mutation, consistent with the earlier exit from the GC. Interestingly, compared to the LLPCs, MBCs may have an increased ability to respond to cross-reactive antigens, as demonstrated with influenza A

and West Nile virus (100, 153, 155). The data are consistent with the importance of MBCs in shaping an increasingly diverse extrafollicular plasmablast response (**Figure 3**).

The impact of GC responses on host survival of an infection depends on the type of pathogen encountered. During acute infections with hit-and-run viruses like norovirus or influenza virus,




(*Caption appears on following page*)

**Figure 3** (*Figure appears on preceding page*)

Shaping of the mature B cell pool by acute and chronic germinal centers generates a pool of B cells with increased responsiveness to pathogens. Transitional B cells continuously emerge from the bone marrow with a largely stochastically derived B cell receptor repertoire. During transition into the mature B cell pool in the spleen, the repertoire is altered through removal of strongly autoreactive B cells. The chronic germinal centers in the Peyer's patches as well as mucosal lymph nodes further shape the B cell pool by expanding and selecting B cells that recognize microbial antigens. Rapid extrafollicular plasmablasts are selected from this diverse pool of B cells through activation of naive B cells as well as switched or nonswitched MBCs. The latter are major precursor pools with a predilection for differentiation into extrafollicular foci. Further repertoire shaping occurs following infections by de novo developing germinal centers, which contribute not only sparsely mutated MBCs but also high-affinity mature plasma cells that reside long-term in the bone marrow. Abbreviation: MBC, memory B cell.

where the virus is cleared within a few days of infection by the innate immune system as well as by the rapidly developing EF responses, GC responses develop too slowly to affect the course of infection. However, GC responses become increasingly important when pathogen clearance cannot be achieved by these rapid immune responses. Already mentioned is the example of infections with *P. yoelii* in mice, where the abrogation of GC responses due to exuberant EF responses led to enhanced mortality (139). One of the most intriguing cases is chronic infection with HIV: Up to 50% of chronically infected individuals develop protective broadly neutralizing antibodies many months to years after infection (156, 157). What distinguishes these antibodies from those generated earlier in the same patients is their ability to bind to subdominant epitopes, that is, epitopes that do not provide strong triggers of B cell activation or epitopes that mimic self-antigens and against which B cell tolerance might have been induced (158–160). The lack of effective activation signals, or the lack of B cell clones with the needed specificity in the peripheral B cell pool, would prevent the development of such highly protective antibody responses. Through the continued presence of the antigen and the ongoing GC responses, sufficient BCR diversification may occur so that such broadly protective B cell clones eventually emerge. During influenza infection, broadly neutralizing antibodies are also directed against subdominant epitopes; here, these are the stalk region epitopes of the hemagglutinin molecules (161). Influenza infections might not be sufficiently long-lived to drive selection of such subdominant B cell clones. Instead, frequent repeat infections with the yearly emerging influenza variants would ensure maximal diversification of the response to influenza. Indeed, this interpretation is supported by recent studies demonstrating that individuals with high titers of anti-influenza antibodies show the greatest degree of repertoire diversification to influenza (162, 163). Given this repertoire broadening through repeat infections, however, the subdominant clones are unlikely strongly selected, as new dominant determinants are favored. Hence, strong broadly neutralizing antibodies against influenza and similar viruses are unlikely to develop after natural infection. If they did, influenza infections would not likely be the continued threat to human health that they are today.

Given the importance of GC responses in diversifying a suboptimal repertoire of specificities, it is not surprising to see that some pathogens cause persistent infections that suppress functional GCs. One example is the rapid collapse of GCs in mice infected with *B. burgdorferi* and the resulting lack of affinity maturation and MBC and LLPC development despite strong extrafollicular-derived antibody responses (164, 165). Another is the suppression of GC responses following *Salmonella* infection (166). Taken together, GC responses are critical for shaping the B cell repertoire of a host, generating MBCs that can induce rapid EF responses following recall infections, but also MBCs that have a broadened repertoire and can engage in heterotypic immunity. The generation of LLPCs provides strongly protective and neutralizing antibodies to prevent reinfections, as well as nonneutralizing antibodies that can rapidly complex antigens and thereby support de novo B cell responses as outlined above (see the section titled Functions of Extrafollicular Focus–Derived Antibodies). Extrafollicular B cell immunity and intrafollicular B cell immunity

work together both to provide rapid responses to the infecting pathogen and to better prepare the host for future pathogen encounters.

