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Review

# B cells in chronic graft-versus-host disease

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (alloHCT) is the definitive therapy for numerous otherwise incurable hematologic malignancies and non-malignant diseases. The genetic disparity between donor and recipient both underpins therapeutic effects and confers donor immune system-mediated damage in the recipient, called graft-versus-host disease (GVHD). Chronic GVHD (cGVHD) is a major cause of late post-transplant morbidity and mortality. B cells have a substantiated role in cGVHD pathogenesis, as first demonstrated by clinical response to the anti-CD20 monoclonal antibody, rituximab. Initiation of CD20 blockade is met at times with limited therapeutic success that has been associated with altered peripheral B cell homeostasis and excess B Cell Activating Factor of the TNF family (BAFF). Increased BAFF to B cell ratios are associated with the presence of circulating, constitutively activated B cells in patients with cGVHD. These cGVHD patient B cells have increased survival capacity and signal through both BAFF-associated and B Cell Receptor (BCR) signaling pathways. Proximal BCR signaling molecules, Syk and BTK, appear to be hyper-activated in cGVHD B cells and can be targeted with small molecule inhibitors. Murine studies have confirmed roles for Syk and BTK in development of cGVHD. Emerging evidence has prompted investigation of several small molecule inhibitors in an attempt to restore B cell homeostasis and potentially target rare, pathologic B cell populations.

## 1. Introduction

Hematopoietic stem cell transplantation is the definitive therapy for a variety of diseases including hematologic malignancies and non-malignant disorders [1,2]. Use of autologous HCT (autoHCT) and allogeneic HCT (alloHCT) is increasing within the United States and globally [2,3]. In autoHCT, a therapy for one subset of diseases, a patient's stem cells are harvested and stored before the patient undergoes either fully myeloablative or non-myeloablative conditioning to eradicate the underlying hematolymphoid disorder or cancer. Because the treatment also ablates the patient's ability to recover immune, blood and platelet cell production, the patient's own stems cells are returned, to allow for blood production, immune recovery, and return to homeostasis. AutoHCT is very rarely associated with immune pathology and graft-versus-host disease (GVHD) is by definition impossible, given donor and recipient are identical. Similarly, patients who undergo syngeneic (identical sibling) HCT very rarely develop GVHD [4]. By contrast, alloHCT is reserved for patients who require additional immunotherapy along with reconstitution of their blood and immune systems. AlloHCT is typically employed for otherwise refractory clonal hematolymphoid or aplastic bone marrow diseases. The patient ('recipient' or 'host') undergoes myeloablative or non-myeloablative conditioning, the donor immune cells are subsequently infused into the recipient, and the donor immune cells ultimately reconstitute in the recipient, replacing the recipient's own blood and immune cells. In alloHCT, the genetic disparity between donor hematolymphoid cells and recipient cells is necessary to eradicate the underlying disease via graft-versus-tumor effects. Polymorphic antigens in the recipient, not found in the donor, are responsible for the development of immune pathology and graft-versus-host disease (GVHD).

In alloHCT recipients, immune reconstitution of donor cells occurs within a 'foreign' host and thus anti-recipient cells develop that can potentially lead to pathological immune targeting and damage of host, manifesting as GVHD [5,6]. Acute GVHD (aGVHD) and chronic GVHD (cGVHD) are well described clinical syndromes with unique symptom constellations, diagnostic criteria, therapeutic considerations, and

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prognoses [7–9]. While T cells have long been known to be critical drivers of alloreactivity in both aGVHD and cGVHD and are reproducibly observed in biopsies of lesional tissue, B cells also have a substantiated role in cGVHD [10,11]. Production of allo- and autoantibodies in patients suffering from cGVHD suggests a distinct ongoing loss of B cell tolerance in this disease. Transferable T cell autoreactivity after development of alloreactivity has been reported in murine models, revealing that alloantigen responses result in autoreactivity [12,13]. Findings from studies of cGVHD patients have implications for *de novo* autoimmune diseases, as well, since inciting alloreactivity likely begets autoreactivity in those diseases [12,14].

Despite clinical and pre-clinical studies aimed at elucidating mechanistic pathways and evaluating potential therapies, largely directed at T cells, cGVHD remains a significant cause of patient morbidity and mortality [8,15–21]. Emerging evidence revealing a key role for B cells in driving disease development and progression has led to the consideration of new therapeutic avenues [20–25]. This review will focus on potential mechanisms underlying loss of B cell tolerance in the post-alloHCT setting and the current understanding of potentially targetable B-cell signaling pathways in cGVHD.

