

# Aberrant B Cell Signaling in Autoimmune Diseases

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**Abstract:** Aberrant B cell signaling plays a critical role in various systemic and organ-specific autoimmune diseases. This is supported by genetic evidence by many functional studies in B cells from patients or specific animal models and by the observed efficacy of small-molecule inhibitors. In this review, we first discuss key signal transduction pathways downstream of the B cell receptor (BCR) that ensure that autoreactive B cells are removed from the repertoire or functionally silenced. We provide an overview of aberrant BCR signaling that is associated with inappropriate B cell repertoire selection and activation or survival of peripheral B cell populations and plasma cells, finally leading to autoantibody formation. Next to BCR signaling, abnormalities in other signal transduction pathways have been implicated in autoimmune disease. These include reduced activity of several phosphatases that are downstream of co-inhibitory receptors on B cells and increased levels of BAFF and APRIL, which support survival of B cells and plasma cells. Importantly, pathogenic synergy of the BCR and Toll-like receptors (TLR), which can be activated by endogenous ligands, such as self-nucleic acids, has been shown to enhance autoimmunity. Finally, we will briefly discuss therapeutic strategies for autoimmune disease based on interfering with signal transduction in B cells.

**Keywords:** autoimmunity; B cell; B cell receptor; kinase; receptor; Toll-like receptor; signal transduction; tolerance



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## 1. Introduction

B lymphocytes have the unique capacity to recognize pathogen-derived antigens through expression of the B cell receptor (BCR) on their cell surface. However, the random nature of the VDJ-recombination process that generates antibody diversity poses the potential danger of producing self-reactive B cells that ultimately contribute to an autoimmune response. Autoreactive B cells play a crucial role in the pathogenesis of various common systemic and organ-specific autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), type 1 diabetes (T1D), cutaneous autoimmune diseases (CAD), and multiple sclerosis (MS). The autoantibodies produced are typically involved in immune complex formation and deposit in target organs. Autoantibodies often appear in the serum many years before clinical disease onset, suggesting that an early breach of B cell tolerance contributes to autoimmune pathogenesis [1,2]. However, the stages of B cell differentiation that account for the breach of self-tolerance or the underlying mechanisms remain largely unknown, as do the numerous genetic and environmental factors at play.

Genome-wide association studies (GWAS) have uncovered many polymorphisms that are associated with autoimmune disorders, although it has been quite challenging to obtain mechanistic insight from these genetic studies [3–5]. For example, more than 30 loci have been identified that show robust association with SLE [6]. These SLE susceptibility genes tend to cluster in Toll-like receptor (TLR), BCR, or Fc-receptor signaling pathways, immune-complex processing, or antigen presentation. Interestingly, SLE susceptibility loci, such as *BLK*, *STAT4*, *TNFAIP3*, *BANK1*, [7], and *PTPN22* [8], have also been implicated in other (systemic) autoimmune diseases.

A critical role for aberrant B cell signaling pathways in autoimmunity is not only supported by GWAS, but also by numerous functional studies using B cells from patients, animal models, or by studies using small-molecule inhibitors. In this review, we evaluate how BCR signaling ensures that autoreactive B cells are removed or silenced during B cell development. Next, we provide an overview of inadvertent B cell activation and the aberrant signaling downstream of the BCR and various other receptors observed in autoimmune disease. Therapeutic strategies for autoimmune disease based on interfering with signal transduction in B cells have been the topic of many recent reviews [9–12] and will be briefly discussed.

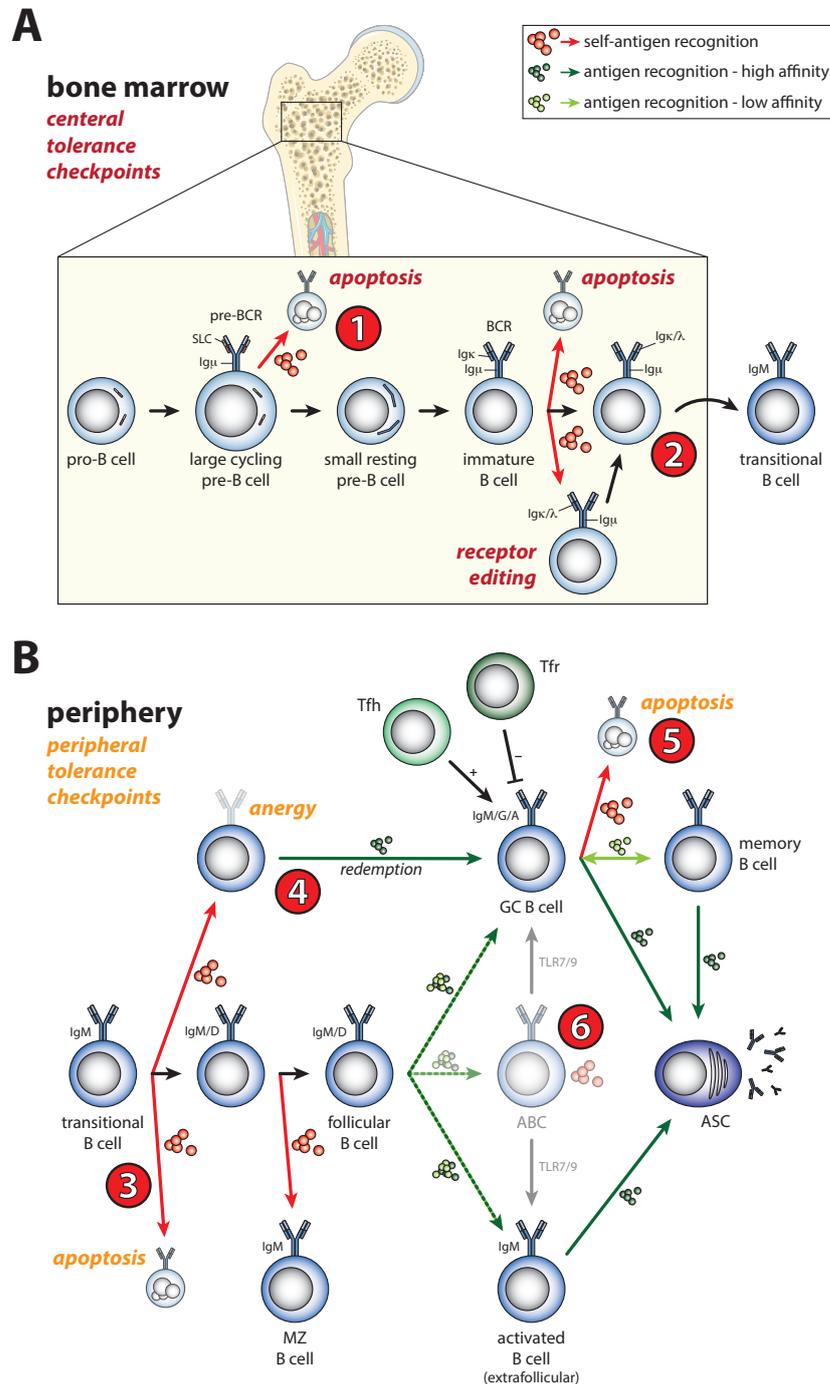
## 2. Shaping of the Naïve B Cell Repertoire during B Cell Development by B Cell Receptor Signals

A diverse antigen receptor repertoire is generated by the unique stochastic process of DNA recombination, mediated by the recombinase-activating gene (RAG) proteins. Hereby, gene segments encoding variable (V), diversity (D), and joining (J) regions of the immunoglobulin (Ig) heavy (H) and light (L) chain loci are assembled in a stepwise fashion [13,14]. Upon expression of a functionally rearranged IgH chain in early B cell precursors, a complex interplay between pre-BCR, interleukin (IL)-7 receptor (IL-7R) and chemokine receptor CXCR4 signaling induces pre-B cell proliferation and subsequent IgL chain recombination (Figure 1A, 1) [15,16]. Hereby, phosphoinositide 3-kinase (PI3K) signaling is required for pre-B cell survival [17], but negative selection of pre-B cells expressing a strongly autoreactive pre-BCR may be facilitated through hyperactivation of the PI3K-AKT pathway, as this leads to metabolic stress and AKT-dependent cell death [18,19]. Following successful IgL chain recombination in small pre-B cells, the high levels of CXCR4 surface expression are sharply reduced, facilitating the export of surface IgM-expressing immature B cells into bone marrow (BM) sinusoids and egress into the circulation [20].

It has been estimated that up to ~75% of B cells that develop in the BM display some degree of autoreactivity and must, therefore, be removed from the repertoire [21]. This frequency was assessed by determining the reactivity of cloned and *in vitro* amplified recombinant antibodies derived from human single B cells from BM. The regulatory mechanism that reduces the frequency of self-reactivity at the immature B cell stage in the BM is referred to as central tolerance and is driven by BCR signals. BCR engagement by self-antigens prevents CXCR4 downregulation, increases the motility and retention of immature B cells within the BM parenchyma, and blocks their egress [20]. Recognition of self-antigens will induce secondary gene rearrangement at the IgL chain loci. This process is termed receptor editing and modifies the specificity of potentially harmful BCRs (Figure 1A, 2). Whereas receptor editing is particularly frequent in IgM<sup>lo</sup> early immature B cells, the subsequent stage of IgM<sup>hi</sup> immature B cells is highly sensitive to antigen-induced apoptosis [22]. Infection or immunization may suppress lymphopoiesis in the BM and can subsequently result in antigen-independent accumulation of RAG-expressing immature B cells in the spleen [23]. Such transient alterations in lymphopoiesis are thought to protect against tolerance and to indirectly enhance B cell memory. Moreover, newly formed B cells that emerge from the BM will have a different repertoire and may, therefore, respond to pathogens in a distinct manner [24]. Interestingly, B cells that develop in the intestinal lamina propria are also subject to receptor editing, resulting in a BCR repertoire that is shaped by extracellular signals from commensal microbes [25].

A substantial proportion of self-reactive B cells (~40%) leaves the BM and further mechanisms ensure that these B cells are kept in check. In contrast to the BM that provides a protective micro-environment for immature B cells that allows for receptor editing, recent new immigrant B cells, called transitional B cells, in the spleen are largely eliminated when recognizing self-antigen (Figure 1B, 3) [26]. Nevertheless, using transgenic mice harboring a green fluorescent reporter, it was shown that a small fraction of transitional B cells in the spleen had an IgM<sup>lo</sup> phenotype and did not terminate RAG expression [27]. Although these cells express substantially lower levels of RAG than immature B cells in the BM [27,28],

they had detectable levels of DNA double-strand breaks. Therefore, receptor editing events in recent BM emigrants may continue to some extent [27].



**Figure 1.** B cell selection is controlled by B cell receptor signals at several points during B cell development and activation. At several checkpoints during B cell development in the bone marrow (central tolerance) and B cell maturation and activation in the periphery (peripheral tolerance), autoreactive B cells can escape negative selection that is dependent on B cell receptor (BCR) signals. (A) (1) A functional pre-BCR will result in a positive selection and proliferation, whereas strong binding of self-antigens by the pre-BCR may induce apoptosis. At this stage, defective selection can result in the survival of B cells bearing a self-reactive BCR. (2) At the immature B cell stage, expression of a fully functional BCR, amongst other factors, results in the survival and positive selection of the B cell. However, expression of an autoreactive BCR should lead to either receptor editing or apoptosis.

Defective selection at this stage can result in the escape of autoreactive B cells. **(B)** (3, 4) Transitional B cells emerging from the bone marrow are subject to the induction of apoptosis or anergy, when they recognize self-antigen. If defective, autoreactive B cells escape apoptosis or will not be constrained by anergy. (5) Germinal center B cells can undergo several rounds of selection and proliferation. During this process, somatic hypermutation generally increases affinity towards the antigen but can also generate B cells with self-reactive BCRs. Normally, such B cells undergo apoptosis, because essential survival signals, particularly those derived from activated T cells, are lacking. By contrast, in autoimmune disease, signals from the BCR may drive survival and differentiation of autoreactive B cells. (6) Various autoimmune diseases show an expansion of age-associated B cells that can be activated by TLR signaling and are prone to autoreactivity. See text for details. ABC: age-associated B cell; GC: germinal center; ASC: antibody secreting cell; MZ: marginal zone; Tfh: follicular T helper cell; Tfr: follicular regulatory T cell.

The high sensitivity of transitional B cells to BCR signaling-induced apoptosis reduces self-reactivity of B cells to ~20% [21,29]. Thus, a significant change in BCR repertoire occurs as transitional B cells enter the stage of long-lived mature B cells [30]. Alternatively, self-reactive B cells may persist in the periphery but are functionally silenced by anergy, which is induced by chronic BCR signaling and the ensuing feedback loops (Figure 1B, 4) [31,32]. B cells recognizing autoantigens are poorly competitive with non-autoreactive naïve B cells to capture B-cell-activating factor (BAFF) [33,34], a tumor necrosis factor (TNF) family member that critically enhances B cell survival [35]. Accordingly, pharmacological inhibition of BAFF by belimumab, the first biological approved for SLE, was shown to be clinically effective in patients [36]. Even if B cells have been selected into the long-lived pool of peripheral B cells, expression of an autoreactive BCR leads to their rapid elimination. This was shown in elegant mouse experiments using inducible Cre-loxP-mediated gene inversion that changed BCR specificity [37].

### 3. Activation of Self-Reactive B Cells under Physiological Conditions

Antigen-activated B cells may undergo clonal expansion, IgH chain class switch recombination (CSR), affinity maturation by somatic hypermutation (SHM), and final differentiation into either memory B cells or antibody-secreting cells. Although it was generally assumed that CSR mainly takes place in germinal centers (GCs), isotype switching has been detected early after B cell activation and in extrafollicular responses [38]. Indeed, convincing evidence was provided that CSR induction precedes GC B cell differentiation and that the majority of CSR events occur outside the GCs prior to the onset of SHM [39]. SHM can increase BCR affinity towards antigens but, at the same time, poses the risk for de novo generation of autoreactive B cells. Only B cells with high antigen affinity that interact with T-helper cells specific for the same antigen will be selected during the GC reaction. GC B cells with affinity for a self-antigen lack proper T cell help and are subject to negative selection (Figure 1B, 5). This is based on the upregulation of the death receptor FAS (CD95; TNF family receptor 6) when B cells are activated by BCR engagement and CD40–CD40L interactions [40]. FAS signaling induces programmed cell death upon interaction with its ligand on activated T cells. The main T cell subset that controls GC B cell selection is the follicular T helper (Tfh) cells, which are characterized by surface expression of chemokine receptor CXCR5 and programmed cell death-1 (PD-1), and by production of IL-21 [41–43]. Recently, a CXCR5<sup>+</sup>PD-1<sup>+</sup> subpopulation of CD8 T cells was identified, which also regulates the GC B cell response and B cell tolerance [44]. Repression of unwanted Tfh and GC B cell activity and promotion of stringent high-affinity B cell selection is further reinforced by FoxP3<sup>+</sup> follicular regulatory T (Tfr) cells (Figure 1B) [45–47].

Apart from the critical role of the BCR signaling cascade in B cell activation following antigen encounter, sustained low-level BCR signaling, also referred to as tonic BCR signaling, is required for survival of both developing and mature B cells [17,48]. For specific B cells, it has been demonstrated that the presence of self-antigen provides a survival signal. In a transgenic mouse model in which B cells carry an autoreactive BCR recognizing

the Thy-1 (CD90) glycoprotein, the presence of self-antigen promoted the accumulation of Thy-1-specific B-1 cells in the peritoneal cavity [49] and directed maturation of naïve immature B cells into the marginal zone B cell subset (Figure 1B) [50]. Given that B-1 cells can be selected and maintained on the basis of their autoreactivity, it is expected that (part of) the natural antibodies in serum will be the product of a self-antigen-driven process. Accordingly, in addition to the role of natural antibodies in early antimicrobial host defense, they facilitate nonimmunogenic clearance of apoptotic cells, removal of self-antigens, and inhibit responses induced by IgG autoantibodies [51–53]. In this context, it is of note that autoreactive IgM antibodies that recognize insulin were very recently shown to act as key regulators of blood glucose and metabolism [54]. These antibodies control the concentration of insulin in blood: whereas low-affinity anti-insulin IgM neutralizes insulin and leads to increased blood glucose, high-affinity anti-insulin IgM protects insulin neutralization by anti-insulin IgG. Consistent with these findings, antibody-deficient mice or immunodeficiency patients have sub-physiological blood glucose concentrations. The phenomenon that IgM autoantibodies have the capacity to prevent autoimmune pathology by competing with self-destructive autoantibodies was coined adaptive tolerance [55]. Intriguingly, these findings imply that self-reactive or poly-reactive B cells, present in the circulation of healthy individuals, have functional relevance beyond a role in host defense.

#### 4. Defective Selection of Self-Reactive B Cells in Autoimmune Disease

Autoantibodies may appear in the circulation of patients many years before the onset of the clinical disease symptoms, suggesting that a break in B cell tolerance is an early event in the pathogenesis of autoimmune disease [1,56–59]. However, controversy exists regarding the stages of B cell development or activation that are defective in autoimmune disease. Patients may suffer from intrinsic B cell defects that hamper counterselection of autoreactive cells in early tolerance checkpoints or later checkpoints upon antigen-driven activation and differentiation in the GC response. Moreover, cell-intrinsic defects can affect specific B cell populations, such as anergic B cells or age-associated B cells (ABCs; described below). Finally, autoimmune pathology may result from dysregulated T cell help or regulatory T cells. It is thought that the controversy in the literature can be explained by major differences between individual autoimmune diseases and a large heterogeneity across patients with the same disease. This heterogeneity is also reflected by differences across the many spontaneous, induced, genetically modified, or humanized mouse models available for human autoimmune diseases, such as SLE, RA, and SjS [60–62]. In the coming section, we will provide a brief overview of the main defects reported in autoimmune patients and mouse models.

It is conceivable that defects in early tolerance checkpoints in the BM or spleen result in the accumulation of autoreactive naïve mature B cells in the circulation of patients with autoimmune disease [63]. These B cells may induce or promote autoimmunity because of their capacity to present self-antigens to T cells. Frequency analysis of antinuclear antibody (ANA)-expressing B cells in two classic lupus-prone mouse strains revealed heterogeneity regarding the B cell stage in which tolerance is first breached [64]. In the MRL/*lpr* mouse, one of the best characterized models for SLE, survival of autoreactive B and T cells is enhanced due to the recessive autosomal *lpr* mutation that results in defective FAS expression [60]. In BM and spleen of MRL/*lpr* mice, proportions of ANA<sup>+</sup> B cells were similar across all B cell subsets and were in the range of nonautoimmune strains, indicating that the early tolerance checkpoints were intact. In contrast, NZB/W mice displayed an increase in ANA<sup>+</sup> naïve mature B cells, suggesting a defect in early pre-immune tolerance [64]. Interestingly, both mouse strains did not display an increase in the proportions of ANA<sup>+</sup> IgG-switched memory B cells and plasmablasts. Rather, a general expansion of switched memory cells resulted in increased numbers of ANA<sup>+</sup> antigen-experienced cells.

Likewise, the frequencies of ANA<sup>+</sup> cells within the circulating populations of IgG<sub>1</sub>-switched memory B cells or plasmablasts in SLE patients were reported to be similar to

healthy controls [64]. Nevertheless, an increase in the total number of ANA<sup>+</sup> IgG<sub>1</sub><sup>+</sup> plasma cells may be due to an overall expansion of the IgG<sub>1</sub><sup>+</sup> plasma cell compartment. These findings indicated that SLE does not reflect a defect in antigen-specific B cell tolerance but results from a generalized aberrant late B cell differentiation. They contradict earlier studies that described BCR repertoire abnormalities in SLE, including differences in IgV gene usage and IgH chain complementarity-determining region-3 characteristics [65]. Analysis of >200 cloned and in vitro expressed antibodies from single human B cells from three SLE patients revealed a ~twofold increase in autoreactivity in the mature naïve B cell population of SLE patients, compared with healthy controls [66]. No significant increase in autoreactive antibodies was found in new immigrant B cells. The level of poly-reactivity was increased in both new immigrant B cells and mature naïve B cells, but counterselection differed substantially between patients. SLE patients in clinical remission also showed elevated numbers of self-reactive or poly-reactive mature naïve B cells, indicating that early checkpoint abnormalities are an integral feature of SLE, regardless of disease status [67]. Taken together, these findings illustrate that, in different SLE patients, different checkpoints are affected.

