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Coordinated Regulation of Extrafollicular B Cell Responses by IL-12 and IFNγ

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ABSTRACT

Upon activation, B cells undergo either the germinal center (GC) or extrafollicular (EF) response. While GC are known to generate high-affinity memory B cells and long-lived plasma cells, the role of the EF response is less well understood. Initially, it was thought to be limited to that of a source of fast but lower-quality antibodies until the GC can form. However, recent evidence strongly supports the EF response as an important component of the humoral response to infection. EF responses are now also recognized as a source of pathogenic B cells in autoimmune diseases. The EF response itself is dynamic and regulated by pathways that are only recently being uncovered. We have identified that the cytokine IL-12 acts as a molecular switch, enhancing the EF response and suppressing GC through multiple mechanisms. These include direct effects on both B cells themselves and the coordinated differentiation of helper CD4 T cells. Here, we explore this pathway in relation to other recent advancements in our understanding of the EF response's role and highlight areas for future research. A better understanding of how the EF response forms and is regulated is essential for advancing treatments for many disease states.

1 | Introduction

B cell immune responses manifest different modes that are induced depending on the infectious or inflammatory context. Upon activation, B cells can form either extrafollicular (EF) or germinal center (GC) responses, each producing terminally differentiated plasma cells and memory B cells. These responses can be exclusive of each other or can be concurrent [1–3]. The GC is a site of efficient affinity maturation and facilitates the formation of long-lived plasma cells and memory B cells [4, 5]. While the GC is well studied, the functions and regulatory mechanisms of the EF response are far less well understood.

The EF response was originally described in studies of protein and hapten immunization, where it was observed as a short burst of B cell proliferation and differentiation outside of the B cell follicle [3, 6, 7]. The GC supports recurrent rounds of B cell somatic hypermutation and positive selection, making it an efficient niche for affinity maturation. In contrast, the EF response has been generally regarded as a fast but limited source of low affinity antibodies to provide some protection until the GC can form, suggesting that the EF response is an interim measure as the relatively slower GC response forms. This view is evolving, as recent studies utilizing models of infection instead suggest that the EF response is an important component of humoral immunity, capable of eliciting protective antibody responses and memory B cells [8–15]. During various viral and bacterial infections, GC formation does not begin until after live pathogen burden is declining [16–20]. At a minimum, this suggests that the GC plays a minor role in the clearance of such infections, instead implicating the EF response as a critical component of effective humoral immunity.

Studies from our group have established that the type I inflammatory cytokines IL-12 and IFNγ promote the EF response, thereby regulating the choice between EF and GC formation [21, 22]. These signals thus provide a means for innate immunity to directly relay infection context cues to the B cell response. Integrating these new findings with the well-appreciated role of type I cytokines in directing T cell differentiation, we propose that in the context of acute infection both the humoral and cellular adaptive immune responses are coordinately regulated to produce terminally differentiated effector cells, plasma cells in the case of B cells, to optimally respond. This elegant design focuses adaptive immunity to the task at hand—during infection, it is to generate an EF response to optimally fight infection, then when infection is controlled, the loss of such innate signals enables the adaptive immune system to refocus toward creation of long-lived immunity via the GC reaction. This design also allows for flexibility in that the severity of infection can be translated through elevated production of proinflammatory mediators; the concentration-dependent effects of these mediators would then scale down GC and scale up the EF response output to match the severity of infection. In support of this, patients who have died from, or are critically ill with severe COVID infections were shown to lack GC, and instead show hallmarks of the EF response [10, 23]. Here we will discuss the EF response as a distinct pathway, discussing *how* critical inflammatory signals regulate both the response types that B cells undergo. We will then highlight immune scenarios in which the EF response may be underappreciated and discuss open questions for future study.

2 | Definition of an Extrafollicular Response

We define an EF response as the B cell differentiation process that occurs outside of the B cell follicle [3]. Upon antigen encounter in the follicle or splenic marginal zone, B cells migrate to the border of the T cell zone and B cell follicle, facilitating cognate interactions [4, 24]. Via mechanisms that are not fully understood, B cells then undergo divergent fate choices and either re-enter the follicle to form GC or leave and form EF foci. We do not consider the earlier stages of B cell activation taking place prior to this divergent fate choice to be included in the definition of an EF response. In the spleen, cells leave the white pulp through the bridging channels and establish EF foci in the bridging channels and red pulp [6, 7, 25]. In the lymph node, following an analogous sequence of events, the EF response takes place in the medullary cords [26]. Potentially of high importance, sites that host EF responses are rich in dendritic cells (DCs) and macrophages. DCs in particular are reported to produce several factors that support plasma cell production, including BAFF and IL-12 [27, 28]. DCs have variably been reported to positively or negatively regulate the EF response, and their exact role may be context-dependent [29–32].

Currently, the EF response is defined primarily by location. While other properties such as antibody affinity have been used to describe EF responses, these attributes are in fact context-dependent and do not definitively identify EF origin. Somatic hypermutation and affinity maturation have now been demonstrated to take place in EF foci in both models of infection and autoimmune disease, discussed in more detail below [33–35]. EF responses can occur in response to both T-dependent and T-independent antigens [6, 7]. Although sustained GC reactions are definitively T-dependent, T-independent responses can undergo a type of partially abortive GC response that can nonetheless generate memory in a BCL6-dependent fashion [36, 37], BCL6 being a critical transcription factor in GC B cells. EF-like responses may also take place outside of secondary lymphoid organs. For example, we showed that in *Ehrlichia muris* infection, which targets the liver, there are local B cell immune responses that undergo V region somatic hypermutation in situ, in an EF-like context, although there are no well-developed tertiary lymphoid tissues [34]. The simultaneous response in the spleen to this infection is extrafollicular; we were able to show clonal B cell sharing of cells in the spleen, potentially suggesting bi-directional flow of cells [34]. Of high interest are local immune responses that form tertiary lymphoid structures within tissues; however, the relation of such cells to the EF response taking place in secondary lymphoid organs remains to be defined. For example, influenza elicits local immune responses in the lung, which in a more chronic setting does induce TLT, which is termed iBALT [38]. It is possible that the requirements for formation are different at each location. As tertiary lymphoid structures have been thoroughly reviewed elsewhere [39–41], we will not cover them in depth here.

3 | The Extrafollicular Response Process

Most of what we know about the EF response comes from analysis of murine systems, either after immunization, infection, or during the spontaneous systemic autoimmune response in lupus mouse models. Observational data are available on putative products of the EF response in humans, but little, if any, of the actual EF process.

While sometimes referred to as the EF plasmablast response, active EF responses in both autoimmunity and infection (such as *Salmonella*) include both proliferating B cell blasts as well as differentiating plasmablasts (PB) [18, 33, 42–45]. The B cell blasts display activation markers, such as CD44 and CD86, but do not yet express definitive plasma cell (lineage markers such as CD138. In an ongoing process, the B cell blasts differentiate into PB. scRNA-seq of B cells in autoimmune mice detected both PB and B cell blasts as part of single, expanding clones, indicating that proliferating blasts give rise to PB at multiple points during clonal expansion [44].