## 2. B cell reconstitution and maturation after HCT

In healthy individuals, B cells contribute to immune function through antibody production and various antibody-independent mechanisms, including antigen presentation and cytokine secretion [26–29]. Development, selection, and activation of B cells occur continuously throughout life (Fig. 1A). B lymphopoiesis begins in the bone marrow, where lymphoid progenitor cells differentiate into immature naïve B cells [29]. Early B cell development includes random immunoglobulin gene segment recombination, carrying the potential for autoreactivity [30]. B cells thus undergo both positive selection, insuring successful signaling through the antigen receptor, and negative selection, insuring a lack of self-reactivity. In the event that a B cell is negatively selected, it will undergo apoptosis, induction of anergy, or receptor editing (additional gene rearrangement) [31,32]. 'Transitional' B cells are then released from the bone marrow into the periphery with a unique B cell receptor (BCR) [33].

Mature B cells that have survived development, positive selection, and negative selection ultimately undergo activation via binding between BCR and the appropriate specific antigen [34–36]. Upon activation, B cells further differentiate into short- or long-lived B cells based on signals within the surrounding immunologic milieu [28,29,34]. Successful development, selection, differentiation, and survival of B cells all notably rely on the presence of numerous soluble factors in appropriate concentrations, including B Cell Activation factor (BAFF). Soluble BAFF is an activation and survival factor, involved in B cell maturation and survival both within the primary lymphoid organ and peripherally [37,38]. BAFF is a member of the tumor necrosis factor (TNF) family, and is produced by macrophages, monocytes, dendritic cells, T cells, and stromal cells [38–41]. BAFF binds to any of three BAFF receptors, mainly expressed on B cells. Excess BAFF is known in mouse models to promote autoreactive B cells in murine models of autoimmunity. Soluble BAFF levels and B-cell immune homeostasis have been shown to be regulated by the presence of peripheral naïve B cells that express BAFF receptor that is occupied by soluble BAFF and therefor unavailable to other B cells [42,43].

After alloHCT, immune reconstitution from donor stem cell products occurs within the host/patient. B cell development and survival occurs under constant exposure to alloantigen and increased levels of essential soluble factors, including BAFF (Fig. 1B). In the post-HCT lymphopenic, alloantigen-rich immunologic microenvironment the peripheral T and B cell compartments are skewed, with inappropriate survival and activation of aberrantly activated T and B cells [44–46]. T cells are critical drivers of T-B cell alloreactivity in ongoing cGVHD [47]. Higher levels of BAFF promote maintenance and survival of immature and mature B cells, while lower levels of BAFF diminishes the likelihood of survival [48–51]. Studies show that increased levels of BAFF, present in the post-alloHCT immune milieu, leads to inappropriate rescue of self-reactive B cells in the peripheral immune compartment, thus disrupting "appropriate" negative selection mechanisms meant to disallow survival of allo- or autoreactive B cells [42,43]. Studies additionally demonstrate that high BAFF to B cell ratios are associated with deranged peripheral B cell homeostasis in cGVHD patients [46,52]. Excess BAFF is not likely simply a result of B lymphopenia, as patients with cGVHD can have normal total numbers of B cells. Which cell types produce excess BAFF, and whether these are of donor or recipient origin, remains an area of active investigation.