Similar BCR repertoire analyses revealed defective central B cell tolerance in patients with RA, T1D, SjS, myasthenia gravis, and neuromyelitis optica spectrum disease [68]. Frequencies of self-reactive or poly-reactive transitional B cells in the circulation of these patient groups were increased, compared with healthy donors. These findings suggest that peripheral B cell tolerance checkpoints are disturbed [68]. In contrast, whereas five out of seven patients with MS displayed unaltered central tolerance, in all seven patients, analyzed peripheral tolerance was hampered. These findings point to a distinct B cell defect in MS.

Evidence for a major role of BCR signaling in shaping the repertoire of naïve B cells is provided by the finding of defective central tolerance in patients with mutations in essential signaling components, such as Bruton's tyrosine kinase (*BTK*) and Wiskott–Aldrich syndrome protein (*WASP*) genes [69,70]. Moreover, TLR signaling critically contributes to central B cell tolerance, given the defective removal of developing autoreactive B cells in patients with mutations in genes encoding myeloid differentiation primary response 88 (*MyD88*), IL-1R-associated kinase-4 (*IRAK-4*), and the UNC-98 chaperone [69–71]. Nevertheless, these patients display an immunodeficiency rather than an autoimmune disease because their B cells are either almost completely lacking (in case of *BTK* deficiency) or are not activated due to the underlying mutation. Transitional and mature naïve B cells from patients or mice deficient for activation-induced cytidine deaminase (*AID*), which mediates CSR and SHM in B cells, also express an abnormal Ig repertoire that is associated with impaired B cell tolerance [72,73]. The mechanisms involved are not well defined but are thought to be B-cell-intrinsic and to depend on *AID* expression at the immature B cell stage in the BM [74]. In particular, it has been shown in mice that BCR and endosomal TLR signals synergize to induce high *AID* expression in immature B cells to levels that approach those of GC B cells. Such *AID*-expressing immature B cells lack antiapoptotic *Mcl-1* and are normally deleted by apoptosis [75,76].

## 5. Defective Activation of Self-Reactive B Cells in Autoimmune Disease

### 5.1. Enhanced Sensitivity of Naïve B Cells for Activating Signals

Although autoimmunity is generally associated with BCR repertoire changes and enhanced persistence of autoreactive B cells in the circulation [77], it is becoming increasingly clear that, in autoimmune patients, naïve B cells probably need fewer strong signals to be activated. Analyses of transcriptomes, methylomes, and chromatin accessibility by Scharer et al. unraveled an SLE-specific epigenomic signature in resting naïve B cells [78,79]. This signature was characterized by increased enrichment of accessible chromatin at loci surrounding genes involved in B cell activation. Sites of open chromatin were enriched for motifs for AP-1 and EGR transcription factors, which have been linked to autoimmunity and are induced by BCR engagement [78,79]. In addition, naïve B cells displayed increased

accessibility at the nuclear receptor subfamily 4 members *NRA4A1* (NUR77) and *NRA4A3*, which are known to be induced in response to BCR and TLR stimulation, respectively. It is thought that the epigenetic profile of naïve B cells is a reflection of both genetic and specific environmental factors. The latter may include unique signals provided by an autoimmune micro-environment, (proinflammatory) serum factors, or interactions with other cells of the immune system, for example, direct dendritic cell–B cell interplay [80]. However, the nature of these signals needs to be further explored.

### 5.2. Activation of Anergic B Cells

Anergy contributes to tolerance but, when anergic self-reactive B cells are reactivated, they may induce autoimmune pathology. Anergic B cells are impaired in their activation, proliferation, and differentiation into plasma cells and have a short life span, particularly when they are competing with non-anergic B cells. Their anergic state is (i) dependent on continuous (self)-antigen binding; (ii) associated with downregulation of surface IgM expression, but not IgD, and enhanced BCR endocytosis; and (iii) involves inhibitory co-receptors that recruit protein phosphatases [32]. In addition, chronic BCR stimulation induces changes in transcription factor expression and epigenetic modifications, which contribute to the anergic state. A defect in anergic B cells has been shown to be an important pathogenic mechanism that contributes to autoimmunity (as reviewed by Franks and Camier [81]). Though it remains largely unclear whether this originates from hampered anergy induction, inappropriate activation of anergic B cell, or both, studies indicate T-helper signals may be responsible for restoring BCR signaling in autoreactive anergic B cells [82,83].

Interestingly, anergic B cells should not be regarded as only potentially dangerous cells that need to be fully silenced. For example, they are advantageous, as their reactivation allows for the generation of broadly neutralizing antibodies (bnAbs) for HIV and influenza virus that have poly-reactive or autoreactive specificities [84,85]. Sequence analysis of isotype-switched memory B cells or somatically mutated bnAbs indicated that the naïve B cells expressing unmutated equivalents of these BCRs were likely anergic. It is assumed that their self-reactivity is removed or their affinity for foreign antigens is enhanced by SHM and selection in GCs in a process called clonal redemption (Figure 1B) [32,86]. Due to a ‘redeeming’ somatic mutation, the chronic anergy-inducing BCR stimulation can change into a tonic-like or antigen-stimulated BCR signal [87].

### 5.3. GC Selection Defects and Spontaneous GC Formation

Given that ANAs in SLE and anticitrullinated protein antibodies (ACPAs) in RA are class-switched and highly somatically hypermutated, it is generally thought that they are GC-derived. This is supported by several findings. It was reported that GC exclusion of autoreactive B cells is defective in human SLE [88]. Moreover, the chemokine receptor CXCR4, which is critical for segregating GC dark and light zone and B cell selection, was significantly upregulated in B cells from SLE patients and positively correlated with disease activity [89]. In systemic autoimmune disease, including SLE, SjS, and RA, an increase in circulating Tfh cells was identified, which correlated with disease activity or autoantibody titers [90–92], and normalized upon B cell depletion therapy [93]. Typically, ectopic GC formation is observed in inflamed tissues, including synovial tissue in RA, lacrimal and salivary glands in SjS, and the meninges of patients with progressive MS, where they act as local centers of the autoimmune response and autoantibody production [94]. Moreover, lymphatic aggregates in the skin, named skin-associated lymphatic tissue, may act as a niche for localized autoantibody production in CAD, such as pemphigus [11].

Activation of autoreactive B cells and the generation of class-switched pathogenic antibodies is thought to occur in spontaneous GCs, in the absence of immunization or any detectable infection, and essentially independent of commensal microbiota [95]. However, it cannot be excluded that endogenous viruses or retroviral elements play a role (reviewed by Domeier et al. [96]). Spontaneous GCs are observed in a wide range of autoimmune

mouse strains, particularly in mice with altered signaling or survival of B cells, for example, due to BAFF overexpression [97], B-cell specific overexpression of BTK [98], or a deficiency in a range of signaling molecules, including the WASP, the SRC-family kinase member Lck/yes-related novel tyrosine kinase (LYN), or Fc-receptor  $\gamma 2b$  [96,99]. On the other hand, spontaneous GCs can also originate from defects in T cells, such as the pathogenic accumulation of Tfh cells induced by IFN $\gamma$  excess in the sanroque lupus model [100] or aberrant production of IL-17 [101]. Moreover, aberrant signaling in T cells has been implicated in autoimmunity, for example, a deficiency for the mTOR inhibitor Tsc1 [102] or a mutation in the phospholipase C $\gamma 1$  (PLC $\gamma 1$ )-binding site of linker for activation of T cells (LAT), downstream of the T cell receptor [103].

In spontaneous GCs, autoreactive B cells engage cognate T cell help and initiate loss of T cell tolerance via B-cell-intrinsic, MHC class-II-dependent antigen presentation and proinflammatory cytokine production. From analyses in WASP-deficient or BTK-overexpressing mice, a picture emerges in which B-cell-specific IL-6 production is critical to achieve cytokine and costimulatory signals that induce spontaneous GC formation [98,99,104,105]. The capacity of antigen-activated autoreactive B cells to engage cognate CD4<sup>+</sup> T cells is facilitated by BCR, TLR, CD40, and IFN $\gamma$  receptor (IFN $\gamma$ R) signals and involves various positive feedback loops. For example, BTK-overexpressing B cells promoted IFN $\gamma$  production by T cells and showed high expression of IL-6 and surface CD86 expression, which was dependent on interactions with T cells [98,105]. Serum IFN $\gamma$  levels are increased in SLE patients, already prior to clinical symptoms, coinciding with the appearance of autoantibodies [106]. A critical role for IFN $\gamma$  is further supported by the finding that it can promote the development of antibody-secreting cells (ASC). Hereby, IFN $\gamma$  synergizes with IL-2 and TLR7 ligands to induce epigenetic remodeling at the loci encoding interferon factor 4 (IRF4), B lymphocyte-induced maturation protein-1 (BLIMP1), and IL-21R [107]. B-cell-derived costimulatory signals were shown to be critical for complete Tfh cell differentiation, and even heterozygous deletion of CD80/CD86 was sufficient to prevent spontaneous autoimmune GC formation [108], further demonstrating the important role for the strength of B–T-cell interactions for proper regulation of the GC response. Whereas B-cell-intrinsic IFN $\gamma$ R, STAT1, and TLR7 signaling are essential for spontaneous GC formation in autoimmune B6.Sle1b mice, TLR9 has a negative regulatory function (see below) [109,110].

Interestingly, epigenetic modulation of GC B cells and ASCs can be influenced by metabolites derived from dietary fibers, such as the short-chain fatty acids butyrate and propionate. These metabolites were shown to decrease expression of AID and BLIMP1 in human and mouse B cells by upregulation of mRNAs [111] and to directly affect the epigenetic landscape at the *BTK* and *SYK* loci [112]. Although the role of the microbiome in pathogenic GC responses in autoimmune disease needs further investigation, these findings illustrate that environmental factors, such as the microbiota, may impact B cell activation.

#### 5.4. Enhanced Plasmablast Differentiation

Not only GCs, but also extrafollicular responses are associated with SHM and CSR and can be involved in the formation of ASC-producing pathogenic autoantibodies. However, the contribution of each of these two pathways differs across patients and autoimmune disorders (reviewed by Malkiel et al. [113]). As described above, the expansion of autoreactive ASCs in SLE patients and mouse models does not appear to reflect defective antigen-specific tolerance but, rather, an overall plasma cell expansion. Because long-lived plasma cells do not respond to B cell depletion therapies, targeting these cells has been challenging. The high level of antibody production in plasma cells induces considerable endoplasmic reticulum (ER) stress. Consequently, plasma cells are very sensitive to proteasome inhibition, which leads to accumulation of misfolded proteins. Proteasome inhibition, which is widely used for the treatment of patients with plasma cell malignancies, was shown to reduce disease symptoms, plasma cell numbers, and autoantibody levels in various mouse models of SLE [114–116]. Favorable therapeutic effects of the proteasome inhibitor bortezomib were also observed in patients with severe/refractory SLE [117,118]. Enlargement of the ER

is induced by the two key transcription regulators of plasma cell differentiation, BLIMP1 and X-box-binding protein 1 (XBP1), which also enhance mitochondrial mass and function, and thus promote oxidative metabolism [119]. Evidence was provided that mitochondrial dysfunction in B cells was associated with plasmablast differentiation and disease activity in SLE. In addition to ER stress, plasma cells also require a large amount of glucose, both as an energy source and for antibody glycosylation. Taken together, these findings imply that, next to the proteasome, XBP1, BLIMP1, and oxidative phosphorylation may also be potential therapeutic targets for autoimmune diseases.

#### 5.5. Expansion of the Age-Associated B Cell Population

In many autoimmune diseases, including SLE, RA, SjS, and MS, an aberrant expansion of a specific B cell subset, commonly referred to as age-associated B cells (ABCs), has been described. These cells have a unique T-bet<sup>+</sup>CD11c<sup>+</sup> phenotype in mice and humans and appear to be present in a preactivated state. ABCs efficiently produce proinflammatory cytokines, such as IFN $\gamma$  and IL-6, have a high capacity to form ASCs, and develop rapidly into antigen-presenting cells. In SLE patients, these cells are major producers of autoantibodies and ABC accumulation correlates with disease activity [120]. ABCs can be detected both in peripheral blood and targeted organs. The unique expression profile of chemokine receptors, integrins, and myeloid markers enables ABCs to migrate to specific locations and to interact with cells in the micro-environment. The generation of ABCs is fueled by hyper-responsiveness to innate signals from endosomal TLR7 and TLR9, as well as adaptive signals, such as BCR engagement and T cell help via CD40/CD40L interaction, and IFN $\gamma$  and IL-6 (Figure 1B, 6). The pathogenic characteristics of ABCs and their role in autoimmunity have recently been extensively reviewed [121,122].

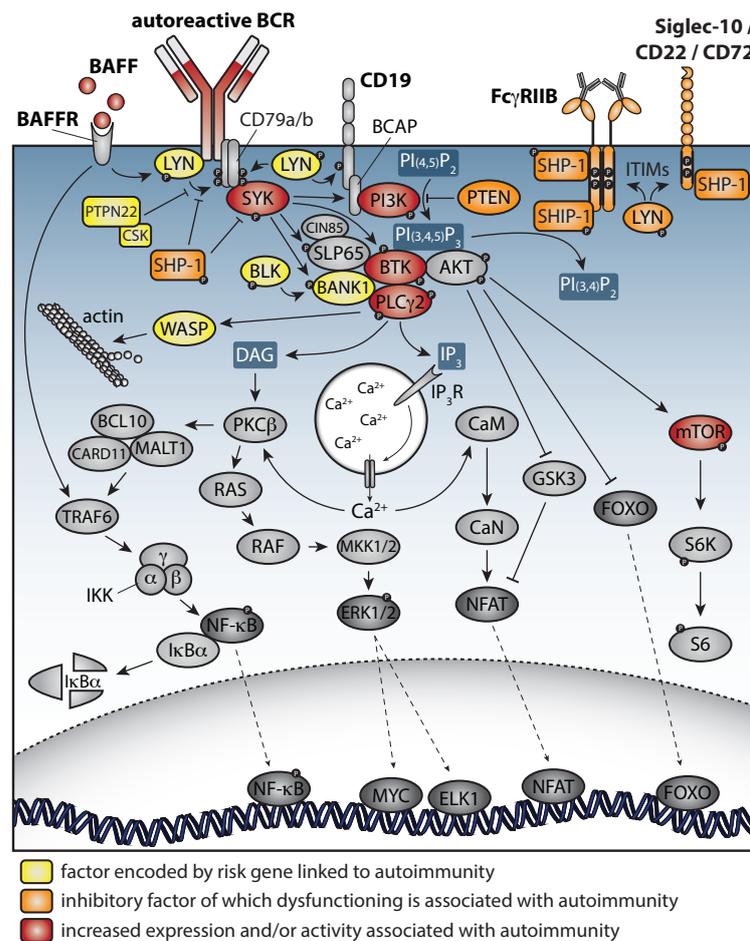
### 6. B Cell Receptor Signaling in Autoimmunity

BCR signaling is directly linked to B cell survival, proliferation, differentiation, and effector functions. Dysregulation of BCR signaling as an important driver of autoimmunity is not only supported by genetic susceptibility associations with BCR signaling proteins and regulators, but also by efficacy of treatments that target signaling molecules in autoimmune animal models. An overview of the signaling pathways downstream of the BCR is shown in Figure 2.

#### 6.1. Dual Role of LYN in BCR Signaling

The SRC family member LYN functions directly downstream of the BCR and can both promote and inhibit downstream signaling [123]. Phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) on the intracellular tails of CD79A/B (Ig $\alpha$ /Ig $\beta$ ) initiates further downstream signaling through spleen tyrosine kinase (SYK), SLP65 (also known as the B cell linker protein BLNK), and Cbl-interacting protein of 85 kD (CIN85), which functions to oligomerize SLP65 and, thereby, poises cells for efficient initiation of downstream BCR signaling [124,125]. Phosphorylated SLP65 provides docking sites for BTK as well as PLC $\gamma$ 2, leading to Ca<sup>2+</sup> mobilization and translocation of the nuclear factor  $\kappa$ -light-chain enhancer of activated B cells (NF- $\kappa$ B) and nuclear factor of activated T cells (NFAT) to the cell nucleus [126,127]. LYN and SYK also promote membrane recruitment and activation of phosphoinositide 3-kinase (PI3K), which results in activation of the protein kinase B (AKT) pathway, inducing B cell survival and proliferation [128,129].

Inhibition of BCR signaling is mediated by LYN through phosphorylation of inhibitory receptors, such as CD22, CD5, and Fc $\gamma$ RIIB, which activate SRC-homology-region 2 (SH2)-domain-containing phosphatase (SHP-1) [130–132]. SHP-1 dephosphorylates LYN, SYK, and BTK, creating a negative feedback loop [133]. Furthermore, LYN promotes a direct feedback loop through activation of C-terminal SRC kinase (CSK), which inhibits activation of SRC family kinases [134]. Fc $\gamma$ RIIB also inhibits PLC $\gamma$ 2, PI3K, BTK, and AKT signaling via SH2-domain-containing inositol polyphosphate 5-phosphatase 1 (SHIP-1) [135,136].



**Figure 2.** Signaling molecules downstream of the B cell receptor that are associated with autoimmunity. The signaling pathway downstream of the B cell receptor (BCR) contains signaling molecules that are partially shared with other pathways. In particular, the BAFF receptor provides essential survival signals and the CD19 co-receptor, which is intimately connected to the BCR. Inhibitory signals are provided by the kinase CSK and various phosphatases, including SHIP-1 and SHP-1, the activity of which is induced by Siglec-10, Fc $\gamma$ RIIb, and CD22 surface receptors, as well as PTEN and PTPN22. Highlighted signaling molecules have been linked to an increased risk in the development of autoimmune disease (yellow), have crucial inhibitory function in BCR signaling by preventing autoimmunity (orange), or show increased expression and/or activity in B cells from autoimmune disease patients (red). Signaling molecule abbreviations are explained in the text.

Due to redundancy within the SRC family, the initiation of downstream signaling is not dependent on LYN. In contrast, LYN does play an essential role in the negative regulation of BCR signaling [130,137,138]. Both complete and B-cell-specific LYN knockout mice display a spontaneous SLE-like phenotype, featuring B and T cell activation, high serum ANA levels, and glomerulonephritis [139,140]. In addition to BCR signaling, LYN may also regulate signaling through TLRs, as deletion of MyD88 attenuates the autoimmune phenotype in *Lyn*<sup>-/-</sup> mice, reducing type I interferon production and GC formation [141–143].

A critical role for LYN, SHIP, and CSK as negative regulators of BCR signaling in SLE would be supported by the finding of reduced expression or impaired activation of LYN and SHIP in B cells of SLE patients [144–147] and the identification of CSK as a genetic susceptibility locus [148].

### 6.2. Aberrant Levels and Activation of SYK, BTK, and PLC $\gamma$ 2 in Autoimmune Disease

In addition to LYN, altered levels or activation of other BCR signaling molecules have been found in various systemic autoimmune diseases. In SLE patients, a population of CD27<sup>-</sup> B cells was identified that had increased expression of SYK protein and phosphorylation, both at baseline and upon BCR stimulation, and showed enhanced differentiation into IgG-producing cells [149]. In another study, enhanced SYK protein and phosphorylation were found in B cells from SLE patients, compared to healthy controls, and correlated with disease activity score [150]. Likewise, phosphorylated BTK (pBTK) and pPLC $\gamma$ 2 were increased in active SLE patients [150]. Moreover, in RA patients, the phosphorylation of SYK was enhanced in B cells, particularly in patients with high ACPA levels in serum, and could be reduced by targeting T cell costimulation with abatacept (a cytotoxic T-lymphocyte-associated protein 4 immunoglobulin fusion protein, CTLA4-Ig) [151]. Inhibition of SYK with fostamatinib in RA patients induced an improvement of symptoms compared to placebo [152,153], although these effects might, in part, arise from expression of SYK beyond B cells [154].