EF responses can occur in the presence or absence of T cell help. T-independent EF responses have been studied for years in the context of either LPS or CpG-linked B cell epitopes (so-called TI-1 responses) or highly polymerized repeating epitopes, such as haptenated polysaccharide Ficoll or bacterial cell walls (so-called TI-2 response) [12, 46–49]. In each case, there is thought to be no peptide-derived T cell epitopes available, and the B cell receives either a Toll-like receptor (TLR)-derived second signal or a very strong and prolonged B cell receptor (BCR) signal. These T-independent responses are characterized by robust extrafollicular B cell generation and PB formation, whereas these immunizations elicit either no GCs or small, transient GCs [37, 47]. Responding B cells and PB are mainly IgM, but in mice isotype switching, especially to IgG3, can be observed [50, 51]. Aside from model immunization systems, T-independent EF

responses also can occur in autoimmunity when the self-antigen is both multivalent and has a TLR ligand, as in the case wherein anti-IgG (rheumatoid factor, RF) B cells are stimulated by immune complexes comprised of antinuclear antibodies and the DNA-/RNA-containing debris shed from cells [52, 53]. Similarly, responses to bacterial polysaccharides [54, 55] and very early responses to infection could be T-independent EF responses. Hence, EF responses do not need T cells to expand, differentiate, and even isotype switch.

However, when T cells are present, as is very often the case in physiological settings, they can greatly enhance the quantity and quality of the EF response. B cell responses to immunization with NP-Ficoll or rheumatoid-factor immune complexes were substantially smaller and had fewer isotype switched cells and V region somatic hypermutation following T cell depletion [11, 52, 53]. Thus, induction of AID and subsequent V region mutation and isotype switching, which have been reported in multiple EF responses, is largely if not fully T cell-dependent.

As EF responses in the spleen occur at the T-zone red pulp border, or in the red pulp, there are adjacent myeloid cells that can and do play roles in regulating the response. The T-zone red pulp border is rich in CD11c+ DCs, mostly of the cDC1 type. These cells could provide sources of cytokines that promote PB development, such as IL-6 and IL-12, along with BAFF and APRIL [28, 56]. In addition to serving as antigen presenting cells for EF helper T cells, adjacent myeloid cells may provide and receive contact-dependent signals to and from both developing B cell and T cell blasts as the EF response proceeds [3, 30].

3.1 | Cells Emanating From the EF Response

The major known B lineage products of the ongoing EF response are PB, PC, and MBC. T cells also participate in EF responses and can be expanded and polarized there [57]. A T helper population termed T extrafollicular helper has been postulated to play a role in EF responses [58, 59]. In most studied cases of acute infection or immunization in the context of a pro-inflammatory adjuvant, T_{H1} type cells are produced. Presumably, some of these cells become polarized CD4 memory cells, although the sites of origin of such memory T cells have not been well studied.

3.2 | EF-Derived PBs Emigrate and Remain at Local Sites

A prominent result of the EF response is the production of PBs, defined as CD138+ cells that are still dividing. These appear locally within EF foci and can be seen histologically intermixed with B cell blasts. These PB mediate effector function by virtue of immediate, early antibody secretion. Close inspection by flow cytometry reveals a heterogeneous population that appears in the process of differentiating from an activated B cell blast into a PB [42, 43, 51]. This includes a spectrum of upregulation of key markers such as CD44 and CD138 and downregulation of other more B cell-specific markers such as B220 (CD45R) and CD22.

Only some of these PB at any one time appear to be proliferating, and it seems likely that they are in the process of coming out of cell cycle in a dynamic way. Indeed, cell cycle arrest is likely required for definitive PC differentiation and is definitely associated with the mature PC phenotype [60, 61]. In addition, PB are relatively short-lived. In autoimmune mice, their half-life seems to be 2–4 days [43, 44]. EF PB responses are similarly transient in the context of hapten-carrier immunization [3, 31, 62, 63].

These EF-derived PB can migrate into the red pulp of the spleen and also into the blood [64]. EF-derived PB that reach the blood can lodge in the bone marrow in a partially CXCR4-dependent way [64, 65]. As EF responses are not thought to create long-lived PC, it seems likely that most of the EF-derived antibody secreting cells (ASCs) that do reach the bone marrow do not survive for long periods thereafter. While PC survival in the bone marrow could be dependent on reaching local supportive niches, it also seems likely that cell-intrinsic features of PB/PC generated at different sites would control the longevity of those cells once they reach definitive sites such as the bone marrow [66].

At early times after infection or immunization—prior to GC formation—or in circumstances in which GC formation is blocked, any such PB almost certainly derives from the EF response itself. However, once the GC initiates, it too may be the source of short-lived PB, even as the EF response continues to also generate them [67]. There is surprisingly little data or experimentation that distinguishes the sources of these early PB and hence whether they differ in properties or functionality. This is an area for future research.

Data suggest that EF responses generate few if any long-lived PC. Rather, most, if not all, are thought to emanate from the GC response. Timed window BrdU labeling from Weisel et al. [14] established that the great majority of long-lived PC are made at later times after immunization with hapten-carrier in alum. The onset of long-lived PC generation in fact is even after the peak of the GC reaction and long after the EF has response has involuted. Nonetheless, both Weisel et al. and later Viant et al. [13] demonstrated that there is an ongoing component of EF responses even at much later time points and that these sites could generate some memory B cells (MBC). Considering this, it is possible that some late-forming long-lived PCs could still originate from EF sites. In this regard, there are some studies in both mouse and humans indicating that T-independent responses, such as to polysaccharides, can induce long-lived antibody responses [46, 47, 68]. These T-independent responses are likely extrafollicularly derived but may also develop from abortive GC [37, 68].

3.3 | Memory

The EF response also generates MBC, detectable at the earliest timepoints after immunization with a protein antigen in alum, or after malaria infection [13, 14, 69]. Several types of MBC can be generated from the EF response. At early time points, the predominant type of MBC lacks expression of both CD80 and PD-L2, termed double-negative or “DN” [14, 70]. These DN MBC in mice are unique in being the only MBC subset known to be able to efficiently seed GC responses during a subsequent re-exposure to antigen [11, 70]. At somewhat later time points, MBC that do express both CD80 and PD-L2 are formed (termed

double-positive or "DP"). DP MBC are also made from GC precursors; in fact, it appears that the GC exclusively produces DP MBC [11]. While EF-derived DP also express CD80 and PD-L2, DP derived from the EF response (termed "DP_{EX}") differ from DP derived from the GC (termed "DP_{GC}") in terms of both gene expression and chromatin state. DP_{EX} also differ from DP_{GC} in having more proliferative potential and less rapid ASC differentiation after stimulation [11].