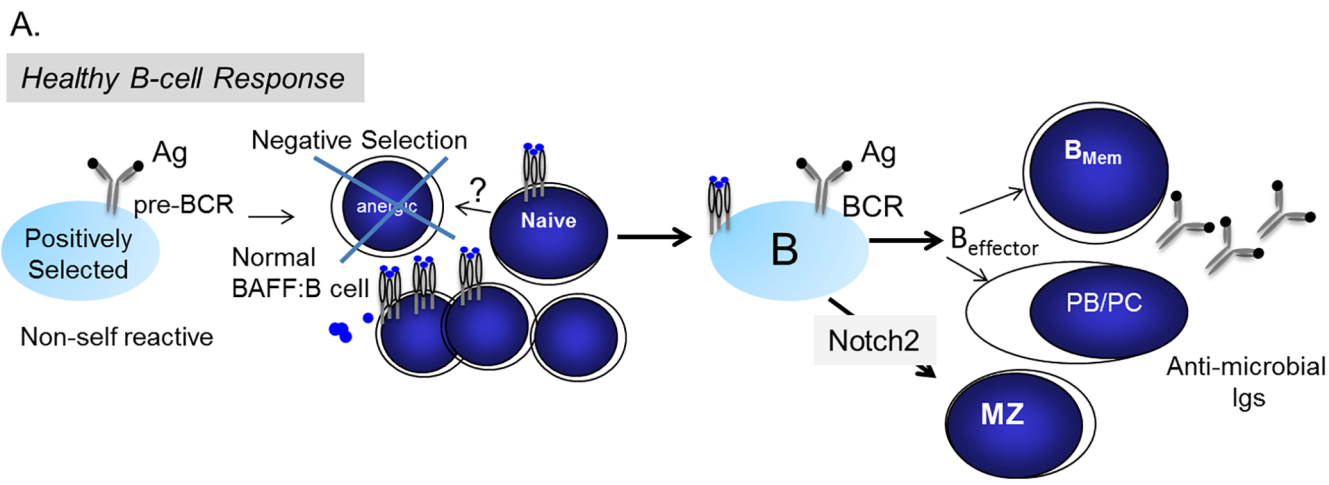


**Fig. 1.** B cell development and maturation in a healthy individual versus in an individual with post-HCT cGVHD: A) Depiction of functional maturation and activation in healthy B cells. Encounter with an appropriate BCR-specific non-self antigen results in positive selection in the bone marrow [110]. After release of B cells from the bone marrow, negative selection (elimination) of potentially autoreactive clones occurs when there is a normal BAFF:B cell ratio (insufficient BAFF to support rare autoreactive clones). Mature B cells, in the absence or presence of NOTCH2 activation, will further differentiate into either effector follicular B cells or Marginal zone cells [111]. B) Depiction of aberrant maturation and activation of B cells in cGVHD: After HCT, a high BAFF:B cell ratio activates B cells and primes them for survival. These B cells manifest BCR hyper-responsiveness that is associated with over-expression of BCR signaling molecules including Syk and BLNK [67]. Alloreactive T cells ($T_{allo}$) are known to cooperate with B cells in human cGVHD [44,47]. Aberrant stimulation of NOTCH2 receptor and BCR likely plays an important role in constitutive B cell stimulation in the altered peripheral B cell compartment [77].

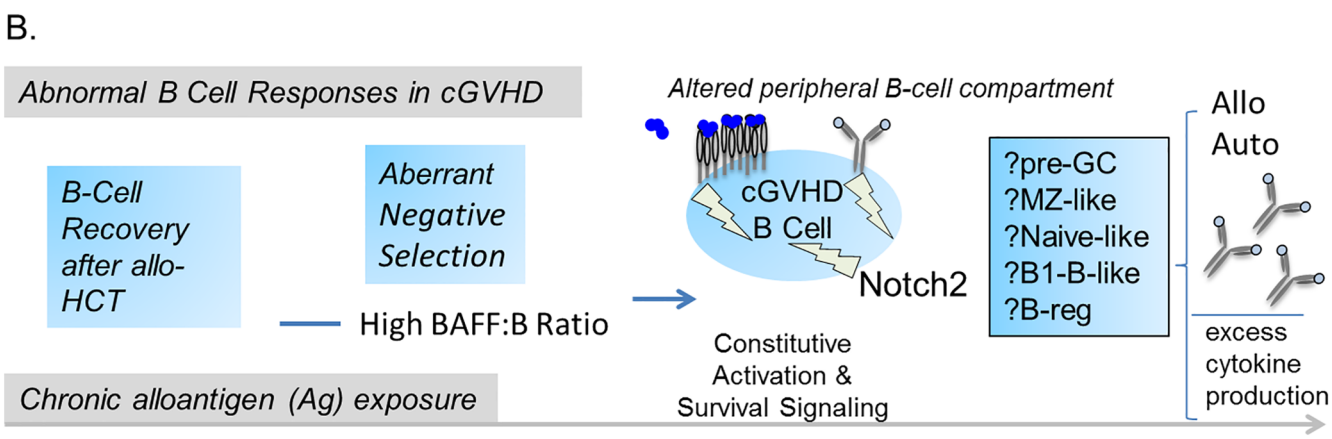


**Fig. 1.** (*continued*)

**Table 1**
Agents that potentially target B cell pathways in cGVHD. Molecular targets and associated mechanisms of action for agents with potential relevance in cGVHD, along with details regarding known efficacy in other diseases and FDA approval status related to cGVHD.