The role of BTK in the pathogenesis of autoimmunity has been studied extensively in animal models. *Btk* deficiency or therapeutic inhibition of Btk was protective in many rodent models of SLE and RA [155–159]. Conversely, increased expression of BTK specifically in B cells induced a spontaneous SLE/SjS-like phenotype in mice [98]. In human autoimmune disease, increased BTK protein levels and phosphorylation were found in B cells from ACPA<sup>+</sup> RA, SjS, and glomerulonephritis with polyangiitis (GPA) patients with active disease [160,161]. Moreover, we found increased anti-Ig-induced phosphorylation of BTK and PLC $\gamma$ 2 in naïve B cells of patients with idiopathic pulmonary fibrosis, a chronic lung disease in which a pathogenic role is less evident [162]. Although autoimmunity may contribute to the disease phenotype, fibrosis is thought to be caused by an impaired healing response to recurrent micro-injuries. High BTK levels correlated with pathogenic T cell activation, and, similar to pSYK in RA, increased BTK protein levels were reduced upon abatacept treatment in SjS, suggesting that T cell interaction may be a driver of aberrant BCR signaling [160]. Inhibition of BTK by small-molecule inhibitors showed high efficacy in several preclinical autoimmune models and clinical efficacy was observed for fenebrutinib in RA and evobrutinib in MS [163,164]. Nevertheless, BTK inhibition also yielded diverging results in clinical trials [165]. We refer to Neys et al. [12] for a recent overview of various BTK inhibitors that are currently evaluated in clinical trials of various autoimmune diseases, including RA and SLE. Because BTK has kinase-independent functions [166,167], it might be more beneficial to target BTK protein levels. As BTK expression is known to be regulated by various micro-RNAs [168,169], it is attractive to target BTK through miRNA mimics [170].

Upon BCR stimulation, Ca<sup>2+</sup> signaling in B cells is promoted through an interaction between B cell scaffold protein with ankyrin repeats (BANK1) and PLC $\gamma$ 2, which is enhanced by the SRC-family B lymphocyte kinase (BLK) [7,171]. Both BANK1 and BLK were identified as genetic risk loci for SLE and are functionally linked to type I interferon repression (Figure 2) [172]. Gain-of-function mutations in the *PLC $\gamma$ 2* gene in both human and mouse lead to a complex, severe immunodeficient and autoimmune phenotype [173–175]. In addition, pPLC $\gamma$ 2 levels are increased in B cells of active SLE and GPA patients [150,161]. However, because of the availability of a large range of well-tolerated BTK inhibitors with clinical efficacy in B cell malignancies, inhibition of BCR signaling as a therapeutic target for autoimmunity is mainly focused on targeting BTK [12], while PLC $\gamma$ 2 is currently not pursued.

### 6.3. PI3K–Akt–mTORC-Regulated Metabolism Is Essential for Normal B Cell Differentiation and Silencing of Autoreactive B Cells

Activation of PI3K induces the AKT–mTOR signaling pathway, which is negatively regulated by phosphatase and tensin homolog (PTEN), and controls cell survival and metabolism throughout B cell development and activation [176]. Balanced regulation of PI3K activity is critical, since patients with activated PI3K $\delta$  syndrome (APDS) due to a

PI3K gain-of-function mutation present with immunodeficiency and lymphoproliferation. Conversely, a subgroup of patients with common variable immunodeficiency (CVID) display disturbed BCR-activated PI3K signaling, particularly in ABCs [177].

Upon BCR-driven activation, naïve B cells switch from a metabolic dependency on fatty acids to glutamine-fueled mitochondrial respiration [178,179]. Additional switches occur during B cell differentiation, for example, as GCs progress. Hereby, the glycogen synthase kinase 3 (GSK3) acts as metabolic sensor that supports both the survival of naïve B cells and the generation and maintenance of GC B cells, which require high glycolytic activity [180]. Memory B cells are formed earlier in the GC response than long-lived plasma cells, and mammalian target of rapamycin complex 1 (mTORc1) expression and metabolism are lower in cells destined to become memory B cells, suggesting that temporal switches in the metabolic state may contribute to the differentiation fate [181,182].

Tightly regulated metabolism is crucial in the counterselection and silencing of autoreactive B cells throughout B cell development and activation. Metabolic reprogramming through Glut-1 contributes to anergy of peripheral transitional B cells [178]. Anergic B cells remain metabolically quiescent upon stimulation, whereas chronically BAFF-stimulated B cells show rapid increased glycolysis, which is crucial for antibody production [178]. Increased BAFF levels, which are often present in autoimmune patients, may rescue autoreactive B cells from immune checkpoints and support the survival of anergic B cells [33,34,183]. Furthermore, it was shown in mice that GC B cells retain a hypoxic state that inhibits mTORc1 activity, promotes cell death, and limits proliferation and class switching to the proinflammatory IgG<sub>2c</sub> isotype [184].

mTORc activity is increased in B cells from SLE patients and correlates with disease activity, plasmablast differentiation, and with B cell accumulation in salivary glands of SjS patients [185,186]. In SLE patients, mTOR-dependent autophagy is also increased in B cells, particularly in transitional and naïve B cells, and correlates with disease activity [187]. As described above, these B cell stages are subject to selection checkpoints, suggesting that increased autophagy may promote the escape of autoreactive B cells from central or peripheral tolerance [188]. Although, in autoimmune disorders, therapeutic approaches that alter B cell metabolism may be attractive, it will be challenging to develop cell-lineage-specific targeting strategies.

A critical role for the PI3K–AKT–mTORc would be supported by findings implicating micro-RNAs that regulate PTEN expression in autoimmune pathogenesis. PTEN expression is controlled by miR-148a, which is upregulated in SLE patients and lupus-prone mice and accelerates development of autoimmune disease in mouse models [189,190]. Although miR-148a regulates >100 genes, only a few target genes, including *PTEN*, drive its function in B cell tolerance [191]. In parallel, various micro-RNAs that limit PTEN expression were shown to control central B cell tolerance and to be dysregulated in B cells from patients with various autoimmune diseases [192–197]. Interestingly, antagonizing miR-7, which regulates PTEN expression, improved disease symptoms in MRL/*lpr* mice, signifying miR-7 antagonism as a potential treatment strategy in autoimmune disease [198]. Novel miRNA dysregulated in autoimmunity are continuously being discovered [199–201], many of which control key pathways in B cell activation, including CD40–CD40L interaction [202,203], TLR and type I interferon signaling [204], the GC response, and AID expression [205–208].

PTEN is also involved in the balance between IgM and IgD expression through upregulation of IgD [209]. It was recently shown that IgD levels on B cells determine the nature and duration of primary immune responses, with decreased levels of IgD leading to an accelerated but prolonged primary immune response and a delayed secondary response with lower levels of protective high-affinity IgM antibodies [210]. IgD has also been shown to attenuate anergy of transitional and mature self-reactive B cells [211]. Several lines of evidence point to a protective role of IgD expression in autoimmunity, including studies of IgD knockout in MRL/*lpr* mice, IgD transgenic mice, and treatment with activating anti-IgD antibodies in various autoimmune mouse models (reviewed by Nguyen et al. [212]).

## 7. Other Signaling Pathways Implicated in Autoimmunity

### 7.1. BAFF and APRIL as Drivers of B-Cell-Mediated Autoimmunity

BAFF signals through three different receptors, exerting differential effects during B cell differentiation: (i) naïve mature B cells require pro-survival signals through the BAFF receptor (BAFFR) [213–215]; (ii) negative regulation and class switch recombination are mediated through transmembrane activator and CAML interactor (TACI) [216–219]; and (iii) B cell differentiation and plasmablast or plasma cell survival are promoted through signals from a third receptor, B cell maturation antigen (BCMA) [220,221]. Many systemic autoimmune patients present with dysregulated BAFF levels in the circulation [222], and BAFF-overexpressing mice develop autoimmune pathology, resembling human SLE [34,97]. In SLE patients, soluble TACI and BCMA levels, but not BAFFR levels, are increased [223].

Binding of BAFF to BAFFR activates PI3K/AKT signaling in mature B cells, hereby regulating protein synthesis, metabolic fitness, and survival. The BAFFR activates the noncanonical NF- $\kappa$ B pathway but can also induce the canonical NF- $\kappa$ B signaling through crosstalk with the BCR, involving CD79A/B, SYK, and BTK (Figure 2) [224,225]. Interestingly, BAFF activates PI3K/AKT only in naïve B cells [226]. BAFF-induced PI3K/AKT signaling requires direct interactions between BAFFR and BCR components CD79A/B and is enhanced by the AKT coactivator TCL1A. BCR expression levels are higher on the surface of naïve B cells than memory B cells, and IgM BCRs interact better with BAFFR than IgG or IgA, allowing stronger pro-survival responses from BAFF by naïve B cells. Furthermore, BCR signaling regulates BAFFR levels, and BAFF supports CD40 expression and T cell costimulation through BAFFR, suggesting the presence of a self-amplifying loop that supports the survival of self-reactive B cells in autoimmunity [227–230].

Signaling through TACI and BCMA is less well studied. TACI induces NF- $\kappa$ B, MAPK, and JNK activation through TRAF 2, 5, and 6, whereas BCMA activates NF- $\kappa$ B, AP-1, and NF-AT through TRAF 1, 2, and 3 [231,232]. TACI expression increases upon TLR9 stimulation [233], and, on marginal zone B cells, TACI interacts with TLR and mTOR signaling through binding of MyD88, together driving IgG class switching and antibody production [234]. TACI can be cleaved from B cells by ADAM10 and acts as a decoy receptor binding BAFF and APRIL, thereby blocking NF- $\kappa$ B activation and B cell survival [235]. Interestingly, increased soluble TACI levels in serum of SLE patients correlate with increased disease severity. Conversely, decreased expression of BCMA on B cells correlates with higher disease severity in SLE [236].

In addition to BAFF, APRIL also signals through TACI (with higher affinity) and BCMA (with lower affinity), thereby promoting IgA class switching and plasma cell survival, respectively [221,237]. APRIL levels in serum of SLE patients are increased [238] and associations with genetic polymorphisms in APRIL have been found [239,240]. Inhibition of BAFF or APRIL are being explored in autoimmune diseases ([clinicaltrials.gov](https://clinicaltrials.gov)). Until now, only belimumab, which specifically targets BAFF, has been approved for treatment of SLE patients [36]. Although promising results were reported in SLE in early trials with atacicept, an IgG1 Fc–TACI fusion protein that binds BAFF and APRIL to inhibit TACI signaling, larger trials reported no clinical effect and increased risk of infection [241–243].

### 7.2. CD40–CD40L Costimulatory Signals and PTPN22 Downregulation in Autoimmunity

The interaction between CD40 and its ligand CD40L, which is highly expressed on activated T cells and T<sub>fh</sub> cells, is critical for GC responses and for the formation of extrafollicular foci and antibody-secreting cells. Thus, it is evident that the CD40–CD40L axis is central to the pathogenesis of many autoimmune diseases, which is also supported by the identification of *CD40* as a susceptibility locus in SLE [244]. Blockade of CD40–CD40L interaction may, therefore, provide an opportunity for therapeutic application [245]. It has been reported that CD40 costimulation also downregulates the expression of the protein tyrosine phosphatase nonreceptor type 2 (PTPN2) and PTPN22 [246]. *PTPN22* is a major autoimmune risk locus: the R620W gain-of-function allele is found at high frequencies in patients with autoimmune disease, including T1D, RA, and SLE. Known functions of

PTPN22 and their link to autoimmunity have recently been extensively reviewed [8,81,247]. It is established that PTPN22 is a negative regulator of SRC-family kinases and co-operates with CSK to inhibit BCR and TCR signaling (Figure 2), whereby the R620W variant interacts with CSK to a lesser extent. PTPN22 impacts BCR signaling in central and peripheral B cell tolerance, as well as activation of GC B cells and ABCs. However, the complete molecular mechanisms explaining the role of PTPN22 in autoimmunity remain unclear, particularly because it is not only expressed in lymphocytes, but in many other immune cells, such as macrophages, monocytes, and dendritic cells.

### 7.3. Inhibitory Co-Receptors of BCR Signaling Acting through SHP-1

As described above, upon BCR ligation, Lyn phosphorylates ITIM motifs on several inhibitory co-receptors that regulate BCR signaling through SHP-1. Depending on the ligand recognized by these inhibitory receptors and their unique expression profiles, they regulate activation of different B cell subsets with specific BCRs [248,249].

CD72 regulates BCR signaling upon binding of Sm/RNP small nuclear ribonucleoprotein particles and co-ligation with the BCR, thereby specifically regulating Sm/RNP-reactive B cells [250]. In addition, CD72 may also regulate TLR7-mediated activation upon Sm/RNP endocytosis, playing an important role in self-tolerance against nucleic-acid-containing antigens [250]. CD72-deficient mice develop a severe SLE-like autoimmune phenotype [251,252], and CD72 has been identified as an MRL gene involved in the autoimmune phenotype of MRL/*lpr* mice [252]. In SLE patients, CD72 expression levels on B cells are decreased [253] and, in children, this decrease is evident during disease flare but not in remission [254]. Furthermore, CD72 polymorphisms have been associated with SLE [255].

CD22 (or Siglec-2) is expressed exclusively on B cells and binds to  $\alpha$ 2,6-linked sialic acids, which are either present on the same cell (*cis*) or expressed by other cells (*trans*) [256–259]. Upon BCR activation, CD22 inhibits  $Ca^{2+}$  signaling in B-2 cells through activation of SHP-1 or GRB-2 (Figure 2) [256,260]. Inhibition of tonic BCR signaling by CD22 is restricted through interaction with the extracellular domain of CD45, which prevents CD22 function [261]. In contrast to the ligand-specific regulation of B cell activation by CD72, CD22-deficient mice show augmented regulation of  $Ca^{2+}$  signaling upon polyclonal BCR stimulation with anti-IgM [256,257,262]. However, depending on the genetic background strain, *Cd22*-deficient mice develop no or only a mild autoimmune phenotype [263]. Nevertheless, in SLE patients, *CD22* has been identified as a genetic susceptibility locus [264].

Another Siglec family member that may be involved in autoimmunity is Siglec-10 (Siglec-G in mice). In mice, Siglec-G regulates B-1 cells through SHP-1 [265,266]. This specificity for the B-1 subset may be due to recognition of  $\alpha$ 2,3-linked sialic acids in addition to  $\alpha$ 2,6-linked sialic acids [267]. In mice, Siglec-G has a protective role on an autoimmune background or collagen-induced arthritis [268,269]. In Guillain–Barré syndrome patients, polymorphisms in *SIGLEC10* have been identified that interfere with ganglioside recognition, which may hamper ganglioside self-tolerance in patients presenting with antiganglioside antibodies [270].

### 7.4. Inhibitory Co-Receptors of BCR Signaling Acting through SHIP-1

Another key phosphatase in the inhibition of BCR signaling is SHIP-1, which can be activated by several receptors. Peripheral tolerance of IgG BCRs is regulated by Fc $\gamma$ RIIB, which crosslinks with the BCR upon binding of antigen-IgG immune complexes. This induces activation of LYN, which phosphorylates the ITIM on Fc $\gamma$ RIIB, allowing subsequent recruitment of SHP-1 and SHIP-1 (Figure 2) [135,138,271,272]. Deficiency of Fc $\gamma$ RIIB in mice leads to enhanced IgG humoral immunity and an SLE-like autoimmune phenotype [273–275]. In SLE patients, polymorphisms in the *Fc $\gamma$ RIIB* gene have been associated with disease, and memory B cells fail to upregulate the expression of Fc $\gamma$ RIIB [276–278]. This is more prevalent in African American patients, suggesting that dysregulation of Fc $\gamma$ RIIB expression may, in part, explain the difference in ethnic susceptibility to SLE [278].

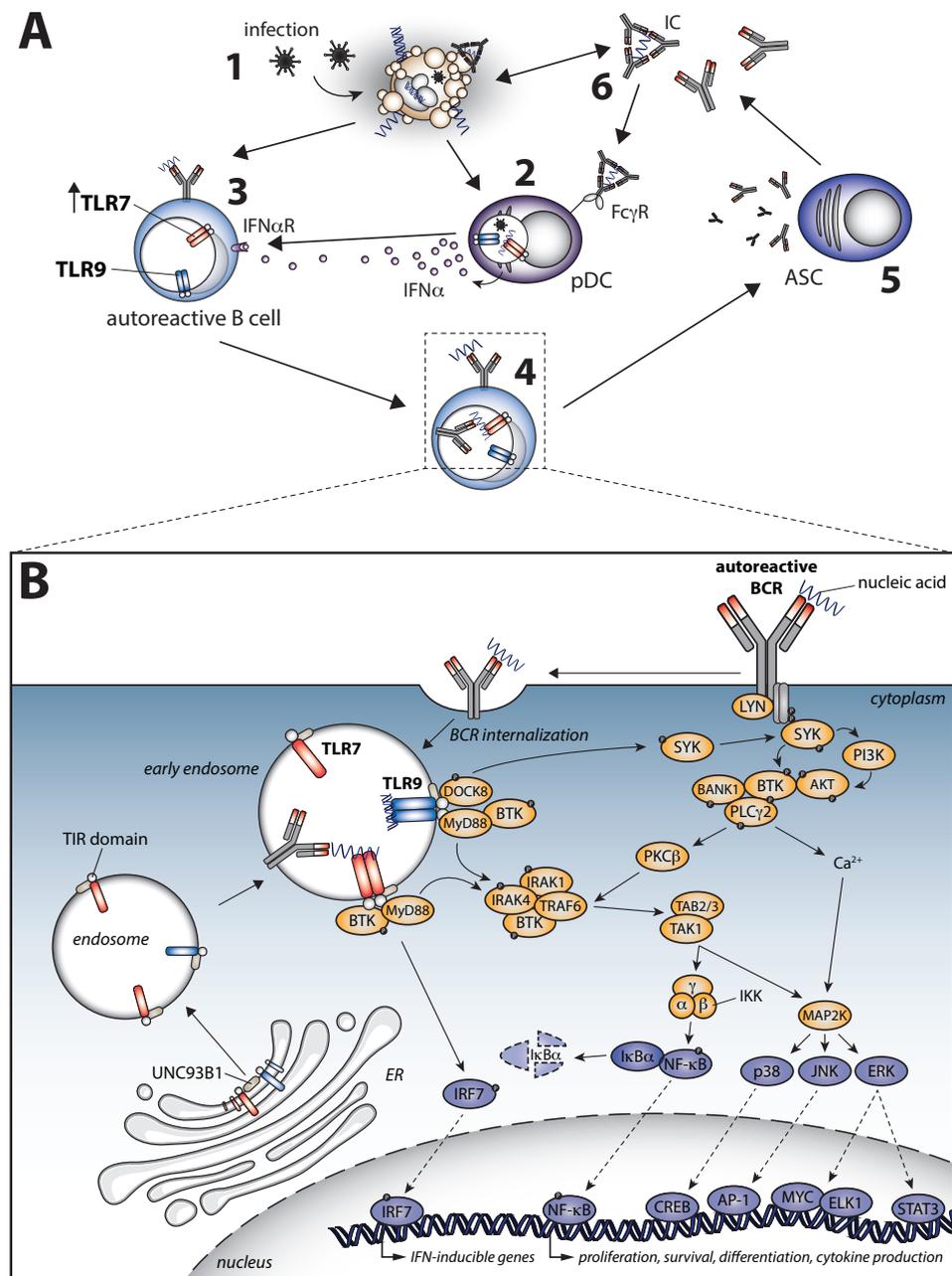
SHIP-1 can also be activated in an Fc $\gamma$ RIIB-independent manner, which involves CD79A and LYN. The exact mechanism has not been fully elucidated, but SHIP-1 may directly interact with the ITAM on the intracellular tail of CD79A or interact with CD79A through adaptor proteins DOK3 and/or GRB-2 [279–283]. CD79A deficiency causes a developmental block at the immature B cell stage, although these cells do show enhanced signaling, suggesting a dual role for CD79A in BCR signaling [284,285]. In peripheral B cells, CD79A may play a role in the induction of B cell anergy through SHIP-1 activation, indicating a role in peripheral tolerance of self-reactive B cells [286–288].