The precursor of EF-derived MBCs has not been definitively identified, but it likely is a proliferating B cell blast that in mice expresses the activation markers CD44, CD86, and is positive for staining with the GL-7 antibody (which recognizes a glycosylation modification) [11, 13, 71]. This cell, which has been termed an "early memory precursor" (EMP), can also generate short-lived PB, but in this context, it may also be able to seed GCs under favorable conditions. Hence, when this cell is transferred under a noninflammatory immunization setting, it will form GCs and, consequently, presumably GC-dependent MBC will form with time. This makes it difficult to state whether there exists a cell that has committed to the EF-derived MBC lineage. Additional work is required to test whether there are identifiable EMPs that have the potential to exclusively differentiate into MBC, rather than also seed a GC. This is further complicated by the fact that EF-derived DN MBCs can seed a GC, so in an ongoing response such cells may differentiate, only to be called into an active GC response in the environment of continued antigen exposure and T cell help.

The presence of proinflammatory signals may further alter the quality of MBC that derive from the EF response in at least two ways. First, we recently showed that with either strong BCR or CD40 signaling, a substantial proportion of EF-derived MBC express CD80 but not PD-L2 (termed "CD80 SP") [11]. The functional significance and capacity of CD80SP cells is not well understood. Spontaneous MBC formation in lupus-prone MRL/lpr mice also features a substantial proportion of CD80 SP MBC [44]. Formally, the origin of these cells has not been demonstrated, but as these mice overwhelmingly make EF responses, and as GCs from normal mice generate almost exclusively DP and not CD80 SP, it is reasonable to assume that these lupus-associated CD80 SP MBC also derive from the EF response that has occurred during the disease state.

EF responses can also spawn age-associated B cells (ABCs), a type of MBC that seems to arise in the context of certain inflammatory signals [44, 45, 72]. These cells are characterized by the expression of CD11c, CD11b, and the transcription factors T-bet [73–75] and ZEB2 [76, 77]. Interestingly, not all EF responses *do* generate ABCs. While MRL/lpr mice and *E. muris* infection robustly generate ABCs, many immunization-induced EF responses do not. Conversely, while EF responses do give rise to ABCs, it is also thought that under some circumstances, such as infection with influenza, GC responses can also produce ABCs [78]. ABCs in mice can express any combination of CD80 and PD-L2, thus suggesting that ABC development and MBC subset development are to some degree independent processes [44]. However, ABCs are enriched for CD80SP and DP in MRL/lpr mice [44], suggesting a correlation of the forces that favor both ABCs and these more differentiated MBC types.

Overall, several questions regarding the in vivo generation of ABCs remain unresolved. First, lineage-tracing studies are largely missing; these are the gold standard for assessing the precursor product relationships that would pin down the source(s) of ABCs under different conditions, whether from EF or GC responses. Second, the signals required in vivo to mediate ABC differentiation have not been unequivocally demonstrated nor fully explored. In vitro, ABC-like cells can be generated by a combination of TLR signals plus IL-21 or IFNγ, whereas IL-4 inhibits ABC generation [79, 80]. IL-21 may act only in conjunction with other signals, as it also promotes effective GC responses that do not produce many ABC [81, 82]. While T-bet is not required to generate ABC, at least in autoimmune mice and in some infections [34, 83], ZEB2 appears essential for ABC development [76, 77]. Given the ability of IFNγ and IL-12 to induce T-bet expression in vitro, it seems likely that they would be important for ABC development in vivo. *Salmonella* infection, while eliciting strong IFNγ and IL-12 production that leads to robust EF and PB responses in the absence of GC [16, 22], does not appear to result in ABC production (our unpublished observation). Hence, these two cytokines are not necessarily sufficient to make ABC. Alternatively, the conditions in some infections, such as *Salmonella*, may be too proinflammatory to allow MBC formation per se, thus negating the effects of the cytokines in shaping the MBC compartment. More experiments are necessary to dissect out these factors. Ideally, systems would be created that enable MBC formation without ABC differentiation, which could then be modified to generate ABC by the addition of other factors, such as defined cytokine combinations. Such an approach would allow direct comparison of MBC that either do or do not carry the ABC program, as well as test which signals are necessary and sufficient to promote ABC generation in vivo.

A population of cells comparable to murine ABCs has been identified in humans and is expanded in some patients with autoimmune and inflammatory diseases as well as with chronic or recurrent infections such as malaria or HIV [2, 84–86]. These have been termed "atypical" MBC and more currently DN2, which stands for "double negative" population number two, denoting the lack of expression of both CD27 and IgD on these cells [2, 87]. In humans, these have been associated with the presence of EF responses [2, 87]. However, despite the likelihood that the appearance of DN2/ABC-like cells is indicative of EF responses, it is quite challenging to formally prove in humans, as EF responses are best defined by direct tissue analysis.

3.4 | Affinity Maturation, Affinity Regulation

B cell blasts in EF responses express AID mRNA, underlying their ability to undergo isotype switch at early time points [59]. As cells in proliferating clusters divide and differentiate during the EF response, they can also turn on the somatic hypermutation process, again enabled by their expression of AID. Cells that begin to differentiate toward the PB fate begin to downregulate AID message, which is directly repressed by the transcription factor Blimp-1, and thus would terminate the ability to undergo both class switching and somatic hypermutation

[88, 89]. The duration of mRNA and resultant AID protein is unclear but presumably activity could continue for some time after transcription is halted. Nonetheless, it is very likely that these processes are mainly limited to the B cell blasts contained within EF foci.

Just as in the GC reaction, affinity-based selection can occur in EF responses. Affinity-based selection has been documented for RF B cells in lupus-prone mice, based on both V region mutation patterns and binding affinity [35, 43]. Anti-DNA antibodies in lupus-prone mice, as well as humans, are classically known to undergo affinity maturation, developing high R/S ratios in CDRs of V regions, along with specific mutations to Arginine residues, which have been shown to increase affinity for DNA [90–93]. It is now recognized that anti-DNA responses occur outside of GCs; hence, these affinity-matured anti-DNA antibodies almost certainly arose at EF sites. Similarly, in the EF response to *Salmonella*, clones with specificity to LPS with V region mutations were isolated, and reversion of the mutations to the germline in various combinations was found to dramatically reduce the affinity of the resultant antibodies for LPS [33].

Selection of higher affinity BCRs at EF sites could be due to both enhanced BCR signaling, proliferation, as well as antigen capture and subsequent presentation to T cells. As in the GC, capture and presentation of antigen by another cell (such as an FDC) is not required for either process to occur efficiently [94, 95]. In mice that lack any secreted antibody, and hence lack a mechanism for FDC or myeloid cells to capture immune complexes, GC reactions are actually enhanced rather than diminished [95, 96]; further, these responses can undergo V region mutation and show evidence of antigen-driven selection of these mutations. There are no FDCs associated with EF responses, and there would be little or no antibody available to capture antigen in the early stages, yet EF responses show dramatic proliferation and expansion, suggesting a network to capture antigen locally may not be required for affinity selection in EF responses.