| Major Target of Agent | Major Mechanism of Action | Published efficacy in other diseases | Names of drugs being investigated in cGVHD |
|---|---|---|---|
| Monoclonal humanized anti-CD20 antibody | • Anti-CD20 antibody | • Non-Hodgkin's Lymphoma [112]<br>• Chronic lymphocytic leukemia [113]<br>• Follicular B-Cell Lymphoma [114]<br>• Rheumatoid arthritis<br>• Granulomatosis with polyangiitis<br>• Idiopathic thrombocytopenic purpura (ITP) | • Rituximab [115]<br>• Ofatumumab [116]<br>• Obinatuzumab [117] |
| BTK and ITK inhibitor | • Inhibition of BTK in B cells with decreased proliferation and survival [118].<br>• Inhibition of ITK in Th1/Th17 with decreased T cell proliferation and survival [119]. | • Chronic lymphocytic leukemia [120].<br>• Mantle cell lymphoma [121].<br>• Previously treated WM [122].<br>• Various B cell malignancies [123]. | • Ibrutinib (Approved for steroid-refractory chronic GVHD in 2017) [124] |
| Syk inhibitor | • Inhibits Syk and activated Syk in monocytes and B cells [125]. | Fostamatinib:<br>• Rheumatoid arthritis [126].<br>• Various B cell malignancies [127].<br>• ITP [128].<br>Entospletinib:<br>• Chronic lymphocytic leukemia [129].<br>Credulatinib (dual Syk/JAK inhibitor):<br>• Rheumatoid arthritis, and<br>• Various B cell malignancies [130]. | • Fostamatinib [131]<br>• Entospletinib [132] |
| EZH2 inhibitor | • Prevents histone methylation (silencing) of tumor suppressor genes | • Follicular lymphoma [134]<br>• Various lymphomas [133]<br>• Epitheliod sarcoma<br>• Mesothelioma | • AUY922 [135] |
| Bcl-6 inhibitor | • BCL6 transcriptional repressor | • DLBCL [136] | • 79-6 [137,138] |
| All-*trans* retinoic acid (ATRA) | • Increases IRF4 expression in human B cells stimulated with CpG [139] | • APML [140] | • ATRA [77]<br>• Etretinate [141] |

Abbreviations: APC, antigen presenting cell; APML, acute promyelocytic leukemia; ATRA, all-*trans* retinoic acid; BCC, basal cell carcinoma; BCL-6, B cell lymphoma-6; BTK, Bruton tyrosine kinase; BO, Bronchiolitis obliterans; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; CpG, cytosine guanine dinucleotide; DLBCL, Diffuse large B cell lymphoma; EZH2, Enhancer of zeste homolog 2; FEV1, forced expiratory volume in 1 s; ITK, IL2-inducible tyrosine kinase; MM, multiple myeloma; MS, multiple sclerosis; NE, neutrophil elastase; OS, overall survival; PFS, progression free survival; PMF, primary myelofibrosis; PV, polycythemia vera; RA, rheumatoid arthritis; Th1, T helper 1; Th17, T helper 17; WM, Waldenstrom macroglobulinemia.

Mouse studies reveal a mechanistic role for BAFF in cGVHD development [53]. Strikingly, rapid naïve B cell recovery, including after umbilical cord transplantation, in which low BAFF to B cell ratio and increased kappa deleting recombination occurs, is associated with a decreased risk of cGVHD [54–56]. Supra-normal numbers of B cells found in patients who never develop cGVHD appear to sequester soluble BAFF on their cell surface receptors and thus may serve to regulate against cGVHD through this sequestration of excess soluble BAFF [57–59]. How BAFF affects IL10-producing B cells that are known to be proportionally decreased and unable to properly signal in patients with active cGVHD remains unknown [57]. Dysregulation of BAFF appears to play a key role in development of cGVHD.

Patients with cGVHD have significantly increased levels of auto- and alloantibodies [60,61]. The decreased antigen binding site diversity present during initial donor B cell re-expansion coupled with higher BAFF expression increases the likelihood for inappropriate B cell activation and survival, including via ubiquitously expressed antigens [62,63]. Both B cell production within the bone marrow and output of B cells from the bone marrow are significantly abnormal, increasing the risk of cGVHD [56,64,65]. Delayed B cell recovery also leads to

decreased numbers of precursor B cells and transitional B cells from the bone marrow [62,64–66]. In cGVHD, constitutive antibody production by the $CD27^+$ B cell sub-population in patients with active disease manifestations suggests antibody production is at least one mechanism by which B cells contribute to cGVHD [67,68]. A role for antibody production in cGVHD genesis has been substantiated [69,70]. Antibodies have been shown to target thymic epithelial cells in mice and a variety of known autoantigen targets of antibodies in cGVHD patients are reported, though no single antibody-mediated pathology has been identified [69,71,72]. Unlike some *de novo* autoimmune diseases, there is no immune complex deposition or other hallmark finding in cGVHD. A coordinated T cell and B cell response has been revealed in both patients and mice [47,73,74]. Additional pathologic functions of B cells such as cross-presentation to T cells and B cell cytokine production in cGVHD remain areas of active investigation.

