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B-cell response in solid organ transplantation

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The transcriptional regulation of B-cell response to antigen stimulation is complex and involves an intricate network of dynamic signals from cytokines and transcription factors propagated from T-cell interaction. Long-term alloimmunity, in the setting of organ transplantation, is dependent on this B-cell response, which does not appear to be halted by current immunosuppressive regimens which are targeted at T cells. There is emerging evidence that shows that B cells have a diverse response to solid organ transplantation that extends beyond plasma cell antibody production. In this review, we discuss the mechanistic pathways of B-cell activation and differentiation as they relate to the transcriptional regulation of germinal center B cells, plasma cells, and memory B cells in the setting of solid organ transplantation.

KEYWORDS

B cells, alloimmunity, transcriptional (regulation), transplant, rejection

Introduction

Despite an overall improvement in 1-year graft survival (1), median kidney allograft survival is 94.3% at 1 year but decreases to 76.3% at 5 years (1, 2). Approximately 40% of kidney allografts fail in 10 years, and nearly 67% of failed allografts are due to T-cell-mediated (TCMR) and/or antibody-mediated rejection (ABMR) (3). Chronic ABMR has been identified as the leading cause of graft loss in kidney transplantation and appears minimally responsive to current immunosuppressive therapies (4). With inconclusive data from clinical trials (5–7), there is currently no standard of care for the treatment of chronic ABMR.

B cells play a key role in the long-term detrimental effect of alloimmune-mediated injury (8). In transplantation, B cells can produce donor-specific antibodies (DSAs). These antibodies promote acute and chronic rejection by activating complement which causes vascular injury and allograft loss. However, there are other effector mechanisms from antibody binding that contribute to allograft destruction. Human leukocyte antigen (HLA) (9) antibodies can have a direct effect on endothelial cell binding *via* Fc receptors on immune cells such as natural killer (NK) cells, macrophages, and neutrophils to

mediate allograft injury (10). This mechanism of inflammation occurs independently of traditional HLA-associated complement activation (11), hence explaining why complement inhibitors alone are not effective against AMR (12, 13). There are also anti-HLA antibodies that are directed toward alleles not found in the recipient (14). Increasing evidence suggests that these pathogenic antibodies can be directed at minor antigens and autoantigens in the transplanted allograft (14, 15).

The transcriptional regulation of B-cell response to antigen stimulation is complex and involves an intricate network of dynamic intra- and extracellular signals from cytokines and transcription factors. There is a strong interest in understanding B-cell immunobiology as it relates to antibody development and production in response to solid organ transplantation. B-cell contribution to alloimmunity ranges from plasma cell (PC) differentiation and maintenance of long-term humoral immunity, serving as antigen-presenting cells, organizing the formation of tertiary lymphoid organs, and secreting pro- and anti-inflammatory cytokines (16). In this review, we will provide a brief overview of B-cell development and differentiation, then discuss the mechanistic pathways of B-cell activation and differentiation, followed by a review of the transcriptional regulation of germinal center (GC) B cells, PCs, and memory B cells as they relate to solid organ transplant rejection.

Overview of B-cell development and differentiation

B-cell development starts as hematopoietic stem cells in the fetal liver at birth and continues in the bone marrow where stromal cells provide cytokines and chemokines to stimulate hematopoiesis (17). Known as “cellular niches,” these microenvironments control B-lymphocytic behavior within the bone marrow during development. The earliest precursors, pre-pro-B cells, require CXC chemokine ligand (CXCL) 12 produced by a small population of stromal cells (18). These stromal cells are scattered throughout the bone marrow and away from interleukin (IL)-7-secreting cells, which cause the maturation of B-cell precursors.

Prior to B-cell lymphopoiesis, hematopoietic stem cells differentiate into common lymphoid progenitor cells that express factors such as c-kit and IL-7R α (19). Activation of these receptors causes expression of transcription factors E2A and early B-cell factor, which cause these progenitor cells to develop into pro-B cells (20). Pro-B cells in the bone marrow undergo V(D)J recombination, resulting in IgM-expressing immature B cells (21), which migrate to the spleen. These early B cells then become immunoglobulin (Ig)D- and IgM-expressing mature B cells that are ready to be activated by foreign antigens (22).

Two signals are required for these mature B cells to differentiate into antibody-secreting PCs. The first signal is from antigen-coupled B-cell receptors and the second signal is

from T-cell or non-T-cell-related antigens. T-cell-independent antigens, such as lipopolysaccharides and glycolipids, cause the differentiation of B cells into short-lived PCs that produce low-affinity antibodies (23). T-cell-dependent activation, *via* antigen stimulation and follicular helper T-cell (Tfh) interaction, causes differentiation into short-lived PCs or cell entry into germinal centers (GCs) (24). It is in GCs where B cells evolve into high-affinity B-cell receptors (BCRs) *via* mutation and selection by CD4⁺ T cells (25). Here, B cells also develop memory in the form of long-lived PCs and memory B cells (26).