4 | Direction of Primary Responses Toward the GC or EF Pathway

4.1 | IL-12 Coordinates Adaptive Immunity Toward EF, Suppressing GC

We have focused our studies on the EF response taking place in the spleen during *Salmonella enterica* serovar Typhimurium (STm) infection of mice. Splenic GCs are suppressed during STm infection [16, 33, 97], thus the EF response is the primary B cell response type and takes place in the T–B bridging channels and the splenic red pulp [98], fitting the classical definition of an EF response. Using this, we have shown that the cytokine IL-12 acts as a switch that coordinately promotes an EF response and suppresses GC formation [21, 22]. A role for IL-12 in GC suppression was identified by studying the T cell response, which showed a strong reduction in T follicular helper cell (T_{FH}) formation [21], cells necessary for GC. Deletion of the IL-12 receptor on T cells, but not IFNγ receptor, rescued T_{FH} differentiation [21]. Intriguingly, IL-12R deficient mice formed GCs; however, T cell-specific IL-12R deletion did not recapitulate this, suggesting additional GC-suppressive effects of IL-12 [22]. By transferring mixtures of wild-type or IL-12 receptor deficient B and/or CD4 T cells, we showed that the IL-12 receptor must be deleted on both CD4 T and B cells to recapitulate the GC restoration observed in global deficient mice [22]. Hence, IL-12 suppresses GC through coordinated effects on T and B cells. Mechanistically, in T cells, IL-12 drives high expression of T-bet, which suppresses T_{FH} differentiation and instead favors T_{H1} differentiation [21, 99], cells which are critical for the clearance of this infection [100]. In B cells, IL-12 both inhibits GC formation and enhances the EF response. Mechanistically, IL-12 initiates a positive feedback loop wherein IL-12 induces IFNγ production, and IFNγ induces IL-12 secretion and upregulates components of the IL-12 and IFNγ signaling pathways (Figure 1) [22]. IL-12 and IFNγ additionally have cooperative effects in B cells such that the loss of both receptors dramatically reduces PC production through the EF pathway, more so than the loss of either receptor alone, indicating the synergistic effects of the cytokines are critical in B cells [22]. Via these several effects, IL-12 coordinates a shift in the adaptive response to promote T_{H1} and PC and suppress T_{FH} and GC.

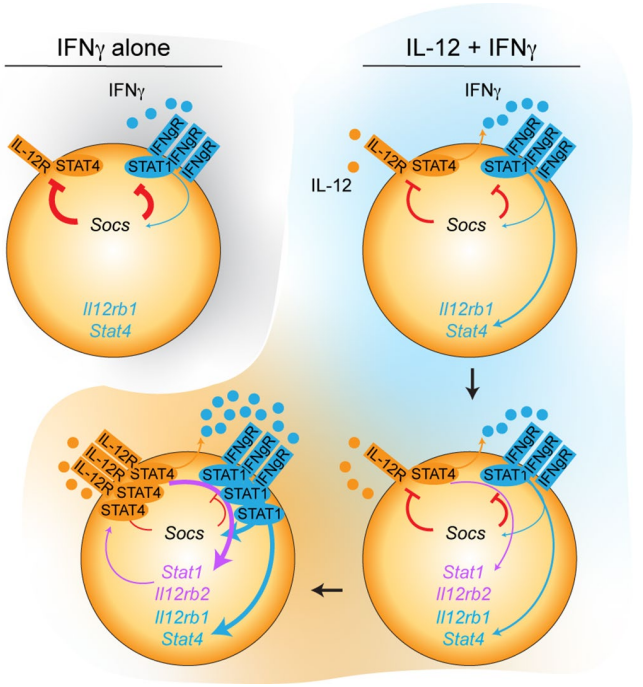

FIGURE 1 | Proposed model of IL-12 and IFNγ signaling in B cells. IFNγ upregulates the expression of suppressor of cytokine signaling family members (SOCS1, SOCS3, CISH). In the absence of other signals, high concentrations of IFNγ are necessary to overcome inhibition. When IL-12 is present, IL-12 upregulates IFNγ production. IFNγ induces the secretion of some IL-12 that is not transcriptionally regulated and transcriptionally promotes the expression of STAT4 and the IL-12Rβ1 subunit of the IL-12 receptor. Additionally, combined signals from IL-12 and IFNγ upregulate STAT1 and the IL-12Rβ2 subunit. IL-12 signaling enhances IFNγ production in a dose-dependent way, establishing a positive feedback loop between IL-12 and IFNγ. Hypothetically, the combined signals overcome IFNγ-induced negative regulation, ultimately promoting PC differentiation.

4.2 | IL-12 Induces a Positive Feedback Loop Between IL-12 and IFNγ Production in B Cells

Positive feedback in type I immunity has been thoroughly described between antigen presenting cells (APCs), particularly DCs and macrophages, and helper T cells [101, 102]. Upon sensing infection, antigen presenting cells (DCs, monocytes, macrophages, B cells, and others) produce IL-12, which directs CD4 T cell differentiation to IFNγ producing T_{H1} cells. DCs are critical early sources of IL-12 [103, 104], but interestingly, IL-12 was originally cloned from Epstein Bar Virus-transformed B cells, which constitutively secrete IL-12 [105, 106]. T_{H1} cells then provide IFNγ to APCs to enhance their killing capacity and their production of IL-12 [101, 107], which then further enhances T_{H1}-cell differentiation—a paracrine positive feedback loop. Others and we have shown that B cells are capable of sensing and producing both IL-12 and IFNγ [22, 27, 108–113], establishing the possibility for a cell-intrinsic positive feedback loop. This quality is notable as it is potentially highly proinflammatory. Accordingly, IL-12 and IFNγ production and signaling appear to be tightly regulated in B cells.

In both mouse and human B cells, IL-12 induces the production of IFNγ [22, 109, 110]. This occurs in a dose-dependent fashion, with higher concentrations of IL-12 more strongly inducing IFNγ transcripts [22]. IFNγ induced the secretion of IL-12, but mechanistically, this does not appear to be transcriptionally controlled nor dose-dependent [22]. Treatment of monocytes with IFNγ enhances their ability to secrete IL-12; however, this is through both transcriptional and post-transcriptional control [114]. In B cells, IFNγ instead appears to transcriptionally regulate the expression of key components of the IL-12 signaling pathway, namely both IL-12 receptor subunits and STAT4, the major signaling protein for IL-12 [22, 109]. Collectively, this suggests the mechanism of positive feedback from IFNγ may be more through enhanced sensing of IL-12 or signaling from the IL-12 receptor rather than enhanced IL-12 secretion per se, though this remains to be formally tested.