## TOLL-LIKE RECEPTOR SIGNALS AND THEIR SHAPING OF B CELL RESPONSES

B cells express surface TLR2 and TLR4 and endosomal TLR3, TLR7, TLR8, and TLR9. Endosomal TLR engagement can enhance FOB cell responses by providing additional proliferation and differentiation signals that synergistically enhance BCR signaling following antigen internalization (167). This enhanced B cell responsiveness supports the robustness of pathogen-specific antibody responses to both viruses and bacteria (168–171), but it may also lead to antibody-mediated autoimmunity (172, 173). Early studies showed a particular dependence of IgG2a/c generation on the expression of MyD88, which has now been linked to MyD88-dependent IFN-γ signaling; this cytokine is long known to drive CSR to IgG2a/c (86, 174). Absence of B cell–intrinsic MyD88 was shown to reduce B cell proliferation and GC responses (167, 175) as well as terminal differentiation to antibody-producing plasmablasts and plasma cells (168–171). These are important observations that have obvious implications for the regulation of B cell responses to pathogens. Interestingly, even in the absence of BCR stimulation, TLR9 and TLR4 signaling of FOB cells induces phosphorylation of Syk (176, 177), and TLR7 signaling phosphorylates Btk (178). Syk and Btk are two critical receptor kinases that orchestrate BCR-mediated downstream signaling. These data demonstrate a remarkable but also puzzling interconnectedness of TLR and BCR signaling that remains to be further explored. It also has to be considered, however, that FOB cells are not particularly sensitive to TLR stimulation. In contrast, B-1 and MZB cells show much stronger responses to TLR engagement, as briefly summarized below.

Thus, noncognate, inflammatory signals induced by infections are critical modulators of cognate B cell responses, affecting their response quality. Emerging data underscore how features of B cell responses during infectious diseases parallel those observed in B cell–mediated autoimmunity. Rather than indicating that autoimmune diseases are triggered by infection, they suggest that PAMPs and damage-associated molecular patterns (DAMPs) may initiate common signaling pathways. Understanding the regulation of pathogen-induced effective humoral responses can inform potential treatment strategies that modulate these pathways to either enhance antipathogen immunity or suppress the unwanted outcomes in autoimmune diseases.

## INNATE-LIKE B CELL SUBSETS IN INFECTION

### B-1 Cells

The first waves of B cells (B-1 cells) emerge in early fetal development, when there is limited exposure to microbial stimuli that could shape their repertoire. Instead B-1 cells, emerging from a developmental path distinct from that of B-2 cells (2, 179), undergo positive selection for recognition of self-antigens (180). It is not surprising, then, that the majority of B-1 cells express BCR-signaling inhibitors, including CD5, Siglec G, and CD148, which strongly curtail their ability to respond to these antigens (181–183). This is consistent with findings that $CD5^+$ B-1 cells do not respond to soluble anti-IgM with clonal expansion (181, 184).

The repertoire of B-1 cells dramatically changes over the course of the first five months of life, even in the absence of microbiota, leading to the emergence of a heavily skewed repertoire containing some large and highly dominant public B cell clones (185, 186). The signals that drive these repertoire changes are unknown, but recent studies with TLR-deficient mice suggest that DAMPs may play a significant role (187). In the presence of microbiota, B-1 cells contribute strongly and continuously throughout life to the IgA-producing plasmablast pools

in the intestinal tract (188, 189). They also generate most of the circulating natural serum IgM, which can bind numerous pathogens (190, 191) and is critical for survival from infections (36, 192, 193). In addition to playing a direct antipathogen role that often involves the activation of complement (194), IgM is required for maximal IgG responses to infections (134, 192, 195, 196). The mechanisms of that are largely unexplored but seem to involve B cell–expressed FcμR (134).

B-1 cells also respond to infections by migrating to secondary lymphoid tissues, where they differentiate rapidly into IgM- and cytokine-secreting cells, providing a first wave of IgM (36). They may also secrete IL-10 (197), and their rapid induction of granulocyte-macrophage colony-stimulating factor (GM-CSF) production has been associated with survival from experimentally induced sepsis (35). Accumulation of body cavity B-1 cells in the lymph tissues depends on type I interferon or MyD88-mediated integrin activation (33, 34). B-1 cells are exquisitely sensitive to TLR-mediated stimulation (198), which causes them to lose expression of CD5 and to proliferate to levels much higher than those of FOB cells (199). TLR-induced differentiation of B-1, but not FOB, cells into plasma cells depends on CMTM7, a surface-expressed protein that supports phosphorylation of p38 (123, 200). In contrast to the case of FOB cells, where stimulation through TLR acts synergistically with BCR-mediated signals, BCR engagement via anti-IgM before or immediately after TLR stimulation inhibits TLR-induced B-1 cell proliferation (199). Thus, in vitro studies suggest that B-1 cells respond mainly through TLR, not BCR, stimuli, although TLR-induced loss of CD5 may alter their responsiveness to subsequent BCR stimulation (199).