#### 7.5. A Pathogenic Crosstalk between B Cell Receptor and Toll-like Receptor Signaling in Autoimmune Disease

TLRs are expressed either on the cell surface or within endosomes and are crucial innate receptors recognizing pathogen-associated molecular patterns. TLRs can, however—in the context of autoimmunity—also be activated by endogenous ligands, such as self-nucleic acids. For example, due to impaired clearance of debris, such as necrotic cells and neutrophil extracellular traps (NETs), autoreactive B cells can be costimulated via TLRs. In this way, TLR activation is a potential pathogenic factor that can promote autoimmunity by stimulating antibody production, antigen presentation, and production of proinflammatory cytokines by autoreactive B cells. Mice lacking DNase1, the enzyme important for nucleic acid breakdown and important for NET clearance, develop an SLE-like phenotype [289]. Likewise, a decreased DNase1 activity has been described in SLE patients [290,291]. Reduced DNase1 activity can result in the accumulation of debris containing self-antigens, including histones and nucleic acids, to which autoantibodies are directed in systemic autoimmunity (Figure 3A).

An important role for TLR signaling in both initiation and progression of systemic autoimmune disease is supported by GWAS that identified risk genes involved in TLR signaling [292–298]. Pathogenic TLR stimulation can induce an autoimmune phenotype in various mouse models, including arthritis [299], experimental autoimmune encephalitis (EAE), a model for MS [300], and lupus [301]. Particularly TLR7, which recognizes single-stranded RNA in endosomes that is a typical feature of viral genomes, and TLR9, which recognizes unmethylated CpG sequences that are common in viral and bacterial DNA, are considered key players. A pathogenic role for TLR7 signaling has been shown in several mouse models [301–307] and, very recently, in SLE patients harboring *TLR7* gene mutations [308]. The TLR7<sup>Y264H</sup> gain-of-function mutant was found to drive aberrant survival of BCR-activated B cells and accumulation of ABCs and GC B cells, resulting in a lupus-like phenotype, associated with aberrant survival of pathogenic autoreactive B cells in a GC-independent manner, suggesting an extrafollicular origin. This was in line with previous evidence that, in SLE, autoreactive B cells derive from extrafollicular responses through enhanced TLR7 responsiveness in combination with IL-21 and IFN $\gamma$  and are poised to differentiate into ASCs [295,309]. The *TLR7* gene is located on the X chromosome and escapes X-chromosome inactivation [310]. As a result, TLR7 expression in pDCs, monocytes, and B cells from females is increased compared with men [311], which may, in part, explain the female bias in systemic autoimmune diseases.

In contrast, TLR8 and -9 signaling in B cells seem to function in a protective manner. Targeted deletion of TLR8 and/or TLR9 in several mouse models leads to a more severe autoimmune phenotype. Whereas this protective role for TLR9 was shown to be B-cell-intrinsic, there is only indirect evidence for TLR8 [307,312–318]. SLE patients display decreased TLR9 responsiveness, indicating an imbalance in TLR7 and 9 signaling in human systemic autoimmunity [319,320]. Both TLR7 and 9 compete for binding of Unc-93 homolog B1 (UNC93B1), a protein that regulates TLR trafficking from the ER to the endosomal compartment [321]. In addition, cessation of TLR7/9 signaling is mediated by the interaction between UNC93B1 and Syntenin-1. Mutations altering the function or interaction of these proteins can lead to systemic autoimmunity [322,323].



**Figure 3.** The vicious cycle of autoreactive B cell activation and the interplay between BCR and TLR signaling. **(A)** 1, A viral infection induces inflammation and cellular apoptosis and necrosis. This can lead to the accumulation of debris, containing autoantigens and nucleic acids. 2, Plasmacytoid dendritic cells (pDCs) are activated during viral infections via Toll-like receptors (TLR) and produce vast amounts of interferon- $\alpha$  (IFN- $\alpha$ ). 3, IFN- $\alpha$  stimulates autoreactive B cells via the IRF $\alpha$  receptor, causing upregulation of TLR7 expression. Meanwhile, the B cell is activated via the B cell receptor (BCR) by self-antigen and internalizes the antigen. 4, The autophagosome, containing self-antigen bound to the BCR, and the endosome, containing TLRs, fuse. Self-antigens, containing TLR ligands, stimulate both BCR and TLR in a synergistic manner. 5, Autoreactive B cells proliferate and differentiate into antibody-secreting cells (ASC). These produce high numbers of autoreactive antibodies. 6, Autoreactive antibodies recognizing self-antigen form immune complexes (IC). In turn, these can promote inflammation at the site of deposition and stimulate pDCs via fragment crystallizable region  $\gamma$  receptor (Fc $\gamma$ R) to increase IFN- $\alpha$  production, completing the cycle. **(B)** Synergy of BCR and TLR signaling pathways leading to the activation of autoreactive B cells. Signaling molecule abbreviations are explained in the text.

Engagement of TLR7 or TLR9 leads to receptor dimerization and subsequent recruitment of MyD88 to the intracellular Toll–interleukin receptor (TIR) domain (Figure 3B). This is followed by activation of IRAK4, IRAK1, and TNF-receptor-associated factor-6 (TRAF6) [324]. Further downstream, this leads to activation of TGF $\beta$ -activated kinase-1 (TAK1), the TAK1-binding proteins (TAB), and the p38/JNK/ERK and the NF- $\kappa$ B pathways. This enables translocation of transcription factors CREB, AP-1, IRF7, and NF- $\kappa$ B, stimulating survival and differentiation of B cells, as well as the production of proinflammatory cytokines, such as IL-6 and type I interferons (IFN-I). The interplay between BCR and TLR signaling, often in the context of autoimmunity, has been a topic of intense research (Figure 3B). First of all, BCR engagement enhances TLR expression [325–327]. Secondly, studies using transgenic mouse models show TLR4, 7, and 9 stimulation-induced B cell proliferation, survival, and cytokine production are significantly reduced or even absent when the BCR or SYK is lacking [328,329]. This TLR-mediated SYK activation was MyD88-independent and resulted in activation of the ERK and PI3K–AKT pathways. SYK was also shown to be indispensable for TLR9-induced B cell activation and differentiation in human B cells [246,330,331]. BTK interacts with the TIR domains of several TLRs [332] and with downstream signaling proteins, such as MyD88 adapter-like (MAL) [333]. The synergistic role of BTK in BCR and TLR9 signaling has been well described in murine and human B cells [334,335]. In addition to SYK and BTK, BANK1 enhances TLR signaling [336,337], whereas BCAP seems to modulate TLR signaling [338,339]. TAK1 was proven central to BCR–TLR synergy, as inhibition led to impaired B cell proliferation, differentiation, and cytokine production in response to combined BCR and TLR stimulation [340]. Dedicator of cytokinesis-8 (DOCK8) also links TLR stimulation to the BCR signaling cascade by inducing activation of SYK and STAT3 [341].

The type I IFN signature, a hallmark of several systemic autoimmune diseases, including SjS and SLE, involves a positive feedback loop including TLR signaling (Figure 3A). Plasmacytoid DCs (pDC) produce vast amounts of IFN- $\alpha$  in response to TLR stimulation, for example, following viral infection or in the excessive presence of apoptotic debris [342]. IFN- $\alpha$  stimulates TLR7 and MyD88 expression in B cells, leaving TLR9 expression unaltered [343]. Autoreactive B cells can take up self-antigens containing nucleic acids via endocytosis, where enhanced TLR7 expression can subsequently facilitate their pathogenic survival and differentiation. In turn, the production of autoantibodies is promoted. These can form immune complexes containing autoantibodies bound to self-antigens and nucleic acids, which can activate pDCs via Fc $\gamma$ RIIA. Overall, this results in a vicious circle where increased TLR–BCR signaling leads to autoreactive B cell activation, which is thought to be important both during disease initiation and progression (Figure 3A,B).

Taken together, synergy of BCR and TLR7 stimulation promotes autoimmunity [344,345], whereas synergy with TLR9 stimulation enhances tolerance [76]. These findings stress the delicate balance in TLR signaling, indicate the importance of crosstalk with the BCR, and pave the way for potential therapeutic targets involved in both BCR and TLR signaling.

## 8. Concluding Remarks and Future Perspective

In this review, we focused on the key role of BCR signals in central and peripheral B cell tolerance checkpoints, as well as the interplay between the BCR and various other signaling pathways in antigen-activated B cells. It is clear that the full impact of aberrant signaling in the etiology of specific autoimmune diseases remains to be established. Research in this area is complicated by the fact that autoimmune disorders generally arise from additive effects of many common genetic risk variants and various environmental factors. Accordingly, the contribution of (i) an altered BCR repertoire, (ii) an increased sensitivity of naïve B cells for signals from the microenvironment, as well as inappropriate (iii) activation, selection, survival, or cytokine profile of B cells upon autoantigen encounter to disease pathology is different across diseases and individual patients. On the basis of the available knowledge

on aberrant signaling pathways in autoimmunity, therapies have been developed, however, with variable efficacy.

Over the past few decades, mouse models for autoimmune diseases have provided a wealth of information and mechanistic insight into B cell signaling and have been of great value to unravel pathogenic pathways. This is particularly the case for SLE, as global defects in central or peripheral tolerance are often associated with ANA formation. This might be explained by the abundance of DNA and RNA molecules that are released upon cell death, which can activate B cells in a T-cell-independent manner. In contrast, it remains challenging to design models for tissue-specific autoimmunity, which are currently largely dependent on the exposure to specific protein autoantigens, such as collagen for RA and myelin oligodendrocyte glycoprotein in the experimental autoimmune encephalomyelitis model for MS. In this context, it is also of note that the nonobese diabetic (NOD) mouse, which is extensively studied as a model for T1D, also develops symptoms of SjS. As autoimmune diseases show multifactorial inheritance patterns, the generation of genetically engineered mouse models will benefit from gene editing tools that have the potential of simultaneous editing of multiple loci [346].

Although animal models will remain of great value, it is becoming increasingly clear that we are reaching limits as we gain more and more in-depth knowledge revealing critical differences in immune pathology between mouse and man [347]. Novel technology will be of great help to uncover factors that are critical for autoimmunity in humans in unprecedented detail. This is already clear from the impact of flow-cytometry-based techniques to study signal transduction pathways: phospho-flow cytometry is now used to measure and quantify phosphorylation of an ever-expanding list of critical B cell signaling proteins in conjunction with cell surface markers [348,349]. These methods allow a rapid and detailed analysis of small, distinct subpopulations of B cells at the single-cell level and provide a more quantitative read-out than classic Western blotting.

Another exciting development is that whole-genome sequencing of patients diagnosed with autoimmune disease has recently identified novel rare mutations. These mutations have provided evidence for a critical pathogenic role of various genes, including partial RAG deficiency [350] and gain-of-function mutations in the *IKFZ1* gene, encoding the Ikaros transcription factor [351] and the *TLR7* gene [308]. Single-cell technology will be instrumental to uncover drivers of interindividual variation in immune cells, which will help to interpret and prioritize risk variants identified by GWAS and to identify critical cell types in autoimmune diseases [352]. Epigenetic processes that determine the accessibility of genes and, thereby, their expression profile are more and more recognized as important factors. It is, therefore, encouraging that autoimmune risk variants, for example, for T1D, could be translated into mechanistic insights by the identification of (cell-specific) regulatory elements by single-cell epigenomics [353].

GWAS in autoimmune disease uncovered a number of critical susceptibility genes and loci, which have been consistently replicated or validated on the protein level in the past couple of years. However, the vast majority of risk-associated single-nucleotide polymorphisms (SNPs) identified in autoimmune disease are located in noncoding regions. Hereby, it often cannot be excluded that nearby SNPs, in high linkage disequilibrium with the identified SNPs, are in fact causal for the disease [354,355]. Risk-associated SNPs in noncoding regions are assumed to be located in regulatory elements, which might be quite distant from the genes they control. It is mostly elusive how SNPs affect gene expression, as they mostly act in a cell-type or activation-status-specific manner. Technology to study epigenetics, as well as various innovative computational tools that are now emerging will help to interpret and prioritize disease-associated SNPs [353,356,357].

At the same time, the obtained knowledge on altered epigenetic regulation in B cells or other cells of the immune system may open new avenues to predict disease outcome or design novel therapeutic strategies for autoimmune disease. Finally, given the promising results of BTK inhibition in RA and MS, it is expected that the field may also benefit from the

ongoing discovery of a wide range of small-molecule inhibitors targeting critical signaling pathways in B cell malignancies.

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## References

1. Arbuckle, M.R.; McClain, M.T.; Rubertone, M.V.; Scofield, R.H.; Dennis, G.J.; James, J.A.; Harley, J.B. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N. Engl. J. Med.* **2003**, *349*, 1526–1533. [[CrossRef](#)] [[PubMed](#)]
2. Volkov, M.; van Schie, K.A.; van der Woude, D. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. *Immunol. Rev.* **2020**, *294*, 148–163. [[CrossRef](#)] [[PubMed](#)]
3. Okada, Y.; Wu, D.; Trynka, G.; Raj, T.; Terao, C.; Ikari, K.; Kochi, Y.; Ohmura, K.; Suzuki, A.; Yoshida, S.; et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* **2014**, *506*, 376–381. [[CrossRef](#)] [[PubMed](#)]
4. Orrù, V.; Steri, M.; Sidore, C.; Marongiu, M.; Serra, V.; Olla, S.; Sole, G.; Lai, S.; Dei, M.; Mulas, A.; et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. *Nat. Genet.* **2020**, *52*, 1036–1045. [[CrossRef](#)]
5. Westra, H.-J.; Martínez-Bonet, M.; Onengut-Gumescu, S.; Lee, A.; Luo, Y.; Teslovich, N.; Worthington, J.; Martin, J.; Huizinga, T.; Klareskog, L.; et al. Fine-mapping and functional studies highlight potential causal variants for rheumatoid arthritis and type 1 diabetes. *Nat. Genet.* **2018**, *50*, 1366–1374. [[CrossRef](#)] [[PubMed](#)]
6. Deng, Y.; Tsao, B.P. Genetic susceptibility to systemic lupus erythematosus in the genomic era. *Nat. Rev. Rheumatol.* **2010**, *6*, 683–692. [[CrossRef](#)]
7. Gómez Hernández, G.; Morell, M.; Alarcón-Riquelme, M.E. The Role of BANK1 in B Cell Signaling and Disease. *Cells* **2021**, *10*, 1184. [[CrossRef](#)]
8. Tizaoui, K.; Terrazzino, S.; Cargnin, S.; Lee, K.H.; Gauckler, P.; Li, H.; Shin, J.I.; Kronbichler, A. The role of PTPN22 in the pathogenesis of autoimmune diseases: A comprehensive review. *Semin. Arthritis Rheum.* **2021**, *51*, 513–522. [[CrossRef](#)] [[PubMed](#)]
9. Zhang, Y.; Tian, J.; Xiao, F.; Zheng, L.; Zhu, X.; Wu, L.; Zhao, C.; Wang, S.; Rui, K.; Zou, H.; et al. B cell-activating factor and its targeted therapy in autoimmune diseases. *Cytokine Growth Factor Rev.* **2022**, *64*, 57–70. [[CrossRef](#)] [[PubMed](#)]
10. Murphy, G.; Isenberg, D.A. New therapies for systemic lupus erythematosus—Past imperfect, future tense. *Nat. Rev. Rheumatol.* **2019**, *15*, 403–412. [[CrossRef](#)] [[PubMed](#)]
11. Fetter, T.; Niebel, D.; Braegelmann, C.; Wenzel, J. Skin-Associated B Cells in the Pathogenesis of Cutaneous Autoimmune Diseases—Implications for Therapeutic Approaches. *Cells* **2020**, *9*, 2627. [[CrossRef](#)] [[PubMed](#)]
12. Neys, S.F.H.; Rip, J.; Hendriks, R.W.; Corneth, O.B.J. Bruton’s Tyrosine Kinase Inhibition as an Emerging Therapy in Systemic Autoimmune Disease. *Drugs* **2021**, *81*, 1605–1626. [[CrossRef](#)] [[PubMed](#)]
13. Tonegawa, S. Somatic generation of antibody diversity. *Nature* **1983**, *302*, 575–581. [[CrossRef](#)] [[PubMed](#)]
14. Jung, D.; Giallourakis, C.; Mostoslavsky, R.; Alt, F.W. Mechanism and control of V(D)J recombination at the immunoglobulin heavy chain locus. *Annu. Rev. Immunol.* **2006**, *24*, 541–570. [[CrossRef](#)] [[PubMed](#)]
15. Clark, M.R.; Mandal, M.; Ochiai, K.; Singh, H. Orchestrating B cell lymphopoiesis through interplay of IL-7 receptor and pre-B cell receptor signalling. *Nat. Rev. Immunol.* **2014**, *14*, 69–80. [[CrossRef](#)] [[PubMed](#)]
16. Mandal, M.; Okoreeh, M.K.; Kennedy, D.E.; Maienschein-Cline, M.; Ai, J.; McLean, K.C.; Kaverina, N.; Veselits, M.; Aifantis, I.; Gounari, F.; et al. CXCR4 signaling directs Igk recombination and the molecular mechanisms of late B lymphopoiesis. *Nat. Immunol.* **2019**, *20*, 1393–1403. [[CrossRef](#)] [[PubMed](#)]
17. Srinivasan, L.; Sasaki, Y.; Calado, D.P.; Zhang, B.; Paik, J.H.; DePinho, R.A.; Kutok, J.L.; Kearney, J.F.; Otipoby, K.L.; Rajewsky, K. PI3 kinase signals BCR-dependent mature B cell survival. *Cell* **2009**, *139*, 573–586. [[CrossRef](#)]
18. Shojaei, S.; Chan, L.N.; Buchner, M.; Cazzaniga, V.; Cosgun, K.N.; Geng, H.; Qiu, Y.H.; von Minden, M.D.; Ernst, T.; Hochhaus, A.; et al. PTEN opposes negative selection and enables oncogenic transformation of pre-B cells. *Nat. Med.* **2016**, *22*, 379–387. [[CrossRef](#)]
19. Stein, M.; Dutting, S.; Mougiakakos, D.; Bosl, M.; Fritsch, K.; Reimer, D.; Urbanczyk, S.; Steinmetz, T.; Schuh, W.; Bozec, A.; et al. A defined metabolic state in pre B cells governs B-cell development and is counterbalanced by Swiprosin-2/EFhd1. *Cell Death Differ.* **2017**, *24*, 1239–1252. [[CrossRef](#)]
20. Beck, T.C.; Gomes, A.C.; Cyster, J.G.; Pereira, J.P. CXCR4 and a cell-extrinsic mechanism control immature B lymphocyte egress from bone marrow. *J. Exp. Med.* **2014**, *211*, 2567–2581. [[CrossRef](#)]