There are two important modulators of B-cell survival: B-cell-activating factors of the tumor necrosis factor (TNF) family (gene name *TNFSF13b*) (BAFF) and TNF ligand superfamily member 13 (APRIL) (27). Both ligands have three receptors, namely, TNF receptor superfamily member 13C [also known as BAFF receptor (BAFF-R) or BLyS receptor 3 (BR3)], TNF receptor superfamily member 17 [also known as B-cell maturation antigen (BCMA)], and TNF receptor superfamily member 13B [also known as transmembrane activator and cyclophilin ligand interactor (TACI)]. BAFF, also known as B-lymphocyte stimulator (BLyS) and TNF-APOL-related leukocyte-expressed ligand (TALL-1), activates nuclear factor kappa B (NF- κ B) signaling pathways upon interaction with BAFF-R. This trigger is important for B-cell survival as it signals the formation and maintenance of B cells (28). In the mouse model, overproduction of BAFF leads to autoimmune diseases like systemic lupus erythematosus (SLE) in humans (29), whereas gene deletion of BAFF prevents the development of an SLE-type disease (30). BAFF and APRIL are produced by myeloid cells, lymphoid cells, and toll-like receptor 9 (TLR9)-activated plasmacytoid dendritic cells and IL-2-activated natural killer cells (31). APRIL has been identified as being important in antibody class switching and plasma cell survival (32). Unlike BAFF, overproduction of APRIL in the animal model does not result in an SLE-type disease (33), but may be a target of interest for inhibiting SLE development in a mouse model (34).

The identification of these factors has led to the FDA-approved monoclonal antibody (mAb) belimumab, specific for BAFF (35), used to halt the immune response in SLE. Although belimumab has shown to have efficacy in reducing SLE disease (35, 36), belimumab has not shown the same results in kidney transplantation. In a double-blind, randomized, placebo-controlled phase 2 trial, Banham et al. observed that treatment with belimumab did not significantly reduce the number of naive B cells in 24 weeks (37). In the United States, studies are underway to further evaluate these findings.

Transcriptional regulation of germinal center B-cell formation

GCs are dynamic structures within peripheral lymphoid organs where T-cell-dependent B-cell selection occurs (38). Antigen-driven PCs and memory B cells from naive B cells

occur in secondary lymphoid tissue in B-cell follicles and in GCs in two phases (Figure 1) (39). Phase 1 starts when antigens attach to the BCR on naive B cells, which then process and present BCR-bound antigen on major histocompatibility complex (MHC) class II molecules (41). This results in short-lived PCs and GC B cells that form in B-cell follicles. These B cells migrate to the interfollicular border of the T- and B-cell zones, causing cell activation, proliferation, and long-term interactions with antigen-specific T cells (42). Most of these activated B cells enter phase 2, in which they differentiate into long-lived PCs and memory B cells in the GC. This B-cell access into the GC has been attributed to interclonal competition for T-cell-associated signals, which occurs outside the follicles (43) and prior to GC formation.

Tfh cells play a crucial role in GC formation and the regulation of GC B cells. Tfh cells are a distinct subset of antigen-activated CD4⁺ T cells that express chemokine receptor (CXCR) 5 and B-cell lymphoma 6 (BCL-6). CXCR5 is a central marker of Tfh cells and shown to be required by B cells for entry into follicles (44). BCL-6 is a transcriptional repressor and master regulator of Tfh cells and GC B cells (Figure 2). This key transcription factor is required for Tfh cell differentiation and is a potent antagonist of B-lymphocyte-induced maturation protein 1 (BLIMP1) (47). Specifically, BCL-6 works to silence PD-1 ligands in GC B cells by binding the promoter region of

PD-L1 and intron of PD-L2 (48). GC precursor cells deficient in BCL-6 cannot migrate to the center of the follicle and become high-affinity, class-switched memory B cells and long-lived PCs (49). Additionally, a recent study in mice by Robinson et al. has suggested that the amount of BCL-6 in B cells shortly after antigen activation determines B-cell fate into and toward the GC (50).