Taken together, data suggest that chronic exposure to ubiquitous foreign antigens in the presence of excessive BAFF likely leads to promotion of B cells with increased BCR responsiveness rather than anergy [45,67]. The mechanism by which BAFF promotes BCR-activated B cells is an area of active investigation [75]. BCR hyper-responsiveness is associated with increased expression of proximal signaling molecules including spleen tyrosine kinase (Syk) and B cell linker (Blnk) protein. Since increased antibody production against auto- and alloantigens are associated with development of cGVHD, these data suggest that rare activated populations might be eliminated if BCR signaling is preferentially blocked [71,72,76]. Of particular interest, all B cells after alloHCT may be primed for increased antigen responsiveness given alterations in the pivotal maturation transcription factors, IRF4 and IRF8 [77]. NOTCH2 activation affords *ex vivo* BCR responsiveness by cGVHD B cells even by exceedingly low levels of surrogate antigen. Inhibition of NOTCH2 pathway using a specific monoclonal antibody successfully blocked the abnormal BCR hyper-responsiveness seen in cGVHD, suggesting that NOTCH2 signaling promotes aberrant BCR activation in cGVHD. These data suggest B cells that survive after HCT have increased BCR responsiveness because of intrinsic molecular defects.

## 3. B cells in active chronic GVHD

While no single set of cell surface markers identifies the aberrantly activated B cell population in cGVHD, certain peripheral B cell subsets have been significantly associated with disease in patients. In the setting of high BAFF to B cell ratio and relative hypogammaglobulinemia, a transitional B cell subset with $CD27^-$ $CD21^{low}$ expression has been associated with increased severity of cGVHD [78–81]. CD27 is normally expressed on B cells after antigen encounter and has been found in cGVHD to constitutively produce antibodies even without BCR activation [45]. CD27+ B cells are proportionally increased in patients with cGVHD [82]. These data suggest a pathological role for distinct B cell subsets in cGVHD, and functional correlations between notable B cell phenotypes merit further investigation [46,81].

How germinal center (GC) reactions and extrafollicular reactions may perpetuate disease remains uncertain [83]. Both pre-GC ($CD27^+CD38^{hi}IgD^+$) and post-GC plasmablast-like ($CD27^+CD38^{hi}IgD^-$) B cells are increased in patients with active cGVHD as compared to healthy counterparts [46]. Of note, this circulating population is typically exceedingly difficult to isolate in healthy subjects but it is proportionally increased in patients with *de novo* autoimmune diseases. GC formation is essential for maintenance of cGVHD and requires the interaction between T follicular helper cells (TFH) and GC B cells [84]. TFH cells produce IL21, known to be essential for GC formation and cGVHD development [73,85]. Despite a relative decrease in number, TFH cells in patients with cGVHD are activated, with a predominance of Th2 and propensity to become Th17 cells potentially linked to increased B cell activation and maturation [44]. Our understanding of TFH cells' role in cGVHD led to targeting this population through eliminating the production of IL21 by donor T cells or blocking IL21 receptor signaling by donor B cells. The use of Rho-associated kinase 2 inhibitor KD025 block IL21 production was associated with decreased STAT3 and increased STAT5 phosphorylation that results in marked reduction of antibody and collagen deposition in the lungs compared to non-cGVHD controls [86,87]. Other targets preventing the interaction between TFH cells and GC B cells have been identified including inducible T cell costimulator (ICOS) and its ligand (ICOS-L), IL40 and its receptor (IL40-R). Blocking TFH/GC B cells interaction and GC formation through these targets have reversed the lung manifestations of cGVHD in mice, and form the basis for some of the ongoing clinical investigation summarized below [73,86].