An important outcome of this positive feedback loop is enhanced production of IFNγ (Figure 1). Addition of IFNγ alone (in the presence of LPS to induce differentiation) can be sufficient to promote PB differentiation, but B cells are quantitatively far less sensitive to IFNγ than they are to IL-12 [22]. Addition of either 200 pg/mL IL-12 or 10 ng/mL IFNγ equivalently enhances B cell differentiation. IL-12 also appears to have distinct concentration-dependent effects, with lower concentrations (5–20 pg/mL) sufficient to promote only proliferation and too high (2 ng/mL) reducing B cell survival [22]. For comparison, in vitro T_{H1} differentiation is often performed in a range of 5–20 ng/mL of IL-12 [99, 115–117]. In T cells, phosphorylation of STAT4 at Serine-721 MAPK p38 activity is dose-dependent [118] and necessary for maximal IFNγ production but not for proliferation [119]. If the same were true in B cells, this would explain why lower concentrations of IL-12 are able to enhance proliferation but not differentiation. However, if that were true, one would hypothesize that IL-12 effects on proliferation would be IFNγ-independent, but we found that both proliferation and differentiation are IFNγ-dependent in vitro [22]. Separating the dose-dependent and -independent effects of IL-12 and IFNγ in the future may provide insights into what cellular functions are regulated by cytokine concentration versus synergistic signaling between IL-12 and IFNγ.

Understanding the activities of both IL-12 and IFNγ alone is important for understanding the mechanisms of their combined activities. However, since IL-12 quickly induces the production of IFNγ, the effects of IL-12 in isolation should be interpreted conservatively. Individually, the effects of IL-12 and IFNγ on B cells are short-lived. Initially, the transcriptional changes induced by IL-12 treatment are highly focused, inducing only three transcripts: *Ifng*, *Ncr1*, and *Csf2*, and of those, only *Ifng* remained upregulated 24 h after stimulation [22]. IFNγ treatment induced far more transcriptional changes, but those also appeared to be short-lived, with only a small portion of expression changes maintained to 24 h [22]. This observation may be explained by the concomitant upregulation of *Socs1*, *Socs3*, and *Cish*, which are members of the Suppressors of Cytokine Signaling family (SOCS, Figure 1) [22]. SOCS1, in particular, has been demonstrated to repress both IL-12 and IFNγ signaling [120–122]. Strikingly, the addition of IL-12 prolonged the increased expression of a portion of IFNγ-induced transcripts [22]. Therefore, a notable combinatorial effect of the two cytokines is to sustain IFNγ-inducible transcriptional changes. We further speculate that high concentrations of IFNγ would also overcome SOCS-mediated suppression, such that either high IFNγ or the addition of IL-12 when IFNγ is low would similarly sustain IFNγ signaling. In summary, an important role of the positive feedback loop is to amplify IFNγ production, which enhances PC differentiation in a concentration-dependent manner.

Potentially revealing an important safeguard in this system, combinations of stimuli seem to be necessary for optimal production of IL-12 and IFNγ from B cells. Groundbreaking work by Harris et al. showed that T_{H1} cells can instruct the formation of IFNγ-secreting B cells [123]. In this cell culture system, IL-12 was not necessary for IFNγ production by B cells, consistent with little, if any, production of IL-12 from T cells, but IFNγ production was necessary. We have demonstrated that IFNγ treatment alone does not significantly induce the transcription of *Ifng* in B cells [22], implying T_{H1} cells provide additional critical instructive cues. T cells provide help through CD40L/CD40 interactions, and CD40 crosslinking on DC's strongly induces IL-12 secretion from LPS stimulated DCs [108, 124]. CD40 ligation can also induce IL-12 production from a subset of human tonsillar non-GC B cells, and this is enhanced by the addition of IFNγ [111]. Additionally, in primary B cells, BCR ligation is not sufficient to elicit IL-12 production [111]. However, coligation of BCR and TLR ligands can elicit IFNγ secretion [125]. Combined stimulation of multiple pattern recognition receptors (PRRs) can elicit high levels of IL-12 secretion by DCs [126]. Stimulation through TLR9 with CpG may be an exception, as it alone appears to elicit IL-12 secretion from B cells [110, 127]. Timing also seems to be a key factor; it was reported that for human B cells, IFNγ stimulation can induce IFNγ transcript but not until 48 h in culture [109]. Collectively, B cells appear to utilize multiple pathways to engage IL-12 and IFNγ production, which may also depend on the timing of contact with T cells, other cytokines, and innate signals.

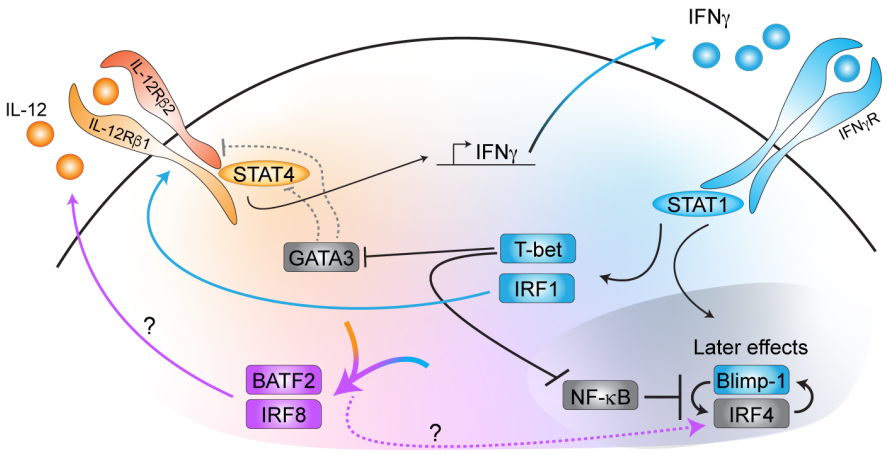

FIGURE 2 | Schematic of putative transcription factor networks in IL-12 and IFNγ-stimulated B cells. Initially upon stimulation with IL-12, B cells produce IFNγ which in turn induces the expression of T-bet and IRF1. In CD4 T cells, IRF1 promotes IL-12Rβ1 subunit expression, and T-bet enhances IL-12Rβ2 and STAT4 indirectly through repression of GATA3. IFNγ also induces the secretion of IL-12, the mechanism for this is unclear, but could involve BATF2 or IRF8. The signaling network evolves over time, leading to enhanced expression of some genes, and synergistic upregulation of a portion of other genes including BATF2 and IRF8 (purple). IFNγ also promotes the expression of Blimp-1 and an inflammatory gene program including NF-κB. T-bet indirectly enhances plasma cell differentiation in part by antagonizing NF-κB. Over time, the positive feedback loop and/or synergistic regulation culminates in enhanced IRF4 expression, which promotes PC differentiation. Many of these proposed connections are based on the transcription factor activities during T_{H1} differentiation, and it remains to be seen whether they function similarly in B cells.