21. Wardemann, H.; Yurasov, S.; Schaefer, A.; Young, J.W.; Meffre, E.; Nussenzweig, M.C. Predominant autoantibody production by early human B cell precursors. *Science* **2003**, *301*, 1374–1377. [[CrossRef](#)] [[PubMed](#)]
22. Melamed, D.; Benschop, R.J.; Cambier, J.C.; Nemazee, D. Developmental regulation of B lymphocyte immune tolerance compartmentalizes clonal selection from receptor selection. *Cell* **1998**, *92*, 173–182. [[CrossRef](#)]
23. Nagaoka, H.; Gonzalez-Aseguinolaza, G.; Tsuji, M.; Nussenzweig, M.C. Immunization and infection change the number of recombination activating gene (RAG)-expressing B cells in the periphery by altering immature lymphocyte production. *J. Exp. Med.* **2000**, *191*, 2113–2120. [[CrossRef](#)] [[PubMed](#)]
24. Giltiay, N.V.; Giordano, D.; Clark, E.A. The Plasticity of Newly Formed B Cells. *J. Immunol.* **2019**, *203*, 3095–3104. [[CrossRef](#)] [[PubMed](#)]
25. Wesemann, D.R.; Portuguese, A.J.; Meyers, R.M.; Gallagher, M.P.; Cluff-Jones, K.; Magee, J.M.; Panchakshari, R.A.; Rodig, S.J.; Kepler, T.B.; Alt, F.W. Microbial colonization influences early B-lineage development in the gut lamina propria. *Nature* **2013**, *501*, 112–115. [[CrossRef](#)] [[PubMed](#)]
26. Sandel, P.C.; Monroe, J.G. Negative selection of immature B cells by receptor editing or deletion is determined by site of antigen encounter. *Immunity* **1999**, *10*, 289–299. [[CrossRef](#)]
27. Yu, W.; Nagaoka, H.; Jankovic, M.; Misulovin, Z.; Suh, H.; Rolink, A.; Melchers, F.; Meffre, E.; Nussenzweig, M.C. Continued RAG expression in late stages of B cell development and no apparent re-induction after immunization. *Nature* **1999**, *400*, 682–687. [[CrossRef](#)]
28. Monroe, R.J.; Seidl, K.J.; Gaertner, F.; Han, S.; Chen, F.; Sekiguchi, J.; Wang, J.; Ferrini, R.; Davidson, L.; Kelsoe, G.; et al. RAG2:GFP knockin mice reveal novel aspects of RAG2 expression in primary and peripheral lymphoid tissues. *Immunity* **1999**, *11*, 201–212. [[CrossRef](#)]
29. Su, T.T.; Rawlings, D.J. Transitional B lymphocyte subsets operate as distinct checkpoints in murine splenic B cell development. *J. Immunol.* **2002**, *168*, 2101–2110. [[CrossRef](#)] [[PubMed](#)]
30. Levine, M.H.; Haberman, A.M.; Sant’Angelo, D.B.; Hannum, L.G.; Cancro, M.P.; Janeway, C.A., Jr.; Shlomchik, M.J. A B-cell receptor-specific selection step governs immature to mature B cell differentiation. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2743–2748. [[CrossRef](#)]
31. Goodnow, C.C.; Crosbie, J.; Adelstein, S.; Lavoie, T.B.; Smith-Gill, S.J.; Brink, R.A.; Pritchard-Briscoe, H.; Wotherspoon, J.S.; Loblay, R.H.; Raphael, K.; et al. Altered immunoglobulin expression and functional silencing of self-reactive B lymphocytes in transgenic mice. *Nature* **1988**, *334*, 676–682. [[CrossRef](#)]
32. Tanaka, S.; Ise, W.; Baba, Y.; Kurosaki, T. Silencing and activating anergic B cells. *Immunol. Rev.* **2022**, *307*, 43–52. [[CrossRef](#)] [[PubMed](#)]
33. Lesley, R.; Xu, Y.; Kalled, S.L.; Hess, D.M.; Schwab, S.R.; Shu, H.B.; Cyster, J.G. Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. *Immunity* **2004**, *20*, 441–453. [[CrossRef](#)]
34. Thien, M.; Phan, T.G.; Gardam, S.; Amesbury, M.; Basten, A.; Mackay, F.; Brink, R. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* **2004**, *20*, 785–798. [[CrossRef](#)] [[PubMed](#)]
35. Schweighoffer, E.; Tybulewicz, V.L. BAFF signaling in health and disease. *Curr. Opin. Immunol.* **2021**, *71*, 124–131. [[CrossRef](#)]
36. Depascale, R.; Gatto, M.; Zen, M.; Saccon, F.; Larosa, M.; Zanatta, E.; Bindoli, S.; Doria, A.; Iaccarino, L. Belimumab: A step forward in the treatment of systemic lupus erythematosus. *Expert. Opin. Biol. Ther.* **2021**, *21*, 563–573. [[CrossRef](#)] [[PubMed](#)]
37. Lam, K.P.; Rajewsky, K. Rapid elimination of mature autoreactive B cells demonstrated by Cre-induced change in B cell antigen receptor specificity in vivo. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13171–13175. [[CrossRef](#)] [[PubMed](#)]
38. Toellner, K.M.; Gulbranson-Judge, A.; Taylor, D.R.; Sze, D.M.; MacLennan, I.C. Immunoglobulin switch transcript production in vivo related to the site and time of antigen-specific B cell activation. *J. Exp. Med.* **1996**, *183*, 2303–2312. [[CrossRef](#)]
39. Roco, J.A.; Mesin, L.; Binder, S.C.; Nefzger, C.; Gonzalez-Figueroa, P.; Canete, P.F.; Ellyard, J.; Shen, Q.; Robert, P.A.; Cappello, J.; et al. Class-Switch Recombination Occurs Infrequently in Germinal Centers. *Immunity* **2019**, *51*, 337–350. [[CrossRef](#)]
40. Rathmell, J.C.; Cooke, M.P.; Ho, W.Y.; Grein, J.; Townsend, S.E.; Davis, M.M.; Goodnow, C.C. CD95 (Fas)-dependent elimination of self-reactive B cells upon interaction with CD4+ T cells. *Nature* **1995**, *376*, 181–184. [[CrossRef](#)]
41. Breitfeld, D.; Ohl, L.; Kremmer, E.; Ellwart, J.; Sallusto, F.; Lipp, M.; Forster, R. Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. *J. Exp. Med.* **2000**, *192*, 1545–1552. [[CrossRef](#)]
42. Kim, C.H.; Rott, L.S.; Clark-Lewis, I.; Campbell, D.J.; Wu, L.; Butcher, E.C. Subspecialization of CXCR5+ T cells: B helper activity is focused in a germinal center-localized subset of CXCR5+ T cells. *J. Exp. Med.* **2001**, *193*, 1373–1381. [[CrossRef](#)] [[PubMed](#)]
43. Schaerli, P.; Willmann, K.; Lang, A.B.; Lipp, M.; Loetscher, P.; Moser, B. CXC chemokine receptor 5 expression defines follicular homing T cells with B cell helper function. *J. Exp. Med.* **2000**, *192*, 1553–1562. [[CrossRef](#)] [[PubMed](#)]
44. Chen, Y.; Yu, M.; Zheng, Y.; Fu, G.; Xin, G.; Zhu, W.; Luo, L.; Burns, R.; Li, Q.Z.; Dent, A.L.; et al. CXCR5(+)PD-1(+) follicular helper CD8 T cells control B cell tolerance. *Nat. Commun.* **2019**, *10*, 4415. [[CrossRef](#)] [[PubMed](#)]
45. Chung, Y.; Tanaka, S.; Chu, F.; Nurieva, R.I.; Martinez, G.J.; Rawal, S.; Wang, Y.H.; Lim, H.; Reynolds, J.M.; Zhou, X.H.; et al. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nat. Med.* **2011**, *17*, 983–988. [[CrossRef](#)]

46. Linterman, M.A.; Pierson, W.; Lee, S.K.; Kallies, A.; Kawamoto, S.; Rayner, T.F.; Srivastava, M.; Divekar, D.P.; Beaton, L.; Hogan, J.J.; et al. Foxp3<sup>+</sup> follicular regulatory T cells control the germinal center response. *Nat. Med.* **2011**, *17*, 975–982. [[CrossRef](#)] [[PubMed](#)]
47. Wollenberg, I.; Agua-Doce, A.; Hernandez, A.; Almeida, C.; Oliveira, V.G.; Faro, J.; Graca, L. Regulation of the germinal center reaction by Foxp3<sup>+</sup> follicular regulatory T cells. *J. Immunol.* **2011**, *187*, 4553–4560. [[CrossRef](#)] [[PubMed](#)]
48. Lam, K.P.; Kuhn, R.; Rajewsky, K. In vivo ablation of surface immunoglobulin on mature B cells by inducible gene targeting results in rapid cell death. *Cell* **1997**, *90*, 1073–1083. [[CrossRef](#)]
49. Hayakawa, K.; Asano, M.; Shinton, S.A.; Gui, M.; Allman, D.; Stewart, C.L.; Silver, J.; Hardy, R.R. Positive selection of natural autoreactive B cells. *Science* **1999**, *285*, 113–116. [[CrossRef](#)]
50. Wen, L.; Brill-Dashoff, J.; Shinton, S.A.; Asano, M.; Hardy, R.R.; Hayakawa, K. Evidence of marginal-zone B cell-positive selection in spleen. *Immunity* **2005**, *23*, 297–308. [[CrossRef](#)]
51. Tsiantoulas, D.; Gruber, S.; Binder, C.J. B-1 cell immunoglobulin directed against oxidation-specific epitopes. *Front. Immunol.* **2012**, *3*, 415. [[CrossRef](#)] [[PubMed](#)]
52. Vas, J.; Grönwall, C.; Marshak-Rothstein, A.; Silverman, G.J. Natural antibody to apoptotic cell membranes inhibits the proinflammatory properties of lupus autoantibody immune complexes. *Arthritis Rheum.* **2012**, *64*, 3388–3398. [[CrossRef](#)] [[PubMed](#)]
53. Manno, K.; Matejuk, A.; Xu, Y.; Beardall, M.; Chen, C. Expression of natural autoantibodies in MRL-lpr mice protects from lupus nephritis and improves survival. *J. Immunol.* **2012**, *188*, 3628–3638. [[CrossRef](#)] [[PubMed](#)]
54. Amendt, T.; Allies, G.; Nicolo, A.; El Ayoubi, O.; Young, M.; Roszer, T.; Setz, C.S.; Warnatz, K.; Jumaa, H. Autoreactive antibodies control blood glucose by regulating insulin homeostasis. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2115695119. [[CrossRef](#)] [[PubMed](#)]
55. Amendt, T.; Jumaa, H. Memory IgM protects endogenous insulin from autoimmune destruction. *EMBO J.* **2021**, *40*, e107621. [[CrossRef](#)]
56. Burbelo, P.D.; Gordon, S.M.; Waldman, M.; Edison, J.D.; Little, D.J.; Stitt, R.S.; Bailey, W.T.; Hughes, J.B.; Olson, S.W. Autoantibodies are present before the clinical diagnosis of systemic sclerosis. *PLoS ONE* **2019**, *14*, e0214202. [[CrossRef](#)]
57. Rantapaa-Dahlqvist, S.; de Jong, B.A.; Berglin, E.; Hallmans, G.; Wadell, G.; Stenlund, H.; Sundin, U.; van Venrooij, W.J. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum.* **2003**, *48*, 2741–2749. [[CrossRef](#)]
58. Theander, E.; Jonsson, R.; Sjostrom, B.; Brokstad, K.; Olsson, P.; Henriksson, G. Prediction of Sjogren’s Syndrome Years Before Diagnosis and Identification of Patients With Early Onset and Severe Disease Course by Autoantibody Profiling. *Arthritis Rheumatol.* **2015**, *67*, 2427–2436. [[CrossRef](#)]
59. Verge, C.F.; Gianani, R.; Kawasaki, E.; Yu, L.; Pietropaolo, M.; Jackson, R.A.; Chase, H.P.; Eisenbarth, G.S. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* **1996**, *45*, 926–933. [[CrossRef](#)]
60. Halkom, A.; Wu, H.; Lu, Q. Contribution of mouse models in our understanding of lupus. *Int. Rev. Immunol.* **2020**, *39*, 174–187. [[CrossRef](#)]
61. Meehan, G.R.; Thomas, R.; Al Khabouri, S.; Wehr, P.; Hilkens, C.M.; Wraith, D.C.; Sieghart, D.; Bonelli, M.; Nagy, G.; Garside, P.; et al. Preclinical models of arthritis for studying immunotherapy and immune tolerance. *Ann. Rheum. Dis.* **2021**, *80*, 1268–1277. [[CrossRef](#)] [[PubMed](#)]
62. Masli, S.; Dartt, D.A. Mouse Models of Sjögren’s Syndrome with Ocular Surface Disease. *Int. J. Mol. Sci.* **2020**, *21*, 9112. [[CrossRef](#)] [[PubMed](#)]
63. Bonasia, C.G.; Abdulahad, W.H.; Rutgers, A.; Heeringa, P.; Bos, N.A. B Cell Activation and Escape of Tolerance Checkpoints: Recent Insights from Studying Autoreactive B Cells. *Cells* **2021**, *10*, 1190. [[CrossRef](#)] [[PubMed](#)]
64. Suurmond, J.; Atisha-Fregoso, Y.; Marasco, E.; Barlev, A.N.; Ahmed, N.; Calderon, S.A.; Wong, M.Y.; Mackay, M.C.; Aranow, C.; Diamond, B. Loss of an IgG plasma cell checkpoint in patients with lupus. *J. Allergy Clin. Immunol.* **2019**, *143*, 1586–1597. [[CrossRef](#)] [[PubMed](#)]
65. Dorner, T.; Lipsky, P.E. Immunoglobulin variable-region gene usage in systemic autoimmune diseases. *Arthritis Rheum.* **2001**, *44*, 2715–2727. [[CrossRef](#)]
66. Yurasov, S.; Hammersen, J.; Tiller, T.; Tsuiji, M.; Wardemann, H. B-cell tolerance checkpoints in healthy humans and patients with systemic lupus erythematosus. *Ann. N. Y. Acad. Sci.* **2005**, *1062*, 165–174. [[CrossRef](#)]
67. Yurasov, S.; Tiller, T.; Tsuiji, M.; Velinzon, K.; Pascual, V.; Wardemann, H.; Nussenzweig, M.C. Persistent expression of autoantibodies in SLE patients in remission. *J. Exp. Med.* **2006**, *203*, 2255–2261. [[CrossRef](#)] [[PubMed](#)]
68. Meffre, E.; O’Connor, K.C. Impaired B-cell tolerance checkpoints promote the development of autoimmune diseases and pathogenic autoantibodies. *Immunol. Rev.* **2019**, *292*, 90–101. [[CrossRef](#)]
69. Castiello, M.C.; Bosticardo, M.; Pala, F.; Catucci, M.; Chamberlain, N.; van Zelm, M.C.; Driessen, G.J.; Pac, M.; Bernatowska, E.; Scaramuzza, S.; et al. Wiskott-Aldrich Syndrome protein deficiency perturbs the homeostasis of B-cell compartment in humans. *J. Autoimmun.* **2014**, *50*, 42–50. [[CrossRef](#)]
70. Ng, Y.S.; Wardemann, H.; Chelnis, J.; Cunningham-Rundles, C.; Meffre, E. Bruton’s tyrosine kinase is essential for human B cell tolerance. *J. Exp. Med.* **2004**, *200*, 927–934. [[CrossRef](#)]

71. Isnardi, I.; Ng, Y.S.; Srdanovic, I.; Motaghedi, R.; Rudchenko, S.; von Bernuth, H.; Zhang, S.Y.; Puel, A.; Jouanguy, E.; Picard, C.; et al. IRAK-4- and MyD88-dependent pathways are essential for the removal of developing autoreactive B cells in humans. *Immunity* **2008**, *29*, 746–757. [[CrossRef](#)] [[PubMed](#)]
72. Kuraoka, M.; Holl, T.M.; Liao, D.; Womble, M.; Cain, D.W.; Reynolds, A.E.; Kelsoe, G. Activation-induced cytidine deaminase mediates central tolerance in B cells. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 11560–11565. [[CrossRef](#)] [[PubMed](#)]
73. Meyers, G.; Ng, Y.S.; Bannock, J.M.; Lavoie, A.; Walter, J.E.; Notarangelo, L.D.; Kilic, S.S.; Aksu, G.; Debre, M.; Rieux-Laucat, F.; et al. Activation-induced cytidine deaminase (AID) is required for B-cell tolerance in humans. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 11554–11559. [[CrossRef](#)] [[PubMed](#)]
74. Mao, C.; Jiang, L.; Melo-Jorge, M.; Puthenveetil, M.; Zhang, X.; Carroll, M.C.; Imanishi-Kari, T. T cell-independent somatic hypermutation in murine B cells with an immature phenotype. *Immunity* **2004**, *20*, 133–144. [[CrossRef](#)]
75. Cantaert, T.; Schickel, J.N.; Bannock, J.M.; Ng, Y.S.; Massad, C.; Oe, T.; Wu, R.; Lavoie, A.; Walter, J.E.; Notarangelo, L.D.; et al. Activation-Induced Cytidine Deaminase Expression in Human B Cell Precursors Is Essential for Central B Cell Tolerance. *Immunity* **2015**, *43*, 884–895. [[CrossRef](#)]
76. Kuraoka, M.; Snowden, P.B.; Nojima, T.; Verkoczy, L.; Haynes, B.F.; Kitamura, D.; Kelsoe, G. BCR and Endosomal TLR Signals Synergize to Increase AID Expression and Establish Central B Cell Tolerance. *Cell Rep.* **2017**, *18*, 1627–1635. [[CrossRef](#)]
77. Tipton, C.M.; Fucile, C.F.; Darce, J.; Chida, A.; Ichikawa, T.; Gregoret, I.; Schieferl, S.; Hom, J.; Jenks, S.; Feldman, R.J.; et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus. *Nat. Immunol.* **2015**, *16*, 755–765. [[CrossRef](#)]
78. Scharer, C.D.; Blalock, E.L.; Barwick, B.G.; Haines, R.R.; Wei, C.; Sanz, I.; Boss, J.M. ATAC-seq on biobanked specimens defines a unique chromatin accessibility structure in naïve SLE B cells. *Sci. Rep.* **2016**, *6*, 27030. [[CrossRef](#)]
79. Scharer, C.D.; Blalock, E.L.; Mi, T.; Barwick, B.G.; Jenks, S.A.; Deguchi, T.; Cashman, K.S.; Neary, B.E.; Patterson, D.G.; Hicks, S.L.; et al. Epigenetic programming underpins B cell dysfunction in human SLE. *Nat. Immunol.* **2019**, *20*, 1071–1082. [[CrossRef](#)]
80. Joo, H.; Coquery, C.; Xue, Y.; Gayet, I.; Dillon, S.R.; Punaro, M.; Zurawski, G.; Banchereau, J.; Pascual, V.; Oh, S. Serum from patients with SLE instructs monocytes to promote IgG and IgA plasmablast differentiation. *J. Exp. Med.* **2012**, *209*, 1335–1348. [[CrossRef](#)]
81. Franks, S.E.; Cambier, J.C. Putting on the Brakes: Regulatory Kinases and Phosphatases Maintaining B Cell Anergy. *Front. Immunol.* **2018**, *9*, 665. [[CrossRef](#)] [[PubMed](#)]
82. Duty, J.A.; Szodoray, P.; Zheng, N.Y.; Koelsch, K.A.; Zhang, Q.; Swiatkowski, M.; Mathias, M.; Garman, L.; Helms, C.; Nakken, B.; et al. Functional anergy in a subpopulation of naïve B cells from healthy humans that express autoreactive immunoglobulin receptors. *J. Exp. Med.* **2009**, *206*, 139–151. [[CrossRef](#)] [[PubMed](#)]
83. Szodoray, P.; Stanford, S.M.; Molberg, Ø.; Munthe, L.A.; Bottini, N.; Nakken, B. T-helper signals restore B-cell receptor signaling in autoreactive anergic B cells by upregulating CD45 phosphatase activity. *J. Allergy Clin. Immunol.* **2016**, *138*, 839–851.e838. [[CrossRef](#)] [[PubMed](#)]
84. Andrews, S.F.; Huang, Y.; Kaur, K.; Popova, L.I.; Ho, I.Y.; Pauli, N.T.; Henry Dunand, C.J.; Taylor, W.M.; Lim, S.; Huang, M.; et al. Immune history profoundly affects broadly protective B cell responses to influenza. *Sci. Transl. Med.* **2015**, *7*, 316ra192. [[CrossRef](#)] [[PubMed](#)]
85. Guthmiller, J.J.; Lan, L.Y.; Fernandez-Quintero, M.L.; Han, J.; Utset, H.A.; Bitar, D.J.; Hamel, N.J.; Stovicek, O.; Li, L.; Tepora, M.; et al. Polyreactive Broadly Neutralizing B cells Are Selected to Provide Defense against Pandemic Threat Influenza Viruses. *Immunity* **2020**, *53*, 1230–1244.e5. [[CrossRef](#)]
86. Sabouri, Z.; Schofield, P.; Horikawa, K.; Spierings, E.; Kipling, D.; Randall, K.L.; Langley, D.; Roome, B.; Vazquez-Lombardi, R.; Rouet, R.; et al. Redemption of autoantibodies on anergic B cells by variable-region glycosylation and mutation away from self-reactivity. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E2567–E2575. [[CrossRef](#)]
87. Reed, J.H.; Jackson, J.; Christ, D.; Goodnow, C.C. Clonal redemption of autoantibodies by somatic hypermutation away from self-reactivity during human immunization. *J. Exp. Med.* **2016**, *213*, 1255–1265. [[CrossRef](#)]
88. Cappione, A., 3rd; Anolik, J.H.; Pugh-Bernard, A.; Barnard, J.; Dutcher, P.; Silverman, G.; Sanz, I. Germinal center exclusion of autoreactive B cells is defective in human systemic lupus erythematosus. *J. Clin. Investig.* **2005**, *115*, 3205–3216. [[CrossRef](#)]
89. Zhao, L.D.; Liang, D.; Wu, X.N.; Li, Y.; Niu, J.W.; Zhou, C.; Wang, L.; Chen, H.; Zheng, W.J.; Fei, Y.Y.; et al. Contribution and underlying mechanisms of CXCR4 overexpression in patients with systemic lupus erythematosus. *Cell. Mol. Immunol.* **2017**, *14*, 842–849. [[CrossRef](#)]
90. Simpson, N.; Gatenby, P.A.; Wilson, A.; Malik, S.; Fulcher, D.A.; Tangye, S.G.; Manku, H.; Vyse, T.J.; Roncador, G.; Huttley, G.A.; et al. Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum.* **2010**, *62*, 234–244. [[CrossRef](#)]
91. Wang, J.; Shan, Y.; Jiang, Z.; Feng, J.; Li, C.; Ma, L.; Jiang, Y. High frequencies of activated B cells and T follicular helper cells are correlated with disease activity in patients with new-onset rheumatoid arthritis. *Clin. Exp. Immunol.* **2013**, *174*, 212–220. [[CrossRef](#)] [[PubMed](#)]
92. Li, X.Y.; Wu, Z.B.; Ding, J.; Zheng, Z.H.; Li, X.Y.; Chen, L.N.; Zhu, P. Role of the frequency of blood CD4(+) CXCR5(+) CCR6(+) T cells in autoimmunity in patients with Sjögren’s syndrome. *Biochem. Biophys. Res. Commun.* **2012**, *422*, 238–244. [[CrossRef](#)]