This raises questions about the specificity of the early B-1 cell response. In support of antigen-specific BCR-mediated B-1 cell activation, infections with *S. pneumoniae* (201), *Borrelia hermsii* (202), *S.* Typhimurium (203), or *Francisella tularensis* (204) indicated B-1 cell antigen recognition, clonal expansion, IgM secretion, and formation of memory B-1 cells (36). In contrast, B-1 cell responses to influenza infection suggested a mainly innate-like response, as the number of influenza-binding, IgM-secreting B-1 cells was not higher after infection in mice compared to the number in noninfected mice (205). Furthermore, IgM responses were abrogated in mice in which B-1 cells lacked intrinsic TLR signaling (187, 199, 206). Further work is required to determine the apparent differences between these infection models. Common to all B-1 cell responses to infections is the rapid induction of IgM-secreting B-1 plasmablasts, similar to those initiated by FOB cells during EF responses. Proliferating B-1 cells rapidly accumulated in the T-B border zone, where they differentiated into extrafollicular, short-lived $CD138^+$ plasmablasts (11, 19, 199, 207) and MBCs that accumulated in body cavities (202, 208). Interestingly, work by Yang and colleagues (209) suggested that antigen-specific B-1 plasma cell differentiation from B-1-derived MBCs during antigen-specific challenge immunization, but not during antigen priming, required TLR4-mediated stimulation. The data point to the importance of innate signals in quickly mobilizing this self-reactive, broadly protective B cell subset.

Thus, fetus-derived B-1 cells differ significantly from FOB cells in their responsiveness to infections. Their unique distribution in the pleural and peritoneal cavities allows localized and rapid responses to infections that breach mucosal barriers. Their contribution to antipathogen immunity is twofold: (*a*) passive, through continued secretion of broadly binding serum natural IgM and IgG and mucosal IgA, a repertoire that is shaped by TLR stimulation, and (*b*) active, through rapid migration to secondary lymphoid tissues, where B-1 cells contribute early short-lived antibody responses and regulatory cytokines, such as GM-CSF and IL-10 (210–212).

## Marginal Zone B Cells

As discussed, splenic MZB cells are critical for humoral immune response development, as they shuffle antigens from the marginal zone into the follicle for antigen presentation by FDCs in the

spleen, while lymph nodes lack this B cell subset (50, 51). Although MZB cell precursors can develop in the fetus, the marginal zone organization seems to require some time to develop (10). MZB cells share many traits with B-1 cells, including enhanced responsiveness to TLR signaling compared to that of FOB cells (213). They also express high levels of CD1, consistent with a repertoire responsive to glycans and lipids. These traits together with their location in the splenic marginal zone enable their rapid responses to blood-borne pathogens or TLR agonists such as LPS (11, 213). These traits also explain the critical role of MZB cells for production of antibodies against glycans, including the polysaccharide capsule antigens of gram-positive pathogens, such as *S. pneumoniae*, and explain the sensitivity of newborns and splenectomized individuals to infections with gram-positive bacteria.

Similar to B-1 cells, MZB cells respond to pathogen encounter by rapidly differentiating into EF plasmablasts in a T cell–dependent or T cell–independent manner (11, 213). Early studies established a predilection of MZB cells for generating nonswitched IgM memory responses to model antigens, although participation in late GC responses was noted in one earlier study (214).

Thus, all peripheral mature B cell populations, FOB cells, B-1 cells, and MZB cells, are poised for rapid EF responses to infections. In addition, B-1 cells provide immune surveillance in the peritoneal and pleural body cavities, and MZB cells are strategically positioned to survey the circulation. B-1 cell and MZB cell sensitivity to innate-like signals, their exclusion from GC responses, and their self-renewal capacity suggest that their repertoires fill critical specificity niche gaps that exist within the FOB cell pool throughout life. Their rapid antibody responses after infection reduce freely available pathogens and PAMPs, thereby reducing the potential for overshooting cellular activation and cytokine responses at a critical window early during infection.

### SUMMARY POINTS

1. Peripheral B cell populations are widely distributed in lymphoid and nonlymphoid tissues, functioning as antibody-secreting effectors as well as sentinels.
2. The structure and organization of lymphoid tissues facilitate the rapid exposure of pathogen-specific B cells to antigens.
3. Extrafollicular plasmablasts are the major humoral effectors in infection.
4. Extrafollicular foci (EFs) are generated by all mature peripheral B cell subsets, B-1 cells, MZB cells, and FOB cells.
5. The effectiveness of the EF response relies on the presence of a diverse repertoire of B cells that is shaped to respond to microbial antigens.
6. Germinal centers (GCs) mold the B cell repertoire by continuously expanding and altering B cell clones against microbial antigens in the chronic GCs of the gastrointestinal tract and in response to infections, generating memory B cells that act as precursors of the EF response.

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