4.3 | Cooperative and Synergistic Effects of IL-12 and IFNγ in B Cells

In addition to the positive feedback loop enhancing production of IL-12 and IFNγ, the synergistic effects of the two cytokines on B cells in the EF response are striking. We investigated this using mixed bone marrow chimeras and found that B cells lacking receptors for both IL-12 and IFNγ made far fewer PC compared to B cells lacking either one of the receptors alone [22]. Synergistic effects were also observed in vitro. A maximal concentration of IL-12 only induced about a third of the amount of IFNγ needed for maximal PB differentiation when IFNγ is given alone [22]. Both the cytokine amplifying feedback loop and synergistic effects are important, which can be seen mechanistically at the transcriptional level by comparing early (4 h) and late (24 h) differentially expressed genes. After 24 h in culture, in the presence of LPS with or without the cytokines, 44% of upregulated differentially expressed genes required both cytokines and, importantly, were not upregulated at 4 h of culture [22]. These gene changes reflect synergistic and/or positive feedback effects that evolve over time when both cytokines are present. How IL-12 and IFNγ induce synergistic gene changes remains to be determined. It will be interesting to investigate chromatin landscape changes and differential binding, particularly of STAT4 and STAT1 over time in B cells. In addition, all of these cells are receiving other upstream mitogenic stimuli (in our case, TLR-driven signals), which could in turn interact with cytokine-driven signals [80, 107, 128–131].

Synergistic signaling is likely to be important in vivo, particularly as optimal concentrations may not be available to all cells at all sites. In STm infected mice, serum cytokine levels only reached approximately 3 pg/mL IL-12 and 3 ng/mL IFNγ [22]. In vitro, both of these concentrations would have limited effects when administered individually, but in combination, these concentrations would be effective to induce both proliferation and differentiation [22]. Myeloid antigen presenting cells are generally thought to contribute to total IL-12 production more so than B cells, although a quantitative comparison between cell types would be difficult to determine in vivo, considering differences in cell numbers and local cytokine secretion. Intriguingly, B cells appear to consume IL-12 faster than they make it since the concentration of IL-12 steadily declines over 4 days in culture [22], which might suggest B cells depend on additional external sources of IL-12 in vivo. Indeed, DCs have been reported to enhance ASC responses through the production of IL-12 [27, 108], and extrafollicular B cell responses are located in areas rich in DCs and macrophages. Therefore, in isolation, suboptimal amounts of IL-12 and IFNγ are unable to sustain proinflammatory signaling, which they may obtain in vivo; whereas, in combination, they can maintain expression of IFNγ-induced transcripts to promote the feedforward loop, as well as induce the expression of numerous transcripts that require both cytokines for their upregulation.

4.4 | Transcriptional Networks Induced by IL-12 and IFNγ in B and T Cells

In both mouse and human B cells, IL-12 and IFNγ induce a transcriptional program that shares common elements with that of T_{H1} differentiation and macrophage type I polarization. Deciphering the regulation of this network in B cells, and how the positive feedback loop and synergy networks function separately and in combination, will be important to understand how this response type is regulated. Here we describe a hypothetical model of how this network may promote plasma cell differentiation, based on the functions of key transcription factors in T_{H1} differentiation (Figure 2).

The roles that IL-12, IFNγ and T-bet play in T_{H1} differentiation have been thoroughly reviewed elsewhere [132, 133]. There appear to be both similarities and differences in the regulation of B cells by IL-12, IFNγ, and T-bet. In B cells, initially, IFNγ stimulation strongly upregulates several transcription factors known to be important in T_{H1} differentiation, including T-bet and IRF1, both of which also regulate several aspects of the IL-12 signaling pathway. While T-bet plays a critical role in T cell differentiation, the in vivo effects of T-bet deficiency in B cells are relatively minor. T-bet is necessary for IgG2c class switching [134] but is dispensable for the IgM ASC response [22], which is the dominant isotype in the early response to *Salmonella* infection [16, 22, 33]. Similar observations were reported following influenza infection in mice [135]. Overall, T-bet does not play a role in determining the quantity of the early EF ASC response. In contrast, IFNγ signaling on B cells is necessary for both the IgM and IgG2c ASC response, and IL-12 preferentially promotes IgM ASC [22]. That IFNγ seems to have a larger impact on B cell differentiation than T-bet has also been observed in a T cell dependent in vitro system [135] and in autoimmune disease in mice [136], but the reasons for this remain to be discovered. Of potential importance is that T-bet expression levels and patterns differ between T_{H1} and B cells. In vivo, we observed relatively low expression of T-bet protein by flow cytometric staining among B cells, and it was only easily detectable following injection of recombinant IL-12 [22]. T-bet was also expressed by B cells, not terminally differentiated PB or PC [22]. In contrast, T-bet expression is readily detected in T cells, continues to be expressed in differentiated IFNγ-secreting effector T cells, and is more highly expressed in T cells from STm infected or IL-12 treated mice compared to mice immunized with heat-killed STm or untreated controls [21]. Oestreich et al. showed that T-bet can form dimers with BCL6, and through this remove BCL6 from its target sites [137, 138]. This may explain how IL-12 suppresses T_{FH} but not how IL-12 directs B cells away from a GC fate, since T-bet deletion only minimally impacted the EF response. Mechanisms that control the level of T-bet expression are only beginning to come to light but could include regulation by cell-type-specific enhancers. Differential T-bet induction has been observed during T_{H1} and NK development based on a cell type specific DNase hypersensitive site [139]. Interestingly, IL-21 is also able to upregulate T-bet protein in NK cells [139]. Since IL-12-stimulated T cells secrete both IFNγ and IL-21, perhaps this contributes to the very high T-bet expression observed in T cells compared to B cells.

What then is the role of T-bet in B cells, as it is not required for the early ASC response? Elegant work by Stone et al. showed that IFNγ, not T-bet, induced both Blimp-1 and an inflammatory gene program, and that T-bet was necessary to restrain the inflammatory program to allow differentiation [135]. T-bet repressed several inflammatory mediators, including NF-κB, and addition of an NF-κB activator inhibited differentiation [135]. Notably, this was in a T-dependent but IL-12-independent culture system [123, 140]. A clue to how T-bet may function in an IL-12-dependent system could come from the primary function of T-bet and IRF1 in T cells in regulating the expression of the IL-12R and STAT4. Naïve CD4 T cells express very little IL-12R, and both receptor subunits (IL-12Rβ1 and IL-12Rβ2) are upregulated upon TCR stimulation [141, 142]. In contrast, naïve B cells are responsive to IL-12, indicating functional expression levels prior to BCR stimulation. Both subunits are further upregulated in B and T cells by IL-12 and IFNγ signaling. IL-12Rβ2 and STAT4 in T cells are upregulated indirectly through T-bet-dependent downregulation of GATA-3 [143]. IRF1 directly binds and upregulates IL-12Rβ1 expression [144]. By analogy, it is possible that the critical function of early IFNγ signaling is to prime the B cell to receive IL-12 signaling by upregulation of the IL-12R and STAT4 through T-bet and IRF1 activity. In vitro, T-bet-deficient B cells fail to respond to IFNγ alone, yet they do respond to IL-12 and IFNγ in combination [22], indicating some synergistic effects of the two cytokines together are T-bet independent. Hence, while basal IL-12 signaling is sufficient for synergistic effects in vitro, T-bet may indirectly enhance synergistic signaling between IL-12 and IFNγ through upregulation of the IL-12 signaling pathway. In vivo, synergy between IL-12 and IFNγ could counterbalance the effect of T-bet deficiency, thus masking any phenotypes from the loss of T-bet. Alternatively, other factors could contribute in vivo to the upregulation of IL-12R in place of T-bet, particularly since regulation of the IL-12R by T-bet in T cells is indirectly through downregulation of GATA-3 [143]. Collectively, while it appears that T cells rely heavily on IL-12 and T-bet, B cells rely more strongly on the combinatorial effects of IL-12 plus IFNγ, which can be T-bet independent.