93. Verstappen, G.M.; Kroese, F.G.; Meiners, P.M.; Corneth, O.B.; Huitema, M.G.; Haacke, E.A.; van der Vegt, B.; Arends, S.; Vissink, A.; Bootsma, H.; et al. B Cell Depletion Therapy Normalizes Circulating Follicular Th Cells in Primary Sjögren Syndrome. *J. Rheumatol.* **2017**, *44*, 49–58. [[CrossRef](#)] [[PubMed](#)]
94. Gago da Graça, C.; van Baarsen, L.G.M.; Mebius, R.E. Tertiary Lymphoid Structures: Diversity in Their Development, Composition, and Role. *J. Immunol.* **2021**, *206*, 273–281. [[CrossRef](#)] [[PubMed](#)]
95. Hong, H.; Alduraibi, F.; Ponder, D.; Duck, W.L.; Morrow, C.D.; Foote, J.B.; Schoeb, T.R.; Fatima, H.; Elson, C.O., 3rd; Hsu, H.C.; et al. Host Genetics But Not Commensal Microbiota Determines the Initial Development of Systemic Autoimmune Disease in BXD2 Mice. *Arthritis Rheumatol.* **2022**, *74*, 634–640. [[CrossRef](#)]
96. Domeier, P.P.; Schell, S.L.; Rahman, Z.S. Spontaneous germinal centers and autoimmunity. *Autoimmunity* **2017**, *50*, 4–18. [[CrossRef](#)]
97. Mackay, F.; Woodcock, S.A.; Lawton, P.; Ambrose, C.; Baetscher, M.; Schneider, P.; Tschopp, J.; Browning, J.L. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. *J. Exp. Med.* **1999**, *190*, 1697–1710. [[CrossRef](#)] [[PubMed](#)]
98. Kil, L.P.; de Bruijn, M.J.; van Nimwegen, M.; Corneth, O.B.; van Hamburg, J.P.; Dingjan, G.M.; Thaiss, F.; Rimmelzwaan, G.F.; Elewaut, D.; Delsing, D.; et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. *Blood* **2012**, *119*, 3744–3756. [[CrossRef](#)]
99. Becker-Herman, S.; Meyer-Bahlburg, A.; Schwartz, M.A.; Jackson, S.W.; Hudkins, K.L.; Liu, C.; Sather, B.D.; Khim, S.; Liggitt, D.; Song, W.; et al. WASp-deficient B cells play a critical, cell-intrinsic role in triggering autoimmunity. *J. Exp. Med.* **2011**, *208*, 2033–2042. [[CrossRef](#)]
100. Lee, S.K.; Silva, D.G.; Martin, J.L.; Pratama, A.; Hu, X.; Chang, P.P.; Walters, G.; Vinuesa, C.G. Interferon- $\gamma$  excess leads to pathogenic accumulation of follicular helper T cells and germinal centers. *Immunity* **2012**, *37*, 880–892. [[CrossRef](#)]
101. Hsu, H.C.; Yang, P.; Wang, J.; Wu, Q.; Myers, R.; Chen, J.; Yi, J.; Guentert, T.; Tousson, A.; Stanus, A.L.; et al. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. *Nat. Immunol.* **2008**, *9*, 166–175. [[CrossRef](#)] [[PubMed](#)]
102. Zhang, S.; Li, L.; Xie, D.; Reddy, S.; Sleasman, J.W.; Ma, L.; Zhong, X.P. Regulation of Intrinsic and Bystander T Follicular Helper Cell Differentiation and Autoimmunity by Tsc1. *Front. Immunol.* **2021**, *12*, 620437. [[CrossRef](#)] [[PubMed](#)]
103. O'Brien, S.A.; Zhu, M.; Zhang, W. Spontaneous Differentiation of T Follicular Helper Cells in LATY136F Mutant Mice. *Front. Immunol.* **2021**, *12*, 656817. [[CrossRef](#)] [[PubMed](#)]
104. Arkatkar, T.; Du, S.W.; Jacobs, H.M.; Dam, E.M.; Hou, B.; Buckner, J.H.; Rawlings, D.J.; Jackson, S.W. B cell-derived IL-6 initiates spontaneous germinal center formation during systemic autoimmunity. *J. Exp. Med.* **2017**, *214*, 3207–3217. [[CrossRef](#)]
105. Corneth, O.B.; de Bruijn, M.J.; Rip, J.; Asmawidjaja, P.S.; Kil, L.P.; Hendriks, R.W. Enhanced Expression of Bruton's Tyrosine Kinase in B Cells Drives Systemic Autoimmunity by Disrupting T Cell Homeostasis. *J. Immunol.* **2016**, *197*, 58–67. [[CrossRef](#)]
106. Munroe, M.E.; Lu, R.; Zhao, Y.D.; Fife, D.A.; Robertson, J.M.; Guthridge, J.M.; Niewold, T.B.; Tsokos, G.C.; Keith, M.P.; Harley, J.B.; et al. Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. *Ann. Rheum. Dis.* **2016**, *75*, 2014–2021. [[CrossRef](#)]
107. Zumaquero, E.; Stone, S.L.; Scharer, C.D.; Jenks, S.A.; Nellore, A.; Mousseau, B.; Rosal-Vela, A.; Botta, D.; Bradley, J.E.; Wojciechowski, W.; et al. IFN $\gamma$  induces epigenetic programming of human T-bet(hi) B cells and promotes TLR7/8 and IL-21 induced differentiation. *eLife* **2019**, *8*, e41641. [[CrossRef](#)]
108. Chiang, K.; Largent, A.D.; Arkatkar, T.; Thouvenel, C.D.; Du, S.W.; Shumlak, N.; Woods, J.; Li, Q.Z.; Liu, Y.; Hou, B.; et al. Cutting Edge: A Threshold of B Cell Costimulatory Signals Is Required for Spontaneous Germinal Center Formation in Autoimmunity. *J. Immunol.* **2021**, *207*, 2217–2222. [[CrossRef](#)]
109. Domeier, P.P.; Chodisetti, S.B.; Soni, C.; Schell, S.L.; Elias, M.J.; Wong, E.B.; Cooper, T.K.; Kitamura, D.; Rahman, Z.S. IFN- $\gamma$  receptor and STAT1 signaling in B cells are central to spontaneous germinal center formation and autoimmunity. *J. Exp. Med.* **2016**, *213*, 715–732. [[CrossRef](#)]
110. Soni, C.; Wong, E.B.; Domeier, P.P.; Khan, T.N.; Satoh, T.; Akira, S.; Rahman, Z.S. B cell-intrinsic TLR7 signaling is essential for the development of spontaneous germinal centers. *J. Immunol.* **2014**, *193*, 4400–4414. [[CrossRef](#)]
111. Sanchez, H.N.; Moroney, J.B.; Gan, H.; Shen, T.; Im, J.L.; Li, T.; Taylor, J.R.; Zan, H.; Casali, P. B cell-intrinsic epigenetic modulation of antibody responses by dietary fiber-derived short-chain fatty acids. *Nat. Commun.* **2020**, *11*, 60. [[CrossRef](#)] [[PubMed](#)]
112. Folkerts, J.; Redegeld, F.; Folkerts, G.; Blokhuis, B.; van den Berg, M.P.; de Bruijn, M.J.; van IJcken, W.F.; Junt, T.; Tam, S.Y.; Galli, S.J.; et al. Butyrate inhibits human mast cell activation via epigenetic regulation of Fc $\epsilon$ RI-mediated signaling. *Allergy* **2020**, *75*, 1966–1978. [[CrossRef](#)] [[PubMed](#)]
113. Malkiel, S.; Barlev, A.N.; Atisha-Fregoso, Y.; Suurmond, J.; Diamond, B. Plasma Cell Differentiation Pathways in Systemic Lupus Erythematosus. *Front. Immunol.* **2018**, *9*, 427. [[CrossRef](#)]
114. Seavey, M.M.; Lu, L.D.; Stump, K.L.; Wallace, N.H.; Ruggeri, B.A. Novel, orally active, proteasome inhibitor, delanzomib (CEP-18770), ameliorates disease symptoms and glomerulonephritis in two preclinical mouse models of SLE. *Int. Immunopharmacol.* **2012**, *12*, 257–270. [[CrossRef](#)] [[PubMed](#)]
115. Ichikawa, H.T.; Conley, T.; Muchamuel, T.; Jiang, J.; Lee, S.; Owen, T.; Barnard, J.; Nevarez, S.; Goldman, B.I.; Kirk, C.J.; et al. Beneficial effect of novel proteasome inhibitors in murine lupus via dual inhibition of type I interferon and autoantibody-secreting cells. *Arthritis Rheum.* **2012**, *64*, 493–503. [[CrossRef](#)]

116. Taylor, E.B.; Barati, M.T.; Powell, D.W.; Turbeville, H.R.; Ryan, M.J. Plasma Cell Depletion Attenuates Hypertension in an Experimental Model of Autoimmune Disease. *Hypertension* **2018**, *71*, 719–728. [[CrossRef](#)]
117. Alexander, T.; Cheng, Q.; Klotsche, J.; Khodadadi, L.; Waka, A.; Biesen, R.; Hoyer, B.F.; Burmester, G.R.; Radbruch, A.; Hiepe, F. Proteasome inhibition with bortezomib induces a therapeutically relevant depletion of plasma cells in SLE but does not target their precursors. *Eur. J. Immunol.* **2018**, *48*, 1573–1579. [[CrossRef](#)]
118. Walhelm, T.; Gunnarsson, I.; Heijke, R.; Leonard, D.; Trysberg, E.; Eriksson, P.; Sjöwall, C. Clinical Experience of Proteasome Inhibitor Bortezomib Regarding Efficacy and Safety in Severe Systemic Lupus Erythematosus: A Nationwide Study. *Front. Immunol.* **2021**, *12*, 756941. [[CrossRef](#)]
119. Shaffer, A.L.; Shapiro-Shelef, M.; Iwakoshi, N.N.; Lee, A.H.; Qian, S.B.; Zhao, H.; Yu, X.; Yang, L.; Tan, B.K.; Rosenwald, A.; et al. XBP1, downstream of Blimp-1, expands the secretory apparatus and other organelles, and increases protein synthesis in plasma cell differentiation. *Immunity* **2004**, *21*, 81–93. [[CrossRef](#)]
120. Wei, C.; Anolik, J.; Cappione, A.; Zheng, B.; Pugh-Bernard, A.; Brooks, J.; Lee, E.H.; Milner, E.C.; Sanz, I. A new population of cells lacking expression of CD27 represents a notable component of the B cell memory compartment in systemic lupus erythematosus. *J. Immunol.* **2007**, *178*, 6624–6633. [[CrossRef](#)]
121. Phalke, S.; Rivera-Correa, J.; Jenkins, D.; Flores Castro, D.; Giannopoulou, E.; Pernis, A.B. Molecular mechanisms controlling age-associated B cells in autoimmunity. *Immunol. Rev.* **2022**, *307*, 79–100. [[CrossRef](#)] [[PubMed](#)]
122. Mouat, I.C.; Goldberg, E.; Horwitz, M.S. Age-associated B cells in autoimmune diseases. *Cell. Mol. Life Sci.* **2022**, *79*, 402. [[CrossRef](#)] [[PubMed](#)]
123. Brodie, E.J.; Infantino, S.; Low, M.S.Y.; Tarlinton, D.M. Lyn, Lupus, and (B) Lymphocytes, a Lesson on the Critical Balance of Kinase Signaling in Immunity. *Front. Immunol.* **2018**, *9*, 401. [[CrossRef](#)]
124. Oellerich, T.; Bremes, V.; Neumann, K.; Bohnenberger, H.; Dittmann, K.; Hsiao, H.H.; Engelke, M.; Schnyder, T.; Batista, F.D.; Urlaub, H.; et al. The B-cell antigen receptor signals through a preformed transducer module of SLP65 and CIN85. *EMBO J.* **2011**, *30*, 3620–3634. [[CrossRef](#)] [[PubMed](#)]
125. Kühn, J.; Wong, L.E.; Pirkuliyeva, S.; Schulz, K.; Schwiegk, C.; Fünfgeld, K.G.; Keppler, S.; Batista, F.D.; Urlaub, H.; Habeck, M.; et al. The adaptor protein CIN85 assembles intracellular signaling clusters for B cell activation. *Sci. Signal.* **2016**, *9*, ra66. [[CrossRef](#)]
126. Yamanashi, Y.; Kakiuchi, T.; Mizuguchi, J.; Yamamoto, T.; Toyoshima, K. Association of B cell antigen receptor with protein tyrosine kinase Lyn. *Science* **1991**, *251*, 192–194. [[CrossRef](#)] [[PubMed](#)]
127. Antony, P.; Petro, J.B.; Carlesso, G.; Shinnars, N.P.; Lowe, J.; Khan, W.N. B-cell antigen receptor activates transcription factors NFAT (nuclear factor of activated T-cells) and NF-kappaB (nuclear factor kappaB) via a mechanism that involves diacylglycerol. *Biochem. Soc. Trans.* **2004**, *32*, 113–115. [[CrossRef](#)] [[PubMed](#)]
128. Beitz, L.O.; Fruman, D.A.; Kurosaki, T.; Cantley, L.C.; Scharenberg, A.M. SYK is upstream of phosphoinositide 3-kinase in B cell receptor signaling. *J. Biol. Chem.* **1999**, *274*, 32662–32666. [[CrossRef](#)]
129. Pogue, S.L.; Kurosaki, T.; Bolen, J.; Herbst, R. B cell antigen receptor-induced activation of Akt promotes B cell survival and is dependent on Syk kinase. *J. Immunol.* **2000**, *165*, 1300–1306. [[CrossRef](#)]
130. Chan, V.W.; Lowell, C.A.; DeFranco, A.L. Defective negative regulation of antigen receptor signaling in Lyn-deficient B lymphocytes. *Curr. Biol.* **1998**, *8*, 545–553. [[CrossRef](#)]
131. Smith, K.G.; Tarlinton, D.M.; Doody, G.M.; Hibbs, M.L.; Fearon, D.T. Inhibition of the B cell by CD22: A requirement for Lyn. *J. Exp. Med.* **1998**, *187*, 807–811. [[CrossRef](#)] [[PubMed](#)]
132. Sen, G.; Bikah, G.; Venkataraman, C.; Bondada, S. Negative regulation of antigen receptor-mediated signaling by constitutive association of CD5 with the SHP-1 protein tyrosine phosphatase in B-1 B cells. *Eur. J. Immunol.* **1999**, *29*, 3319–3328. [[CrossRef](#)]
133. Zhang, J.; Somani, A.K.; Siminovitch, K.A. Roles of the SHP-1 tyrosine phosphatase in the negative regulation of cell signalling. *Semin. Immunol.* **2000**, *12*, 361–378. [[CrossRef](#)]
134. Okada, M.; Nada, S.; Yamanashi, Y.; Yamamoto, T.; Nakagawa, H. CSK: A protein-tyrosine kinase involved in regulation of src family kinases. *J. Biol. Chem.* **1991**, *266*, 24249–24252. [[CrossRef](#)]
135. Ono, M.; Bolland, S.; Tempst, P.; Ravetch, J.V. Role of the inositol phosphatase SHIP in negative regulation of the immune system by the receptor Fc(gamma)RIIB. *Nature* **1996**, *383*, 263–266. [[CrossRef](#)] [[PubMed](#)]
136. Bolland, S.; Pearse, R.N.; Kurosaki, T.; Ravetch, J.V. SHIP modulates immune receptor responses by regulating membrane association of Btk. *Immunity* **1998**, *8*, 509–516. [[CrossRef](#)]
137. Saijo, K.; Schmedt, C.; Su, I.H.; Karasuyama, H.; Lowell, C.A.; Reth, M.; Adachi, T.; Patke, A.; Santana, A.; Tarakhovsky, A. Essential role of Src-family protein tyrosine kinases in NF-kappaB activation during B cell development. *Nat. Immunol.* **2003**, *4*, 274–279. [[CrossRef](#)] [[PubMed](#)]
138. Chan, V.W.; Meng, F.; Soriano, P.; DeFranco, A.L.; Lowell, C.A. Characterization of the B lymphocyte populations in Lyn-deficient mice and the role of Lyn in signal initiation and down-regulation. *Immunity* **1997**, *7*, 69–81. [[CrossRef](#)]
139. Hibbs, M.L.; Tarlinton, D.M.; Armes, J.; Grail, D.; Hodgson, G.; Maglitto, R.; Stacker, S.A.; Dunn, A.R. Multiple defects in the immune system of Lyn-deficient mice, culminating in autoimmune disease. *Cell* **1995**, *83*, 301–311. [[CrossRef](#)]
140. Lamagna, C.; Hu, Y.; DeFranco, A.L.; Lowell, C.A. B cell-specific loss of Lyn kinase leads to autoimmunity. *J. Immunol.* **2014**, *192*, 919–928. [[CrossRef](#)]