It was commonly believed that the GC is also where immunoglobulin (Ig) class-switch recombination (CSR) occurs. CSR is an intrachromosomal DNA rearrangement of the Ig heavy chain locus, thus allowing mature B cells to express antibodies of IgA, IgG, or IgE classes without altering the specificity for the antigen. CSR relies on the activation of activation-induced cytidine deaminase (51), uracil-DNA glycosylase (UNG), and apurinic-apyrimidinic endonuclease 1 (APE1) to target switch (S) regions (52). Activation-induced cytidine deaminase (AID) is essential for both somatic hypermutation (SHM) and CSR, and is expressed primarily in GCs (53). However, in a mouse model, Roco et al. showed that CSR is initiated over the first few days during the primary immune response (at the T-cell to B-cell interaction) and stops after B cells become GC cells and SHM starts (54). SHM is a major component of affinity maturation, in which the variable regions of the Ig gene produce high-affinity antibodies. The timeline of CSR suggests that CSR occurs outside the GC and

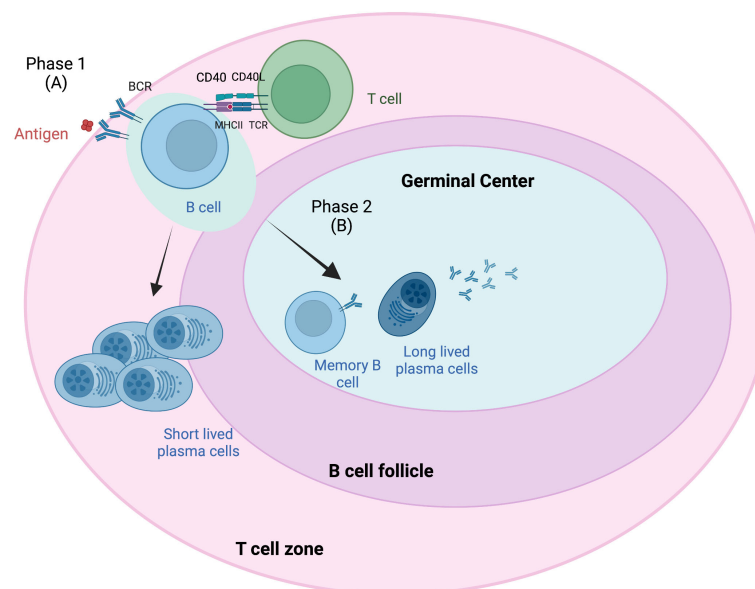


FIGURE 1

Germinal center response overview. The germinal center (GC) response consists of two phases (39). Phase 1 (A) involves the presentation of B-cell receptor (BCR)-bound antigens on major histocompatibility complex (MHC) class II T cells following antigen attachment and presentation to BCR on naive B cells. These B cells migrate to the interfollicular border of the T- and B-cell zones, causing cell activation, proliferation, and long-term interactions with antigen-specific T cells. Some of these activated B cells become short-lived plasma cells (PCs). Most of these activated B cells enter phase 2 (B), where they differentiate into long-lived PCs and memory B cells in the GC. B-cell access into the GC has been attributed to interclonal competition for T-cell-associated signals, which occurs outside the follicles and prior to GC formation. Adapted from Versteegen et al. (40) Figure created with BioRender.com.

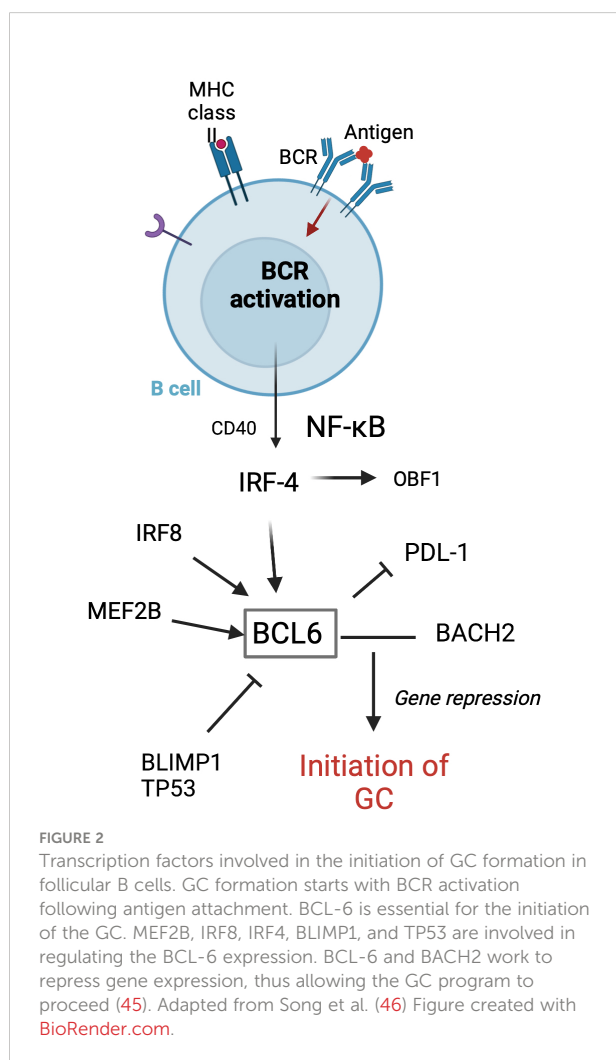
restricting CSR in GC B cells potentially keeps a reservoir of more “naive-like” memory B cells. This is important as IgM⁺ memory B cells are considered more stable over time compared to that of class-switched memory B cells, and they can be rapidly activated in the setting of antigen interaction (infection or foreign pathogen) (55). These new discoveries may help us to understand the generation of pathogenic antibodies during allograft reaction (56).