Other potentially important molecules regulated by the synergistic effects of IL-12 and IFNγ include BATF2 and IRF8 (Figure 2) [22]. In macrophages, BATF2 promotes the expression of IL-12p35, IL-12p40, CXCR3, and CXCL9 [145], of which CXCR3 and CXCL9 were also upregulated in B cells. IRF8 has been studied in B cells [146]. Initially upon activation, B cells upregulate both IRF8 and IRF4, which antagonize each other such that the balance of the two determines GC and plasma cell fates, with IRF8 higher in GC B cells [146, 147]. It is therefore not immediately obvious if or how IRF8 may contribute to the EF response. One possibility is that IRF8 promotes the production of IL-12. In macrophages, IRF8 and IRF1, both alone and in combination, promote IL-12 production [148, 149]. How IRF8 and IRF4 expression evolve in the presence of IL-12 and IFNγ remains to be determined, but, at least in cells that commit to the PB fate, we know that the outcome is higher IRF4 protein expression. How IRF4 may be regulated by IL-12 and IFNγ is unknown, and seemingly a conundrum given that IRF4 in DCs and macrophages antagonizes the type-1 program [150, 151]. One way to resolve this potential conflict, and to integrate the role of IRF8 in a process that culminates in IRF4-dominated cell type, is to consider the likelihood that IRF4 and IRF8 are regulated in two (or more) phases in B cells. In the first phase, IRF8 promotes the production of IL-12 and the IFNγ-dependent positive feedback loop. Subsequently, IL-12 effects progressively induce IRF4 production, which then overcomes IRF8-repression to switch the cells to differentiate into PC. T-bet may also be involved in this pathway since IRF4 activity was predicted to be reduced in T-bet-deficient B cells [135]. Further studies into how IL-12 and IFNγ promote higher expression of IRF4 at later times of culture may provide insights into this.

Some less well-studied transcription factors and receptors of potential importance include KLF6, Id3, Tcf7l2, Jun, and IL-2Ra—all of which are synergistically induced by the combination of IL-12 and IFNγ—as well as RUNX3 and Id2, which were

induced additively by the two cytokines [22]. The function of KLF6 is unclear, but a recent study identified an enhancer in the *Tbx21* (T-bet) locus that is bound by KLF6, which induces a subset of TH_{17} cells to switch to IFNγ production in the intestine [152]. Id2 and Id3 antagonize each other during T_{H1}/T_{FH} differentiation, with Id2 promoting T_{H1} and Id3 promoting T_{FH} development [153]. Naïve B cells express Id3, which functions to block their differentiation to PC [154]. There is reportedly little to no expression of Id2 among B cells during hapten immunization; however, this immunization does not induce much IL-12 production [22]. In T cells, RUNX3 is expressed at T_{H1} commitment and enhances IFNγ production, reinforcing the T_{H1} fate [155]. RUNX3 was also necessary and sufficient for upregulation of *Irf4*, *Prdm1* (Blimp-1), and *Id2* transcription in vitro [156]. IL-2 receptor alpha chain was also synergistically upregulated by IL-12 and IFNγ in our in vitro cultures [22], presumably rendering them more sensitive to IL-2 signals. IL-2 signaling represses T_{FH} differentiation through upregulation of Blimp-1 [157–159], and IL-2 promotes B cell proliferation and differentiation [160, 161]. IL-2 and IL-12 also synergistically promote Blimp-1 expression in CD8 T cells [117].

In summary, an intricate biological system has evolved to induce the EF response under inflammatory conditions, in which IL-12 coordinately directs T cell and B cell differentiation to generate effector cells, suppressing GC formation until the infection is controlled. An outstanding question is whether this paradigm/axis is a general principle of adaptive immunity—in other words, do similar mechanisms exist for type 2 and type 17 differentiation? If so, then there would be coordinated cytokine and transcription factor networks that would simultaneously, synergistically, and cooperatively coordinate both B cell and T cell differentiation, constituting a general principle of immune response coordination.

5 | B Cell Interactions With Dendritic Cells and T Cell Polarization

Although we describe a B cell-intrinsic mechanism for IL-12 and IFNγ activity, other cellular sources of each cytokine are likely important in vivo. It seems likely that, when an EF response is about to develop in vivo, activated B and T cells are initially exposed to IFNγ, which is produced within hours after stimulation of NK cells [162] and neutrophils [163] with LPS. During STm infection, the early secretion of IFNγ is critical to control the infection. IFNγ-deficient mice succumb to infection earlier than Rag-deficient or IL-12R-deficient mice [164, 165], highlighting the importance of IFNγ production from innate cells early during infection. In the context of the EF response, this IFNγ may prime B cells to receive IL-12.

IFNγ also primes DCs and macrophages for increased secretion of IL-12. While we have demonstrated that B cells are a critical source of IL-12 during the STm response [22], they are certainly not the sole source. We infer this in part because we did not observe that LPS stimulation of B cells was sufficient to induce IL-12 or IFNγ secretion in vitro [22]. It remains to be seen whether B cells require an external source of IL-12 in vivo. The EF response takes place in locations where DCs and macrophages likely influence B cell responses [32]. DCs can provide IL-12 that enhances PC differentiation and IgM secretion from both mouse and human B cells [27, 108]. DCs also provide other factors that promote PC differentiation, such as BAFF and APRIL [28], type I IFNs, and IL-6 [166], but they can also mediate inhibitory effects through CD22 [167]. The formation of EF foci, and potential interactions between DCs and B cells, likely precedes significant production of IFNγ from CD4 T cells. In fact, EF-derived PC can be detected as early as 4 days post challenge, prior to the emergence of a T-dependent ASC response in STm infection [21]. We have also shown that B cell-derived IL-12 is necessary for optimal early PC differentiation [22]; therefore, it is likely that both innate cells and B cells are important sources of IL-12 in vivo.