141. Hua, Z.; Gross, A.J.; Lamagna, C.; Ramos-Hernandez, N.; Scapini, P.; Ji, M.; Shao, H.; Lowell, C.A.; Hou, B.; DeFranco, A.L. Requirement for MyD88 signaling in B cells and dendritic cells for germinal center anti-nuclear antibody production in Lyn-deficient mice. *J. Immunol.* **2014**, *192*, 875–885. [[CrossRef](#)] [[PubMed](#)]
142. Lamagna, C.; Scapini, P.; van Ziffle, J.A.; DeFranco, A.L.; Lowell, C.A. Hyperactivated MyD88 signaling in dendritic cells, through specific deletion of Lyn kinase, causes severe autoimmunity and inflammation. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E3311–E3320. [[CrossRef](#)] [[PubMed](#)]
143. Silver, K.L.; Crockford, T.L.; Bouriez-Jones, T.; Milling, S.; Lambe, T.; Cornall, R.J. MyD88-dependent autoimmune disease in Lyn-deficient mice. *Eur. J. Immunol.* **2007**, *37*, 2734–2743. [[CrossRef](#)]
144. Flores-Borja, F.; Kabouridis, P.S.; Jury, E.C.; Isenberg, D.A.; Mageed, R.A. Decreased Lyn expression and translocation to lipid raft signaling domains in B lymphocytes from patients with systemic lupus erythematosus. *Arthritis Rheum.* **2005**, *52*, 3955–3965. [[CrossRef](#)] [[PubMed](#)]
145. Liossis, S.N.; Solomou, E.E.; Dimopoulos, M.A.; Panayiotidis, P.; Mavrikakis, M.M.; Sfikakis, P.P. B-cell kinase lyn deficiency in patients with systemic lupus erythematosus. *J. Invest. Med.* **2001**, *49*, 157–165. [[CrossRef](#)]
146. Liu, Y.; Dong, J.; Mu, R.; Gao, Y.; Tan, X.; Li, Y.; Li, Z.; Yang, G. MicroRNA-30a promotes B cell hyperactivity in patients with systemic lupus erythematosus by direct interaction with Lyn. *Arthritis Rheum.* **2013**, *65*, 1603–1611. [[CrossRef](#)] [[PubMed](#)]
147. Taher, T.E.; Parikh, K.; Flores-Borja, F.; Mletzko, S.; Isenberg, D.A.; Peppelenbosch, M.P.; Mageed, R.A. Protein phosphorylation and kinase profiling reveal altered regulation of multiple signaling pathways in B lymphocytes from patients with systemic lupus erythematosus. *Arthritis Rheum.* **2010**, *62*, 2412–2423. [[CrossRef](#)]
148. Manjarrez-Orduno, N.; Marasco, E.; Chung, S.A.; Katz, M.S.; Kiridly, J.F.; Simpfendorfer, K.R.; Freudenberg, J.; Ballard, D.H.; Nashi, E.; Hopkins, T.J.; et al. CSK regulatory polymorphism is associated with systemic lupus erythematosus and influences B-cell signaling and activation. *Nat. Genet.* **2012**, *44*, 1227–1230. [[CrossRef](#)]
149. Fleischer, S.J.; Giesecke, C.; Mei, H.E.; Lipsky, P.E.; Daridon, C.; Dorner, T. Increased frequency of a unique spleen tyrosine kinase bright memory B cell population in systemic lupus erythematosus. *Arthritis Rheumatol.* **2014**, *66*, 3424–3435. [[CrossRef](#)]
150. Iwata, S.; Yamaoka, K.; Niuro, H.; Jabbarzadeh-Tabrizi, S.; Wang, S.P.; Kondo, M.; Yoshikawa, M.; Akashi, K.; Tanaka, Y. Increased Syk phosphorylation leads to overexpression of TRAF6 in peripheral B cells of patients with systemic lupus erythematosus. *Lupus* **2015**, *24*, 695–704. [[CrossRef](#)]
151. Iwata, S.; Nakayamada, S.; Fukuyo, S.; Kubo, S.; Yunoue, N.; Wang, S.P.; Yoshikawa, M.; Saito, K.; Tanaka, Y. Activation of Syk in peripheral blood B cells in patients with rheumatoid arthritis: A potential target for abatacept therapy. *Arthritis Rheumatol.* **2015**, *67*, 63–73. [[CrossRef](#)]
152. Weinblatt, M.E.; Kavanaugh, A.; Genovese, M.C.; Musser, T.K.; Grossbard, E.B.; Magilavy, D.B. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. *N. Engl. J. Med.* **2010**, *363*, 1303–1312. [[CrossRef](#)] [[PubMed](#)]
153. Kang, Y.; Jiang, X.; Qin, D.; Wang, L.; Yang, J.; Wu, A.; Huang, F.; Ye, Y.; Wu, J. Efficacy and Safety of Multiple Dosages of Fostamatinib in Adult Patients With Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Front. Pharm.* **2019**, *10*, 897. [[CrossRef](#)] [[PubMed](#)]
154. Cha, H.S.; Boyle, D.L.; Inoue, T.; Schoot, R.; Tak, P.P.; Pine, P.; Firestein, G.S. A novel spleen tyrosine kinase inhibitor blocks c-Jun N-terminal kinase-mediated gene expression in synoviocytes. *J. Pharm. Exp. Ther.* **2006**, *317*, 571–578. [[CrossRef](#)] [[PubMed](#)]
155. Jansson, L.; Holmdahl, R. Genes on the X chromosome affect development of collagen-induced arthritis in mice. *Clin. Exp. Immunol.* **1993**, *94*, 459–465. [[CrossRef](#)]
156. Nyhoff, L.E.; Barron, B.L.; Johnson, E.M.; Bonami, R.H.; Maseda, D.; Fensterheim, B.A.; Han, W.; Blackwell, T.S.; Crofford, L.J.; Kendall, P.L. Bruton's Tyrosine Kinase Deficiency Inhibits Autoimmune Arthritis in Mice but Fails to Block Immune Complex-Mediated Inflammatory Arthritis. *Arthritis Rheumatol.* **2016**, *68*, 1856–1868. [[CrossRef](#)]
157. Smith, H.R.; Chused, T.M.; Steinberg, A.D. The effect of the X-linked immune deficiency gene (xid) upon the Y chromosome-related disease of BXSB mice. *J. Immunol.* **1983**, *131*, 1257–1262.
158. Steinberg, B.J.; Smathers, P.A.; Frederiksen, K.; Steinberg, A.D. Ability of the xid gene to prevent autoimmunity in (NZB X NZW)F1 mice during the course of their natural history, after polyclonal stimulation, or following immunization with DNA. *J. Clin. Invest.* **1982**, *70*, 587–597. [[CrossRef](#)]
159. Rip, J.; Van Der Ploeg, E.K.; Hendriks, R.W.; Corneth, O.B.J. The Role of Bruton's Tyrosine Kinase in Immune Cell Signaling and Systemic Autoimmunity. *Crit. Rev. Immunol.* **2018**, *38*, 17–62. [[CrossRef](#)]
160. Corneth, O.B.J.; Verstappen, G.M.P.; Paulissen, S.M.J.; de Bruijn, M.J.W.; Rip, J.; Lukkes, M.; van Hamburg, J.P.; Lubberts, E.; Bootsma, H.; Kroese, F.G.M.; et al. Enhanced Bruton's Tyrosine Kinase Activity in Peripheral Blood B Lymphocytes From Patients With Autoimmune Disease. *Arthritis Rheumatol.* **2017**, *69*, 1313–1324. [[CrossRef](#)]
161. von Borstel, A.; Abdulahad, W.H.; Sanders, J.S.; Rip, J.; Neys, S.F.H.; Hendriks, R.W.; Stegeman, C.A.; Heeringa, P.; Rutgers, A.; Corneth, O.B.J. Evidence for enhanced Bruton's tyrosine kinase activity in transitional and naive B cells of patients with granulomatosis with polyangiitis. *Rheumatology* **2019**, *58*, 2230–2239. [[CrossRef](#)] [[PubMed](#)]
162. Neys, S.F.H.; Heukels, P.; van Hulst, J.A.C.; Rip, J.; Wijsenbeek, M.S.; Hendriks, R.W.; Corneth, O.B.J. Aberrant B Cell Receptor Signaling in Naïve B Cells from Patients with Idiopathic Pulmonary Fibrosis. *Cells* **2021**, *10*, 1321. [[CrossRef](#)] [[PubMed](#)]
163. Cohen, S.; Tuckwell, K.; Katsumoto, T.R.; Zhao, R.; Galanter, J.; Lee, C.; Rae, J.; Toth, B.; Ramamoorthi, N.; Hackney, J.A.; et al. Fenebrutinib versus Placebo or Adalimumab in Rheumatoid Arthritis: A Randomized, Double-Blind, Phase II Trial (ANDES Study). *Arthritis Rheumatol.* **2020**, *72*, 1435–1446. [[CrossRef](#)] [[PubMed](#)]

164. Montalban, X.; Arnold, D.L.; Weber, M.S.; Staikov, I.; Piasecka-Stryczynska, K.; Willmer, J.; Martin, E.C.; Dangond, F.; Syed, S.; Wolinsky, J.S.; et al. Placebo-Controlled Trial of an Oral BTK Inhibitor in Multiple Sclerosis. *N. Engl. J. Med.* **2019**, *380*, 2406–2417. [[CrossRef](#)]
165. Isenberg, D.; Furie, R.; Jones, N.S.; Guibord, P.; Galanter, J.; Lee, C.; McGregor, A.; Toth, B.; Rae, J.; Hwang, O.; et al. Efficacy, Safety, and Pharmacodynamic Effects of the Bruton's Tyrosine Kinase Inhibitor Fenebrutinib (GDC-0853) in Systemic Lupus Erythematosus: Results of a Phase II, Randomized, Double-Blind, Placebo-Controlled Trial. *Arthritis Rheumatol.* **2021**, *73*, 1835–1846. [[CrossRef](#)]
166. Middendorp, S.; Dingjan, G.M.; Maas, A.; Dahlenborg, K.; Hendriks, R.W. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity. *J. Immunol.* **2003**, *171*, 5988–5996. [[CrossRef](#)]
167. Middendorp, S.; Zijlstra, A.J.; Kersseboom, R.; Dingjan, G.M.; Jumaa, H.; Hendriks, R.W. Tumor suppressor function of Bruton tyrosine kinase is independent of its catalytic activity. *Blood* **2005**, *105*, 259–265. [[CrossRef](#)]
168. Belver, L.; de Yébenes, V.G.; Ramiro, A.R. MicroRNAs prevent the generation of autoreactive antibodies. *Immunity* **2010**, *33*, 713–722. [[CrossRef](#)] [[PubMed](#)]
169. Chen, J.; Li, Y.; Xie, X. MicroRNA-425 inhibits proliferation of chronic lymphocytic leukaemia cells through regulation of the Bruton's tyrosine kinase/phospholipase C $\gamma$ 2 signalling pathway. *Exp. Ther. Med.* **2020**, *20*, 1169–1175. [[CrossRef](#)] [[PubMed](#)]
170. Bottoni, A.; Rizzotto, L.; Lai, T.H.; Liu, C.; Smith, L.L.; Mantel, R.; Reiff, S.; El-Gamal, D.; Larkin, K.; Johnson, A.J.; et al. Targeting BTK through microRNA in chronic lymphocytic leukemia. *Blood* **2016**, *128*, 3101–3112. [[CrossRef](#)] [[PubMed](#)]
171. Bernal-Quiros, M.; Wu, Y.Y.; Alarcon-Riquelme, M.E.; Castillejo-Lopez, C. BANK1 and BLK act through phospholipase C gamma 2 in B-cell signaling. *PLoS ONE* **2013**, *8*, e59842. [[CrossRef](#)] [[PubMed](#)]
172. Jiang, S.H.; Athanasopoulos, V.; Ellyard, J.I.; Chuah, A.; Cappello, J.; Cook, A.; Prabhu, S.B.; Cardenas, J.; Gu, J.; Stanley, M.; et al. Functional rare and low frequency variants in BLK and BANK1 contribute to human lupus. *Nat. Commun.* **2019**, *10*, 2201. [[CrossRef](#)] [[PubMed](#)]
173. Martin-Nalda, A.; Fortuny, C.; Rey, L.; Bunney, T.D.; Alsina, L.; Esteve-Sole, A.; Bull, D.; Anton, M.C.; Basagana, M.; Casals, F.; et al. Severe Autoinflammatory Manifestations and Antibody Deficiency Due to Novel Hypermorphous PLCG2 Mutations. *J. Clin. Immunol.* **2020**, *40*, 987–1000. [[CrossRef](#)]
174. Ombrello, M.J.; Remmers, E.F.; Sun, G.; Freeman, A.F.; Datta, S.; Torabi-Parizi, P.; Subramanian, N.; Bunney, T.D.; Baxendale, R.W.; Martins, M.S.; et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *N. Engl. J. Med.* **2012**, *366*, 330–338. [[CrossRef](#)] [[PubMed](#)]
175. Yu, P.; Constien, R.; Dear, N.; Katan, M.; Hanke, P.; Bunney, T.D.; Kunder, S.; Quintanilla-Martinez, L.; Huffstadt, U.; Schroder, A.; et al. Autoimmunity and inflammation due to a gain-of-function mutation in phospholipase C gamma 2 that specifically increases external Ca<sup>2+</sup> entry. *Immunity* **2005**, *22*, 451–465. [[CrossRef](#)]
176. Limon, J.J.; Fruman, D.A. Akt and mTOR in B Cell Activation and Differentiation. *Front. Immunol.* **2012**, *3*, 228. [[CrossRef](#)]
177. Harder, I.; Münchhalfen, M.; Andrieux, G.; Boerries, M.; Grimbacher, B.; Eibel, H.; Maccari, M.E.; Ehl, S.; Wienands, J.; Jellusova, J.; et al. Dysregulated PI3K Signaling in B Cells of CVID Patients. *Cells* **2022**, *11*, 464. [[CrossRef](#)]
178. Caro-Maldonado, A.; Wang, R.; Nichols, A.G.; Kuraoka, M.; Milasta, S.; Sun, L.D.; Gavin, A.L.; Abel, E.D.; Kelsoe, G.; Green, D.R.; et al. Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. *J. Immunol.* **2014**, *192*, 3626–3636. [[CrossRef](#)]
179. Waters, L.R.; Ahsan, F.M.; Wolf, D.M.; Shirihai, O.; Teitell, M.A. Initial B Cell Activation Induces Metabolic Reprogramming and Mitochondrial Remodeling. *iScience* **2018**, *5*, 99–109. [[CrossRef](#)] [[PubMed](#)]
180. Jellusova, J.; Cato, M.H.; Apgar, J.R.; Ramezani-Rad, P.; Leung, C.R.; Chen, C.; Richardson, A.D.; Conner, E.M.; Benschop, R.J.; Woodgett, J.R.; et al. Gsk3 is a metabolic checkpoint regulator in B cells. *Nat. Immunol.* **2017**, *18*, 303–312. [[CrossRef](#)]
181. Inoue, T.; Shinnakasu, R.; Kawai, C.; Ise, W.; Kawakami, E.; Sax, N.; Oki, T.; Kitamura, T.; Yamashita, K.; Fukuyama, H.; et al. Exit from germinal center to become quiescent memory B cells depends on metabolic reprogramming and provision of a survival signal. *J. Exp. Med.* **2021**, *218*, e20200866. [[CrossRef](#)] [[PubMed](#)]
182. Weisel, F.J.; Zuccarino-Catania, G.V.; Chikina, M.; Shlomchik, M.J. A Temporal Switch in the Germinal Center Determines Differential Output of Memory B and Plasma Cells. *Immunity* **2016**, *44*, 116–130. [[CrossRef](#)] [[PubMed](#)]
183. Malkiel, S.; Jeganathan, V.; Wolfson, S.; Manjarrez Orduno, N.; Marasco, E.; Aranow, C.; Mackay, M.; Gregersen, P.K.; Diamond, B. Checkpoints for Autoreactive B Cells in the Peripheral Blood of Lupus Patients Assessed by Flow Cytometry. *Arthritis Rheumatol.* **2016**, *68*, 2210–2220. [[CrossRef](#)] [[PubMed](#)]
184. Cho, S.H.; Raybuck, A.L.; Stengel, K.; Wei, M.; Beck, T.C.; Volanakis, E.; Thomas, J.W.; Hiebert, S.; Haase, V.H.; Boothby, M.R. Germinal centre hypoxia and regulation of antibody qualities by a hypoxia response system. *Nature* **2016**, *537*, 234–238. [[CrossRef](#)] [[PubMed](#)]
185. Torigoe, M.; Iwata, S.; Nakayamada, S.; Sakata, K.; Zhang, M.; Hajime, M.; Miyazaki, Y.; Narisawa, M.; Ishii, K.; Shibata, H.; et al. Metabolic Reprogramming Commits Differentiation of Human CD27(+)IgD(+) B Cells to Plasmablasts or CD27(-)IgD(-) Cells. *J. Immunol.* **2017**, *199*, 425–434. [[CrossRef](#)] [[PubMed](#)]
186. Blokland, S.L.M.; Hillen, M.R.; Wichers, C.G.K.; Zimmermann, M.; Kruize, A.A.; Radstake, T.; Broen, J.C.A.; van Roon, J.A.G. Increased mTORC1 activation in salivary gland B cells and T cells from patients with Sjogren's syndrome: mTOR inhibition as a novel therapeutic strategy to halt immunopathology? *RMD Open* **2019**, *5*, e000701. [[CrossRef](#)]