Tfh cells exhibit seven distinction functions that affect B-cell activity: proliferation, survival, PC differentiation, SMH, CSR, adhesion, and attraction (44). Tfh cells express the CD40 ligand (CD40L) that provides a helper signal for maintaining B-cell survival, and produce IL-21 for promoting cell proliferation and differentiation. CD40L stimulation is a dominant mechanism for T-cell to B-cell interaction. T-cell-derived IL-4 and IL-21 cause transcriptional activation of signal transducer and activator of transcription (STAT) 6 and STAT4, which promote BCL-6 and the subsequent confinement of B cells in the GC (49).

The GC becomes divided into dark and light zones (DZ and LZ), which are organized by chemokines CXCR4 and CXCR5,

respectively. CXCR4 expression, a response to CXCL12, helps B cells localize in the DZ. There, GC B cells undergo SMH, which generates a wide repertoire of antigen specificity (26). This occurs through AID, which induces DNA damage in the Ig genes that is then converted into mutations by DNA repair enzymes (51). BCL-6 must be co-expressed to repress the DNA damage response program that would otherwise induce apoptosis. Upregulation of BCL-6 appears to facilitate the migration of GC precursor B cells to the center of the follicle and enhance integrin-dependent conjugation of B and T cells (49). Forkhead box protein O1 (FOXO1) with BCL-6 represses the expression of BLIMP1 to maintain this GC DZ B-cell program (57). Positively selected GC B cells eventually acquire avian myelocytomatosis virus oncogene cellular homolog (c-Myc) expression, which allows LZ B cells to re-enter the DZ (58). However, recent *ex-vivo* experiments by Radtke et al. showed that subsets of DZ cells expressed BLIMP-1 even during low proliferation states (59). The authors speculated that BLIMP-1 may be induced in certain DZ cells even in the absence of Tfh cells. Similarly, Santamaria et al. observed that human GC B cells that do not express CD23 are likely to differentiate into PC (59). Pae et al. reported that certain DZ B cells appeared to adopt a distinct E2F^{high}/c-Myc^{low} profile, allowing for a rapid and continuous cyclin D3-dependent proliferation despite the absence of signaling from Tfh cells (60). This is most evident in malignant processes, such as Burkitt's lymphoma, where the gain of function mutation leads to increased DZ proliferation and subsequent B-cell lymphoproliferation.

The LZ is characterized by Tfh cells, follicular dendritic cells, and macrophages. There are fewer B cells here compared to the DZ. Dark zone B cells move to the LZ *via* CXCR5, where the Tfh cells, follicular dendritic cells, and macrophages help select modified B-cell receptors for antigen binding. Chemoattraction by CXCL13, a ligand for CXCR5 and GC Tfh cells, causes the recruitment of B cells to co-localize with Tfh cells. It can also modify B-cell adhesion and lymphotoxin synthesis, as CXCL13 has cytokine-type functions. Through positive selection, newly generated LZ B cells that do not produce favorable antibodies undergo apoptosis. B cells can recirculate between LZ and DZ to optimize antigen affinity through repeated SHM, which leads to the generation of high-affinity memory B cells and PCs. In GC B cells, signals from CD40, *via* NF-κB, and BCR are required to induce c-Myc (61). These two signals induce p-S6 in GC B cells, which allows for cell cycle entry. Using single-cell RNA sequencing, Nakagawa et al. identified three different subpopulations of c-Myc⁺, suggesting how positive selection can lead to clonal diversity during affinity maturation (62). Liu et al. observed in a mouse model that GC B cells upregulate C-C motif chemokine ligand 22 and 17 (CCL22 and CCL17, respectively), which interacts with CCR4 on Tfh cells (63). This highlights higher-affinity GC B cells, resulting in affinity maturation. B cells without CCL22 and CCL17 receive less T-cell help and are unable to undergo affinity maturation. Similarly, Li



et al. showed that strong CD40 and BCR signals caused Cbl degradation resulting in increased interferon regulatory factor (IRF) 4 expression and exit from GC affinity selection (64).