## 4. Targeting B cell pathways in chronic GVHD

Monoclonal antibodies against the B cell surface marker CD20 have been used extensively in cGVHD. Rituximab, the original monoclonal anti-CD20 antibody, is a principal element in the treatment of B cell malignancies and has been studied in cGVHD. While rituximab has been studied as both prophylactic therapy against GVHD and as a therapeutic agent to treat steroid-refractory cGVHD, the evidence is currently fairly limited to a small number of prospective trials with relatively few patients included, and variable response rates [84,88,89]. Of note, patients with a failure to reconstitute a functional peripheral B cell compartment were unresponsive to rituximab, presumably because abolishing all $CD20^+$ B cells perpetuated altered B cell homeostasis [84,90]. Thus, pursuit of novel targeted agents that may eliminate aberrantly activated B cells and maintain or even restore B cell homeostasis are under investigation.

Syk is important for BCR and FcR signaling. It is not expressed by mature T cells but one study showed that the Syk inhibitor, fostamatinib, blocked phosphorylation in T cells. Studies show increased amounts of Syk in B cells of patients with active cGVHD [63,91,92]. Small molecule inhibitors of Syk have been shown to be effective therapies in mouse models of GVHD [91,93]. The Syk inhibitor fostamatinib successfully reversed manifestations of cGVHD in a murine model of B-cell dependent bronchiolitis obliterans, though was less efficacious in a monocyte-driven murine model of scleroderma [91,94]. Targeting Syk via fostamatinib (renamed TAVALISSE, Rigel Pharmaceuticals) was recently FDA approved for immune thrombocytopenia purpura and is being actively investigated in a cGVHD patient clinical trial, based on mouse and human studies in cGVHD [95]. Importantly, administration of fostamatinib in a mouse model prior to the development of cGVHD resulted in both disease attenuation and improved immune recovery, with increased total B and T cell numbers, suggesting Syk blockade early after HCT is safe and may be more effective at averting cGVHD [96]. Another Syk inhibitor, entospletinib, was granted orphan drug designation for prevention of cGVHD based on mouse data, however a randomized control trial testing efficacy as first-line therapy was closed early due to lack of efficacy [97]. Another agent, ibrutinib, is the first drug to be approved by the FDA for steroid-refractory cGVHD [98]. Ibrutinib blocks BCR as well as T-cell Bruton tyrosine kinase (BTK) and IL2 inducible tyrosine kinase (ITK) activation. ITK has been linked to many effector functions of TFH and T17 cells, as well as antibody formation by GC B cells [99,100]. Blocking B cell activation via BTK and T cell activation via ITK was shown in mice to decrease the GC reaction and lung fibrosis in sclerodermatous murine model, suggesting a therapeutic role in cGVHD [101–103]. A large randomized clinical trials testing the efficacy of ibrutinib as a front-line agent in cGVHD is underway [104].

In addition to BCR pathway inhibition, other available inhibitors may effectively target dysregulated B cells (Table 1). Transcriptional pathways that facilitate GC formation can be targeted in cGVHD including BCL6, which functions in cooperation with chromatin associated factors; EZH2 lysine methyltransferase; and BRD4 epigenetic reader protein [98]. Targeting BCL6 via small molecule BCL6 inhibitor

79-6 in mice decreased GC formation and lung collagen [105]. Likewise, selectively inhibiting EZH2 has decreased GC formations and prevented cGVHD [106,107]. Using epigenetic readers recognizing histone modifications as JQ1 in mice has significantly inhibited BO and collagen deposition [73]. NOTCH blockade resulted in many genetic alterations in cGVHD B cells, with up-regulation of some molecules and down-regulation of others. Marginal zone (MZ)-like B cells genes including CR2/CD21 and FCRL4/IRTA1 are among the genes down-regulated via NOTCH blockade, indicating possible interplay between cGVHD B cell and MZ-like cell populations. Conversely, FOS is among genes up-regulated with NOTCH blockade, confirming its suppressive effect on BCR-mediated proliferation. At the transcriptional level, NOTCH stimulation may alter the IRF4/IRF8 balance in cGVHD B cells through an effect on BCR [77,108,109], pointing to a role for All-*Trans* Retinoic Acid (ATRA) in normalization of B cell maturation after allo-HCT [77].

B cell homeostasis and signaling encompasses a vitally important avenue of pre-clinical and clinical investigation in the field of cGVHD. Further studies into specific culprit B cell populations and their associated signaling pathways will be especially informative. As we further elucidate the role of B cell dysregulation in the overall development of cGVHD, combination of B-cell-targeted and non-B-cell-targeted therapies may emerge that stabilize, prevent or reverse cGVHD.

## Author contributions

W.C.M, A.H., and S.S. wrote the paper.

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