Intriguingly, B cells were also a critical source of IL-12 for early T_{H1} differentiation [22]. Our prior studies showed that IL-12 and T-bet suppress T_{FH} differentiation in the context of STm infection [21]. At the time, this was somewhat unexpected, given that in vitro differentiation studies suggested that IL-12 may promote T_{FH} differentiation, particularly from human T cells [168, 169]. Since a similar T_{FH}-suppressing effect for IL-12 was shown during *Toxoplasma* infection in mice [99], it was speculated that IL-12 may act differently on mouse and human T cells. Several recent and more detailed studies suggest those differences were more likely either due to IL-12 concentrations [170], or limitations of in vitro T cell differentiation (the only setting studied in humans) [81, 99, 171], and likely also confounded by other inflammatory context-dependent signals and T cell plasticity [133, 172]. IL-12 also strongly enhances proliferation [173–175], so the frequency of T_{FH} in vivo may reflect differences either in proliferation or differentiation and is often not distinguished. The resolution of these seemingly conflicting concepts on how IL-12 affects T_{FH} vs. T_{H1} differentiation may be that a low level IL-12 is necessary for an optimal T_{FH} response, perhaps by promoting initial proliferation, while relatively higher concentrations of IL-12, observed during infections such as STm and *Toxoplasma*, drive high expression of T-bet that commits cells to T_{H1} differentiation and suppresses T_{FH} differentiation. Notably, during T_{H1} differentiation, T-bet (*Tbx21*) RNA is expressed in two waves, which peak at days 1 and 5, respectively. Either IL-12 or IFNγ can induce T-bet expression at day 1, but the second wave of T-bet expression at day 5 is IL-12-dependent, and expression of T-bet at this point is critical for full commitment to T_{H1} differentiation [115, 132, 176]. This dependence on IL-12 at day 5 would coincide with the formation of EF responses in vivo, and, as stated above, we showed that B cell-derived IL-12 is necessary for optimal early T_{H1} commitment [22].

How the EF response continues to evolve at even later time points remains to be fully studied. The ASC response to STm infection shows evidence of T cell dependence after day 7 [16]. While IgG2c (IgG2a in BALB/c mice) is dependent on CD40L and CD28, the IgM ASC response is not [16], which together with our other data suggests that the IL-12/IFNγ cytokine response is necessary and sufficient for IgM ASC, but also that IFNγ alone is not sufficient for IgG2c class switching, which requires additional T cell signals. At this time point, it seems likely T_{H1} cells would contribute IFNγ to the EF B cell response, and they may also produce IL-21, another contributor to EF PB development [58, 59], depending on the inflammatory milieu. Although high and persistent IL-12 exposure fully commits CD4

T cells to T_{H1} differentiation, lower concentrations of IL-12 can promote a population of "T_{FH1}" cells that secrete IL-21 and IFNγ [170]. Intriguingly, the IgG2c ASC response during STm infection is dependent on T cell expression of BCL6, but not IL-21 [58, 82]. Consistent with the lack of dependence on IL-21, EF PBs also downregulate expression of the IL-21R [177]. However, in model systems with less severe inflammation, IL-21 and IL-21R are necessary for early IgG1 cells in EF foci [178], and IL-21 contributes to the development of ABCs, which are thought to arise from EF responses [179].

In summary, there is strong evidence for T cell support of the EF response, particularly as it matures, but T cell differentiation and, in turn, the cytokines that mediate this support appear to be dependent on the inflammatory context. Furthermore, innate immune cells likely support the early EF response through the provision of IL-12 and IFNγ in the absence of T cell help, primarily promoting an IgM ASC response. Finally, B cells support T_{H1} differentiation, while T cell interactions with DCs are well-documented, collectively forming a triad (or more) of paracrine enhancement of the EF response through amplification of the IL-12/IFNγ cytokine axis. Although some of these interactions remain to be directly visualized, we propose that the EF foci represent a unique niche that supports cellular interactions that enhance the production of T and B effector cells in a coordinated fashion.

6 | Concluding Remarks and Outstanding Questions

The significance of the EF B cell response has been underscored by recent studies that demonstrate that non-GC B cell responses are sufficient to clear and protect against influenza infection [8, 9] and by older studies showing that they drive autoimmune disease in autoimmune-prone mouse strains [35, 52, 180–185]. These murine studies match more recent work in human lupus patients that suggest an extrafollicular origin for pathogenic B cell subsets [2, 87]. Furthermore, EF B cells are an important source of neutralizing antibodies during influenza and COVID-19 infections [9, 10]. However, the mechanisms regulating the EF response are only just now being elucidated, with many open questions.

We have identified a role for IL-12 in redirecting adaptive immunity toward the EF response and suppressing the GC response. This raises the question of whether and how other cytokines influence the EF response. Within the type 1-associated set of cytokines, several play notable roles, including IL-18, IL-2, and TNFα. TNFα has been shown to recruit monocytes that contribute to the suppression of the GC response even at a distance [186]. IL-18 exacerbates autoimmune disease, promotes B cell differentiation, and synergistically enhances IFNγ production from CD4 T cells [187]. Understanding how this cytokine axis regulates B cells is an important area for future research. Additionally, how other cytokine axes, such as type 2 inflammation or signals that favor the formation of GCs, including IL-21, IL-6, and type I IFNs [1], may counterregulate or antagonize this program could further elucidate the spectrum of B cell and helper T cell responses, and whether coordinated differentiation may be a theme that applies to other disease types and states. This seems likely to be the case, as we already know in vitro that IL-4 can antagonize the upregulation of T-bet in B cells, and the early development of ABC-like B cells [80].

Furthermore, it is unclear how B cell responses that occur locally in tissues relate to the bona fide EF response that takes place in secondary lymphoid organs. Given that EF B cell responses can occur without the assistance of cognate T cells, and we have described a B cell-intrinsic mechanism of regulation by IL-12 and IFNγ, it is possible that local responses in tissues function similarly in certain contexts. However, tissue-based EF responses can recruit T cells and show T-dependence [34, 78, 188], suggesting that local EF-like niches could form and recreate the cellular and cytokine positive feedback loops that are characteristic of EF responses in secondary lymphoid tissue.

Importantly, the dysregulation of EF responses in the context of disease remains poorly understood. While significant progress has been made in understanding the cellular signals and transcriptional networks that promote the formation of ABCs and related cell types in humans, the mechanisms by which the formation of such cells is prevented or differently controlled in less inflammatory situations remain to be investigated. Such studies could lead to novel approaches to treating various disease states.

Overall, the EF response is a powerful arm of humoral immunity that remains relatively underexplored. We have identified a novel regulatory pathway that significantly enhances EF responses. These and other recent studies offer promising avenues to make substantial progress in our understanding of this B cell response type. Such studies will likely reveal additional modes and types of EF responses, perhaps depending on the nature of the provocative milieu. They are also likely to unveil novel regulatory mechanisms that enable targeting of the EF response at its source for the treatment of certain autoimmune diseases as well as overexuberant pathogen responses. Conversely, they may suggest strategies to elicit or enhance EF responses where they may be beneficial.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No new data were generated for this review article.

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