In disease processes with dysregulated GC reactions, such as B-cell lymphoma and autoimmune diseases, B cells with mutated BCRs have also been shown to enter the LZ and compete for antigen expression on follicular dendritic cells (65, 66). Those B cells with the highest affinity for the antigen can outcompete other B cells and present peptides on class II MHC. The cells can then receive positive selection signals when they interact with Tfh. However, the ability for BCR mutations to undergo affinity maturation is likely specific to the genetic signature of the disease process. Not all cells with BCR mutations go to the LZ. A recent study by Stewart et al. suggests that mutated BCRs are replaced following SHM, as they rarely reach the LZ (67). These mutated cells undergo apoptosis, whereas functional BCRs re-enter the cell cycle or migrate to the LZ. Additionally, in the murine model, IL-21 has shown to be important in not only sustaining the GC but also promoting the entry of antigen-specific LZ B cells into the cell cycle (68). In IL-21-deficient mice, there was a deficit of LZ B cells entering the S phase of the cell cycle. In the presence of IL-21, Tfh cell interaction with LZ B cells showed a transient expression of *c-Myc*, which appears necessary for centroblast proliferation (68). Gene expression analysis has shown that deficiency in *c-Myc* expression by Tfh cells leads to deregulation of DZ B-cell division and subsequent B-cell lymphoma (69). There are also lower-affinity B cells that do not undergo apoptosis and remain in the GC (62). These retained cells have been associated with aberrations in Fas and BCL-2, which are also seen in B-cell lymphoma (70).

There are several key factors associated with GC development. BCL-6 is key for the initiation of the GC reaction, including the downregulation of sphingosine-1-phosphate receptor type 1 (S1PR1) which otherwise helps mediate B-cell trafficking out of the follicle (9). Myocyte-specific enhancer factor (MEF2C) is required for GC formation, as it has a role in B-cell proliferation immediately after antigen stimulation (71). Interferon regulatory factors (47) are a family of transcription factors that play important roles in innate and adaptive immune responses, such as immune cell development and differentiation and pathogen response (72). Interferon regulatory factor 4 (IRF4) regulates myeloid cell development, thus playing an important role in regulating the inflammatory response. IRF4 has been found to both activate and repress BCL-6 transcription (73) and regulate Tfh cells (74). Early in GC formation, a transient and low expression of IRF4 leads to BCL-6 expression (75), while a more sustained and high level of IRF4 with BLIMP1 upregulates X-box binding protein 1 (XBP1), a transcription factor required for PC differentiation (73). In IRF4 knockout models, IRF4⁻ B cells failed to differentiate into GC B cells (73). Additionally, BCL-6 has also been shown to increase complement activation required for

positive selection in the murine model (76). As a transcriptional repressor, BCL-6 inhibits complement regulators thus allowing C3aR/C5aR signaling required for positive selection despite the presence of Tfh.

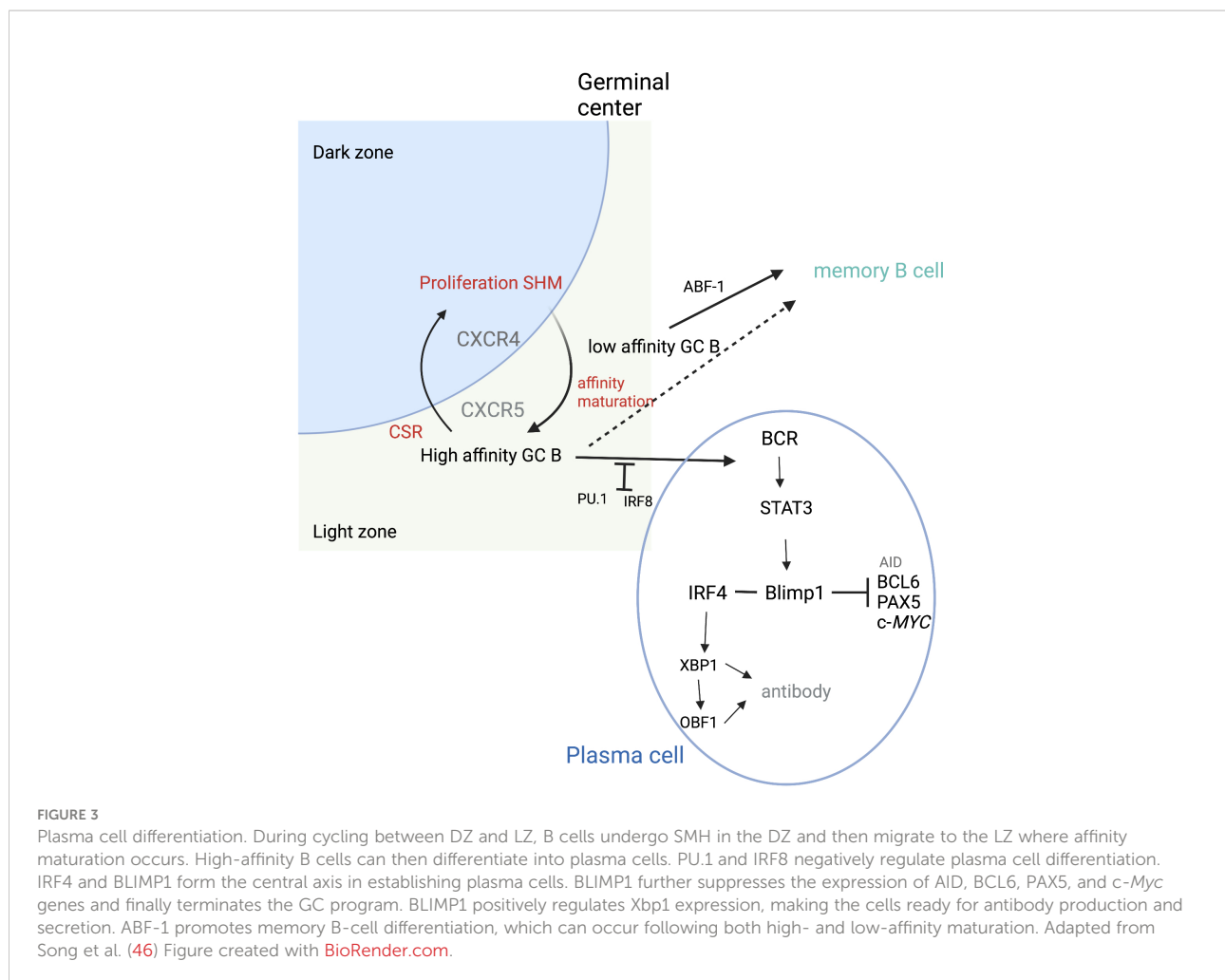
Overall, there are multiple distinct transcription factors that work in a complex but cohesive manner to activate or repress GC development. Understanding how GC development occurs is important in understanding how PC differentiation is regulated. This becomes especially pertinent when evaluating alloimmunity in the setting of chronic rejection in solid organ transplantation.

Transcriptional regulation of plasma cell differentiation

Antibody production occurs in terminally differentiated B cells or PCs. Following GC exit, B cells either become memory cells or PCs (Figure 3). PC fate has been associated with the degree of antigen affinity (77). As mentioned previously, NF- κ B pathways are activated by CD40 signals, inducing *c-Myc* or IRF4 expression. High sustained levels of IRF4 expression are required for PC differentiation (73). BLIMP1, the transcription repressor that can induce plasmablast differentiation, can also increase the level of IRF4 (78). High levels of IRF4 downregulate BCL-6 and induce BLIMP1 expression. Together, IRF4 and BLIMP1 repress the GC program and activate the PC differentiation program. STAT3 regulates PC differentiation by promoting cell survival through activation of such prosurvival genes as B-cell leukemia 2-like 1 (BLC2L1) and myeloid cell leukemia-1 (MCL1) (79). Conversely, IRF8 with PU.1 transcription factor inhibits GC B-cell differentiation to PCs (80). The balance between IRF4 and IRF8 may be crucial in determining B-cell fate (80).

There are several cytokines that appear to play important roles in B-cell proliferation. IL-21 is the most potent cytokine for stimulating PC differentiation and is key in B-cell proliferation (81). BTB domain and CNC homolog 2 (BACH2) and paired box 5 (PAX5) are upregulated in the light zone GC B cells. BACH2 appears to regulate light zone B cells to commit to the memory B-cell pathway by repression of BCL-6 (45), as BACH2 deficiency leads to lower memory B-cell differentiation (82). Activated B-cell factor 1 (ABF-1) blocks the PC differentiation program (83). In the ABF-1-ER mouse model, ABF-1 promotes GC formation and memory B-cell differentiation. BCL-6 inhibits PC differentiation by repressing PR/SET domain 1 (*PRDM1*) expression (84). STAT5 appears to modulate BCL-6 expression, which then represses *PRDM1* expression, thus promoting memory B-cell differentiation. When *PRDM1* expression occurs, BLIMP1 is encoded, thus allowing for PC differentiation.

PC differentiation is also controlled by epigenetic programs. In an *in-vivo* T-cell-independent B-cell differentiation model, Schärer et al. described a cellular division-dependent *cis*-regulatory element (85). Enhancer of zeste 2 polycomb



repressive complex 2 (EZH2), a catalytic subunit of the polycomb complex, provides a repressive histone modification of H3K27m3 (trimethylation of histone H3 lysine 27) necessary for B-cell development during the GC reaction (86). Chemical inhibition of EZH2 resulted in enhanced PC formation *ex vivo* (85), as well as premature expression of BLIMP1. Barwick et al. showed that *de-novo* DNA methylation limits the regulation of PC differentiation by repressing the PC chromatin state (87).

PC generated during the GC reaction migrates to the bone marrow, where PCs can stay quiescent for a long duration of time. This may provide an important clue as to the chronic activation of the immune response during solid organ transplantation, despite immunosuppressive therapy.

Allogenic B-cell response and transplant rejection

Although alloreactive T cells are traditionally considered to be the primary culprit in mediating allograft reaction, it is the T-

and B-cell interaction that plays a key role in generating humoral alloimmune responses so detrimental to the longevity of the solid organ transplant. As discussed previously, memory B cells are generated from low-affinity GC B cells in the light zone and will eventually enter the circulation as patrolling cells or stay in lymphoid or target organs. Solid organ allografts, such as in kidney transplantation, become ectopic lymphoid-like structures (88), where alloreactive B cells can form an extrafollicular response as short-lived PCs or return to B-cell follicles to initiate a GC reaction (89). In the GC, B cells can undergo SHM and compete for Tfh cell interactions for high antigen affinity. These B cells can then transition into long-lived PCs, while the lower affinity B cells remain as a more diverse pool of B cells (90). The lower affinity B cells can then circulate in their quiescent form until a recognizable antigen is encountered.

Follicular regulatory T (Tfr) cells are a unique subset of forkhead box P3 (FoxP3)⁺ regulatory T cells (Tregs) that inhibit Tfh and B cells. Tfr cells downregulate the co-stimulatory molecule cluster of differentiation 86 (91) (CD86) on B cells, producing inhibitory cytokines such as IL-10 (92). Like other

Tregs, Tfr cells can also express Helios, a marker reflecting enhanced immunosuppressive function (93). The balance between Tfr and Tfh is crucial for immune homeostasis and tolerance, as an aberrant Tfr/Tfh ratio has been linked to autoimmune diseases (94) such as systemic lupus erythematosus and myasthenia gravis (95). In kidney transplantation, antibody-mediated rejection has also been associated with an imbalance in circulating Tfr and Tfh cells (96).

As described previously, Tfh cells play an important role in alloreactivity and provide help to alloantigen-activated B cells. This is also evident in solid organ transplantation. Tfh cells are present in kidney transplant allografts with the pathological findings of T-cell-mediated rejection (97, 98). They can also stimulate alloantibody production, which mediates humoral responses against the transplanted organ (99). Tfr cells are found to be impaired in this setting, leading to an uncontrolled allogeneic response from Tfh cells following transplantation. Similarly, Louis et al. observed a loss of regulatory T and B cells in kidney transplant recipient serum in the setting of ABMR (100). Similar to Treg cells, transitional B cells (Trb) play a role in immune suppression, as the authors found that Trb suppressed Tfh activation, Tfh- to B-cell activation, and antibody generation *in vivo*.

Immunosuppression has been found to alter the absolute number of Tfr and Tfh cells in kidney transplant recipients. Niu et al. showed that peripheral Tfr cells significantly decreased with calcineurin inhibitor-based therapy (101), while Tfh did not change. When transplant recipients were treated with alemtuzumab, a monoclonal antibody that binds CD52, there were lower numbers of total and subset Tfr cells and total Tfh cells, suggesting an impairment of the homeostatic proliferation of Tfr cells. Similarly, Macdeo et al. showed a significant decrease in Tregs in peripheral blood mononuclear cells (PBMCs) of kidney transplant recipients compared to that of non-immunosuppressed healthy controls (102). Despite lymphodepletion, this shift to Tfh cells may result in increased memory B-cell formation and PCs, potentially increasing the risk of antibody-mediated rejection. Clinically, patients treated with alemtuzumab have been shown to have a higher incidence of chronic antibody-mediated rejection and donor-specific antibodies despite this antirejection therapy (103).

Another therapy being used on kidney transplant recipients is belatacept, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) co-stimulatory inhibitor. Belatacept targets CD80/86 to prevent interaction with CD28 and CTLA-4, thus preventing the T- and B-cell interactions required for class-switch recombination and GC response. In early clinical trials, belatacept demonstrated a significant reduction in the incidence of DSA (104) but increased early rejection in this group (105, 106), suggesting the need for combination treatment. In non-human primate data, Schroder et al. showed feasibility of using co-stimulatory blockade *via* CTLA-4 Ig with plasma cell inhibition (*via* carfilzomib) for pretransplant desensitization and ABMR treatment (107, 108). The authors report that the selective targeting of CD28 reduced DSA, Tfh, and

B-cell expansion while preserving Treg cells and promoting naive T and B cells. With strong evidence supporting the reduction of DSA using belatacept alone and with combination therapy, there are two ongoing clinical trials investigating the use of plasma cell inhibitors (carfilzomib (109) or daratumumab (110)) and belatacept for desensitization in patients awaiting kidney transplant.

Humoral immunity against the allograft may be due to a steady production of donor-specific antibodies created from alloreactive T- and B-cell interactions, despite immunosuppressive therapy. In mouse studies, B cells recognizing one specific donor MHC can receive stimulatory help from T cells specific to another donor MHC, thus stimulating alloantibodies against an allograft (111). When naive CD4⁺ T cells were depleted by co-stimulation blockade of CD40/CD154, interferon-gamma (IFN- γ)-producing memory CD4⁺ T cells were still able to activate B cells (112). Thus, alloantibody response can be initiated prior to transplant due to the diverse repertoire in memory B cells (113). This may be undetectable in the serum, as donor-reactive memory B cells are not measured during immunologic risk assessments prior to transplant. Additionally, the failure of immunosuppressive therapy suggests that there is a heterogeneity of B-cell lymphocyte populations and functions.

Targeting memory B-cell longevity may be the answer to resolving immunosuppression failure in solid organ transplantation. In vaccine studies, B-cell-intrinsic autophagy has been shown to be critical for memory B-cell longevity (114) and maintenance (115). Chen et al. observed that autophagy was found to be essential for memory B-cell maintenance against viral infections in mice. The authors found decreased spontaneous cell death and increased B-cell survival in the presence of autophagy, as evidenced by increased FOXO1 and FOXO3 expression in memory B cells over time (115). In the absence of autophagy, there was increased oxidative stress and memory B-cell loss. FOXO3 silencing also led to a suppression of autophagy gene expression in memory B cells. In a subsequent study by Kodali et al., the authors demonstrated that in the presence of Nix- and Bnip3-mediated mitochondrial autophagy (116), there was maintenance of metabolic quiescence and longevity of memory B cells. In a transplant mouse model, Fribourg et al. showed the effect of autophagy in memory B cells in transplantation. By inhibiting autophagy through the chemical inhibitor 3-methyladenine, the authors demonstrated a decrease in DSA responses to alloantigens in treated versus control mice. Such important findings provide potential therapeutic targets against autophagy, which may help mitigate the B-cell response in clinical transplantation.

Summary

The intrinsic relationship between T- and B-cell pathways results in a complex interplay activating rejection pathways in solid organ transplantation. Transcriptional factors, such as IRF4, initially appear to affect allogenic T-cell effector

pathways (117), modulating the inflammatory response. Within this response, B-cell pathways become activated (118), creating a chronic pathway of rejection that is currently untreatable with current immunosuppressive therapies. Emerging evidence suggests that transcriptional regulation through B cells is the key to transplant tolerance. Elucidating various B-cell subtypes, like T-cell subtypes, may also be necessary to better understand early B-cell response on a transcriptional level. Future modalities investigating both metabolic and epigenetic regulation will prove useful in understanding the complexities within B-cell response in transplantation. Such information can provide important insights as to the early detection of immune risk prior to transplantation, specifically as it relates to B-cell response, as well as the development of therapeutic modalities for both prophylaxis and treatment against chronic allograft rejection.

Author contributions

SY and WC conceived and wrote the review. SY, AG, and WC contributed to the article and approved the submitted version.

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Conflict of interest

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Glossary

ABF-1	activated B-cell factor 1
AID	activation-induced cytidine deaminase
ABMR	antibody-mediated rejection
APE1	apurinic-apyrimidinic endonuclease 1
c-Myc	avian myelocytomatosis virus oncogene cellular homolog
BAFF	B-cell activation factor of the TNF family
BCL-6	B-cell lymphoma 6
BCL2LC1	B-cell leukemia 2-like 1
BCMA	B-cell maturation antigen
BCR	B-cell receptor
BCRP	B-cell receptor protein
BLIMP1	B-lymphocyte-induced maturation protein 1
BR3	BLyS receptor 3
BACH2	BTB domain and CNC homolog 2
CCL22	C-C motif chemokine ligand 22
CCL17	C-C motif chemokine ligand 17
CD40L	CD40 ligand
CXCR	chemokine receptor
CD	cluster of differentiation
CXCL	CXC chemokine ligand
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DZ	dark zone
DSAs	donor-specific antibodies
EZH2	enhancer of zeste 2 polycomb repressive complex 2
Tfh	follicular helper T cells
Tfr	follicular regulatory T cells
FOXO1	forkhead box protein O1
FOXO3	forkhead box protein O3
FoxP3	forkhead box P3
GC	germinal center
HLA	human leukocyte antigen
Ig	immunoglobulin
IFN- γ	interferon-gamma
IRF	interferon regulatory factor
IL	interleukin
LZ	light zone
MHC	major histocompatibility complex
mAb	monoclonal antibody
MCL-1	myeloid cell leukemia-1
MEF2C	myocyte-specific enhancer factor
NK	natural killer
NF- κ B	nuclear factor kappa B
PAX5	paired box 5
PBMCs	peripheral blood mononuclear cells
PCs	plasma cells
PRDM1	PR/SET domain 1
STAT	signal transducer and activator of transcription

Continued

SHM	somatic hypermutation
S1PR1	sphingosine-1-phosphate receptor type
SLE	systemic lupus erythematosus
TALL-1	TNF-APOL-related leukocyte expressed ligand
TCMR	T-cell-mediated rejection
TACI	transmembrane activator and cyclophilin ligand interactor
Trb	transitional B cells
H3K27m3	trimethylation of histone H3 lysine 27
TNF	tumor necrosis factor
UNG	uracil-DNA glycosylase
XBP1	X-box binding protein

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