187. Clarke, A.J.; Ellinghaus, U.; Cortini, A.; Stranks, A.; Simon, A.K.; Botto, M.; Vyse, T.J. Autophagy is activated in systemic lupus erythematosus and required for plasmablast development. *Ann. Rheum. Dis.* **2015**, *74*, 912–920. [[CrossRef](#)]
188. Raza, I.G.A.; Clarke, A.J. B Cell Metabolism and Autophagy in Autoimmunity. *Front. Immunol.* **2021**, *12*, 681105. [[CrossRef](#)]
189. Gonzalez-Martin, A.; Adams, B.D.; Lai, M.; Shepherd, J.; Salvador-Bernaldez, M.; Salvador, J.M.; Lu, J.; Nemazee, D.; Xiao, C. The microRNA miR-148a functions as a critical regulator of B cell tolerance and autoimmunity. *Nat. Immunol.* **2016**, *17*, 433–440. [[CrossRef](#)]
190. Chauhan, S.K.; Singh, V.V.; Rai, R.; Rai, M.; Rai, G. Differential microRNA profile and post-transcriptional regulation exist in systemic lupus erythematosus patients with distinct autoantibody specificities. *J. Clin. Immunol.* **2014**, *34*, 491–503. [[CrossRef](#)]
191. Ma, F.; Zhan, Y.; Bartolomé-Cabrero, R.; Ying, W.; Asano, M.; Huang, Z.; Xiao, C.; González-Martín, A. Analysis of a miR-148a Targetome in B Cell Central Tolerance. *Front. Immunol.* **2022**, *13*, 861655. [[CrossRef](#)]
192. Lai, M.; Gonzalez-Martin, A.; Cooper, A.B.; Oda, H.; Jin, H.Y.; Shepherd, J.; He, L.; Zhu, J.; Nemazee, D.; Xiao, C. Regulation of B-cell development and tolerance by different members of the miR-17 approximately 92 family microRNAs. *Nat. Commun.* **2016**, *7*, 12207. [[CrossRef](#)]
193. Benhamou, D.; Labi, V.; Getahun, A.; Benchetrit, E.; Dowery, R.; Rajewsky, K.; Cambier, J.C.; Melamed, D. The c-Myc/miR17-92/PTEN Axis Tunes PI3K Activity to Control Expression of Recombination Activating Genes in Early B Cell Development. *Front. Immunol.* **2018**, *9*, 2715. [[CrossRef](#)]
194. Xiao, C.; Srinivasan, L.; Calado, D.P.; Patterson, H.C.; Zhang, B.; Wang, J.; Henderson, J.M.; Kutok, J.L.; Rajewsky, K. Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat. Immunol.* **2008**, *9*, 405–414. [[CrossRef](#)]
195. Hines, M.J.; Coffre, M.; Mudianto, T.; Panduro, M.; Wigton, E.J.; Tegla, C.; Osorio-Vasquez, V.; Kageyama, R.; Benhamou, D.; Perez, O.; et al. miR-29 Sustains B Cell Survival and Controls Terminal Differentiation via Regulation of PI3K Signaling. *Cell Rep.* **2020**, *33*, 108436. [[CrossRef](#)]
196. Wu, X.N.; Ye, Y.X.; Niu, J.W.; Li, Y.; Li, X.; You, X.; Chen, H.; Zhao, L.D.; Zeng, X.F.; Zhang, F.C.; et al. Defective PTEN regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus. *Sci. Transl. Med.* **2014**, *6*, 246ra299. [[CrossRef](#)]
197. Smith, M.J.; Ford, B.R.; Rihaneck, M.; Coleman, B.M.; Getahun, A.; Sarapura, V.D.; Gottlieb, P.A.; Cambier, J.C. Elevated PTEN expression maintains anergy in human B cells and reveals unexpectedly high repertoire autoreactivity. *JCI Insight* **2019**, *4*, e123384. [[CrossRef](#)]
198. Wang, M.; Chen, H.; Qiu, J.; Yang, H.X.; Zhang, C.Y.; Fei, Y.Y.; Zhao, L.D.; Zhou, J.X.; Wang, L.; Wu, Q.J.; et al. Antagonizing miR-7 suppresses B cell hyperresponsiveness and inhibits lupus development. *J. Autoimmun.* **2020**, *109*, 102440. [[CrossRef](#)]
199. Xiao, C.; Nemazee, D.; Gonzalez-Martin, A. MicroRNA control of B cell tolerance, autoimmunity and cancer. *Semin. Cancer Biol.* **2020**, *64*, 102–107. [[CrossRef](#)]
200. Chi, M.; Ma, K.; Li, Y.; Quan, M.; Han, Z.; Ding, Z.; Liang, X.; Zhang, Q.; Song, L.; Liu, C. Immunological Involvement of MicroRNAs in the Key Events of Systemic Lupus Erythematosus. *Front. Immunol.* **2021**, *12*, 699684. [[CrossRef](#)]
201. Heinicke, F.; Zhong, X.; Flâm, S.T.; Breidenbach, J.; Leithaug, M.; Mæhlen, M.T.; Lillegraven, S.; Aga, A.B.; Norli, E.S.; Mjaavatten, M.D.; et al. MicroRNA Expression Differences in Blood-Derived CD19+ B Cells of Methotrexate Treated Rheumatoid Arthritis Patients. *Front. Immunol.* **2021**, *12*, 663736. [[CrossRef](#)] [[PubMed](#)]
202. Cho, S.; Lee, H.M.; Yu, I.S.; Choi, Y.S.; Huang, H.Y.; Hashemifar, S.S.; Lin, L.L.; Chen, M.C.; Afanasiev, N.D.; Khan, A.A.; et al. Differential cell-intrinsic regulations of germinal center B and T cells by miR-146a and miR-146b. *Nat. Commun.* **2018**, *9*, 2757. [[CrossRef](#)] [[PubMed](#)]
203. Amrouche, L.; You, S.; Sauvaget, V.; Manda, V.; Lamarthee, B.; Desbuissons, G.; Tinel, C.; Rabant, M.; Nguyen, C.; Isnard, P.; et al. MicroRNA-146a-deficient mice develop immune complex glomerulonephritis. *Sci. Rep.* **2019**, *9*, 15597. [[CrossRef](#)]
204. Tang, Y.; Luo, X.; Cui, H.; Ni, X.; Yuan, M.; Guo, Y.; Huang, X.; Zhou, H.; de Vries, N.; Tak, P.P.; et al. MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. *Arthritis Rheum.* **2009**, *60*, 1065–1075. [[CrossRef](#)] [[PubMed](#)]
205. Teng, G.; Hakimpour, P.; Landgraf, P.; Rice, A.; Tuschl, T.; Casellas, R.; Papavasiliou, F.N. MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. *Immunity* **2008**, *28*, 621–629. [[CrossRef](#)]
206. de Yebenes, V.G.; Belver, L.; Pisano, D.G.; Gonzalez, S.; Villasante, A.; Croce, C.; He, L.; Ramiro, A.R. miR-181b negatively regulates activation-induced cytidine deaminase in B cells. *J. Exp. Med.* **2008**, *205*, 2199–2206. [[CrossRef](#)]
207. de Yebenes, V.G.; Bartolome-Izquierdo, N.; Nogales-Cadenas, R.; Perez-Duran, P.; Mur, S.M.; Martinez, N.; Di Lisio, L.; Robbiani, D.F.; Pascual-Montano, A.; Canamero, M.; et al. miR-217 is an oncogene that enhances the germinal center reaction. *Blood* **2014**, *124*, 229–239. [[CrossRef](#)]
208. Kaga, H.; Komatsuda, A.; Omokawa, A.; Ito, M.; Teshima, K.; Tagawa, H.; Sawada, K.; Wakui, H. Downregulated expression of miR-155, miR-17, and miR-181b, and upregulated expression of activation-induced cytidine deaminase and interferon-alpha in PBMCs from patients with SLE. *Mod. Rheumatol.* **2015**, *25*, 865–870. [[CrossRef](#)]
209. Setz, C.S.; Khadour, A.; Renna, V.; Iype, J.; Gentner, E.; He, X.; Datta, M.; Young, M.; Nitschke, L.; Wienands, J.; et al. Pten controls B-cell responsiveness and germinal center reaction by regulating the expression of IgD BCR. *EMBO J.* **2019**, *38*, e100249. [[CrossRef](#)]
210. Amendt, T.; Ayoubi, O.E.; Linder, A.T.; Allies, G.; Young, M.; Setz, C.S.; Jumaa, H. Primary Immune Responses and Affinity Maturation Are Controlled by IgD. *Front. Immunol.* **2021**, *12*, 709240. [[CrossRef](#)]

211. Sabouri, Z.; Perotti, S.; Spierings, E.; Humburg, P.; Yabas, M.; Bergmann, H.; Horikawa, K.; Roots, C.; Lambe, S.; Young, C.; et al. IgD attenuates the IgM-induced anergy response in transitional and mature B cells. *Nat. Commun.* **2016**, *7*, 13381. [[CrossRef](#)] [[PubMed](#)]
212. Nguyen, T.G. The therapeutic implications of activated immune responses via the enigmatic immunoglobulin D. *Int. Rev. Immunol.* **2022**, *41*, 107–122. [[CrossRef](#)] [[PubMed](#)]
213. Ng, L.G.; Sutherland, A.P.; Newton, R.; Qian, F.; Cachero, T.G.; Scott, M.L.; Thompson, J.S.; Wheway, J.; Chtanova, T.; Groom, J.; et al. B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. *J. Immunol.* **2004**, *173*, 807–817. [[CrossRef](#)]
214. Thompson, J.S.; Bixler, S.A.; Qian, F.; Vora, K.; Scott, M.L.; Cachero, T.G.; Hession, C.; Schneider, P.; Sizing, I.D.; Mullen, C.; et al. BAFF-R, a newly identified TNF receptor that specifically interacts with BAFF. *Science* **2001**, *293*, 2108–2111. [[CrossRef](#)]
215. Sasaki, Y.; Casola, S.; Kutok, J.L.; Rajewsky, K.; Schmidt-Supprian, M. TNF family member B cell-activating factor (BAFF) receptor-dependent and -independent roles for BAFF in B cell physiology. *J. Immunol.* **2004**, *173*, 2245–2252. [[CrossRef](#)]
216. Castigli, E.; Wilson, S.A.; Scott, S.; Dedeoglu, F.; Xu, S.; Lam, K.P.; Bram, R.J.; Jabara, H.; Geha, R.S. TACI and BAFF-R mediate isotype switching in B cells. *J. Exp. Med.* **2005**, *201*, 35–39. [[CrossRef](#)]
217. Seshasayee, D.; Valdez, P.; Yan, M.; Dixit, V.M.; Tumas, D.; Grewal, I.S. Loss of TACI causes fatal lymphoproliferation and autoimmunity, establishing TACI as an inhibitory BlyS receptor. *Immunity* **2003**, *18*, 279–288. [[CrossRef](#)]
218. Shulga-Morskaya, S.; Dobles, M.; Walsh, M.E.; Ng, L.G.; MacKay, F.; Rao, S.P.; Kalled, S.L.; Scott, M.L. B cell-activating factor belonging to the TNF family acts through separate receptors to support B cell survival and T cell-independent antibody formation. *J. Immunol.* **2004**, *173*, 2331–2341. [[CrossRef](#)]
219. Yan, M.; Wang, H.; Chan, B.; Roose-Girma, M.; Erickson, S.; Baker, T.; Tumas, D.; Grewal, I.S.; Dixit, V.M. Activation and accumulation of B cells in TACI-deficient mice. *Nat. Immunol.* **2001**, *2*, 638–643. [[CrossRef](#)]
220. Avery, D.T.; Kalled, S.L.; Ellyard, J.I.; Ambrose, C.; Bixler, S.A.; Thien, M.; Brink, R.; Mackay, F.; Hodgkin, P.D.; Tangye, S.G. BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. *J. Clin. Investig.* **2003**, *112*, 286–297. [[CrossRef](#)]
221. O'Connor, B.P.; Raman, V.S.; Erickson, L.D.; Cook, W.J.; Weaver, L.K.; Ahonen, C.; Lin, L.L.; Mantchev, G.T.; Bram, R.J.; Noelle, R.J. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J. Exp. Med.* **2004**, *199*, 91–98. [[CrossRef](#)] [[PubMed](#)]
222. Pers, J.O.; Daridon, C.; Devauchelle, V.; Jousse, S.; Saraux, A.; Jamin, C.; Youinou, P. BAFF overexpression is associated with autoantibody production in autoimmune diseases. *Ann. N. Y. Acad. Sci.* **2005**, *1050*, 34–39. [[CrossRef](#)] [[PubMed](#)]
223. Vincent, F.B.; Kandane-Rathnayake, R.; Koelmeyer, R.; Hoi, A.Y.; Harris, J.; Mackay, F.; Morand, E.F. Analysis of serum B cell-activating factor from the tumor necrosis factor family (BAFF) and its soluble receptors in systemic lupus erythematosus. *Clin. Transl. Immunol.* **2019**, *8*, e01047. [[CrossRef](#)] [[PubMed](#)]
224. Schweighoffer, E.; Vanes, L.; Nys, J.; Cantrell, D.; McCleary, S.; Smithers, N.; Tybulewicz, V.L. The BAFF receptor transduces survival signals by co-opting the B cell receptor signaling pathway. *Immunity* **2013**, *38*, 475–488. [[CrossRef](#)] [[PubMed](#)]
225. Shinnars, N.P.; Carlesso, G.; Castro, I.; Hoek, K.L.; Corn, R.A.; Woodland, R.T.; Scott, M.L.; Wang, D.; Khan, W.N. Bruton's tyrosine kinase mediates NF-kappa B activation and B cell survival by B cell-activating factor receptor of the TNF-R family. *J. Immunol.* **2007**, *179*, 3872–3880. [[CrossRef](#)]
226. Sevdali, E.; Block, V.; Lataretu, M.; Li, H.; Smulski, C.R.; Briem, J.S.; Heitz, Y.; Fischer, B.; Ramirez, N.J.; Grimbacher, B.; et al. BAFFR activates PI3K/AKT signaling in human naive but not in switched memory B cells through direct interactions with B cell antigen receptors. *Cell Rep.* **2022**, *39*, 111019. [[CrossRef](#)]
227. Castro, I.; Wright, J.A.; Damdinsuren, B.; Hoek, K.L.; Carlesso, G.; Shinnars, N.P.; Gerstein, R.M.; Woodland, R.T.; Sen, R.; Khan, W.N. B cell receptor-mediated sustained c-Rel activation facilitates late transitional B cell survival through control of B cell activating factor receptor and NF-kappaB2. *J. Immunol.* **2009**, *182*, 7729–7737. [[CrossRef](#)]
228. Smith, S.H.; Cancro, M.P. Cutting edge: B cell receptor signals regulate BlyS receptor levels in mature B cells and their immediate progenitors. *J. Immunol.* **2003**, *170*, 5820–5823. [[CrossRef](#)]
229. Stadanlick, J.E.; Kaileh, M.; Karnell, F.G.; Scholz, J.L.; Miller, J.P.; Quinn, W.J., 3rd; Brezski, R.J.; Trembl, L.S.; Jordan, K.A.; Monroe, J.G.; et al. Tonic B cell antigen receptor signals supply an NF-kappaB substrate for prosurvival BlyS signaling. *Nat. Immunol.* **2008**, *9*, 1379–1387. [[CrossRef](#)]
230. Zhang, F.; Song, S.S.; Shu, J.L.; Li, Y.; Wu, Y.J.; Wang, Q.T.; Chen, J.Y.; Chang, Y.; Wu, H.X.; Zhang, L.L.; et al. BAFF upregulates CD28/B7 and CD40/CD154 expression and promotes mouse T and B cell interaction in vitro via BAFF receptor. *Acta Pharm. Sin.* **2016**, *37*, 1101–1109. [[CrossRef](#)]
231. von Bülow, G.U.; Bram, R.J. NF-AT activation induced by a CAML-interacting member of the tumor necrosis factor receptor superfamily. *Science* **1997**, *278*, 138–141. [[CrossRef](#)] [[PubMed](#)]
232. Hatzoglou, A.; Roussel, J.; Bourgeade, M.F.; Rogier, E.; Madry, C.; Inoue, J.; Devergne, O.; Tsapis, A. TNF receptor family member BCMA (B cell maturation) associates with TNF receptor-associated factor (TRAF) 1, TRAF2, and TRAF3 and activates NF-kappa B, elk-1, c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase. *J. Immunol.* **2000**, *165*, 1322–1330. [[CrossRef](#)] [[PubMed](#)]
233. Katsenelson, N.; Kanswal, S.; Puig, M.; Mostowski, H.; Verthelyi, D.; Akkoyunlu, M. Synthetic CpG oligodeoxynucleotides augment BAFF- and APRIL-mediated immunoglobulin secretion. *Eur. J. Immunol.* **2007**, *37*, 1785–1795. [[CrossRef](#)]

234. Sintes, J.; Gentile, M.; Zhang, S.; Garcia-Carmona, Y.; Magri, G.; Cassis, L.; Segura-Garzón, D.; Ciociola, A.; Grasset, E.K.; Bascones, S.; et al. mTOR intersects antibody-inducing signals from TACI in marginal zone B cells. *Nat. Commun.* **2017**, *8*, 1462. [[CrossRef](#)] [[PubMed](#)]
235. Hoffmann, F.S.; Kuhn, P.H.; Laurent, S.A.; Hauck, S.M.; Berer, K.; Wendlinger, S.A.; Krumbholz, M.; Khademi, M.; Olsson, T.; Dreyling, M.; et al. The immunoregulator soluble TACI is released by ADAM10 and reflects B cell activation in autoimmunity. *J. Immunol.* **2015**, *194*, 542–552. [[CrossRef](#)]
236. Salazar-Camarena, D.C.; Ortiz-Lazareno, P.C.; Cruz, A.; Oregon-Romero, E.; Machado-Contreras, J.R.; Muñoz-Valle, J.F.; Orozco-López, M.; Marín-Rosales, M.; Palafox-Sánchez, C.A. Association of BAFF, APRIL serum levels, BAFF-R, TACI and BCMA expression on peripheral B-cell subsets with clinical manifestations in systemic lupus erythematosus. *Lupus* **2016**, *25*, 582–592. [[CrossRef](#)]
237. Castigli, E.; Scott, S.; Dedeoglu, F.; Bryce, P.; Jabara, H.; Bhan, A.K.; Mizoguchi, E.; Geha, R.S. Impaired IgA class switching in APRIL-deficient mice. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 3903–3908. [[CrossRef](#)]
238. Chu, V.T.; Enghard, P.; Schurer, S.; Steinhäuser, G.; Rudolph, B.; Riemekasten, G.; Berek, C. Systemic activation of the immune system induces aberrant BAFF and APRIL expression in B cells in patients with systemic lupus erythematosus. *Arthritis Rheum.* **2009**, *60*, 2083–2093. [[CrossRef](#)]
239. Koyama, T.; Tsukamoto, H.; Masumoto, K.; Himeji, D.; Hayashi, K.; Harada, M.; Horiuchi, T. A novel polymorphism of the human APRIL gene is associated with systemic lupus erythematosus. *Rheumatology* **2003**, *42*, 980–985. [[CrossRef](#)]
240. Lee, Y.H.; Ota, F.; Kim-Howard, X.; Kaufman, K.M.; Nath, S.K. APRIL polymorphism and systemic lupus erythematosus (SLE) susceptibility. *Rheumatology* **2007**, *46*, 1274–1276. [[CrossRef](#)]
241. Dall’Era, M.; Chakravarty, E.; Wallace, D.; Genovese, M.; Weisman, M.; Kavanaugh, A.; Kalunian, K.; Dhar, P.; Vincent, E.; Pena-Rossi, C.; et al. Reduced B lymphocyte and immunoglobulin levels after atacept treatment in patients with systemic lupus erythematosus: Results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. *Arthritis Rheum.* **2007**, *56*, 4142–4150. [[CrossRef](#)] [[PubMed](#)]
242. Isenberg, D.; Gordon, C.; Licu, D.; Copt, S.; Rossi, C.P.; Wofsy, D. Efficacy and safety of atacept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). *Ann. Rheum. Dis.* **2015**, *74*, 2006–2015. [[CrossRef](#)] [[PubMed](#)]
243. Kaegi, C.; Steiner, U.C.; Wuest, B.; Crowley, C.; Boyman, O. Systematic Review of Safety and Efficacy of Atacept in Treating Immune-Mediated Disorders. *Front. Immunol.* **2020**, *11*, 433. [[CrossRef](#)]
244. Vazgiourakis, V.M.; Zervou, M.I.; Choulaki, C.; Bertias, G.; Melissourgaki, M.; Yilmaz, N.; Sidiropoulos, P.; Plant, D.; Trouw, L.A.; Toes, R.E.; et al. A common SNP in the CD40 region is associated with systemic lupus erythematosus and correlates with altered CD40 expression: Implications for the pathogenesis. *Ann. Rheum. Dis.* **2011**, *70*, 2184–2190. [[CrossRef](#)]
245. Ramanujam, M.; Steffgen, J.; Visvanathan, S.; Mohan, C.; Fine, J.S.; Putterman, C. Phoenix from the flames: Rediscovering the role of the CD40-CD40L pathway in systemic lupus erythematosus and lupus nephritis. *Autoimmun. Rev.* **2020**, *19*, 102668. [[CrossRef](#)] [[PubMed](#)]
246. Weißenberg, S.Y.; Szelinski, F.; Schrezenmeier, E.; Stefanski, A.L.; Wiedemann, A.; Rincon-Arevalo, H.; Welle, A.; Jungmann, A.; Nordström, K.; Walter, J.; et al. Identification and Characterization of Post-activated B Cells in Systemic Autoimmune Diseases. *Front. Immunol.* **2019**, *10*, 2136. [[CrossRef](#)]
247. Armitage, L.H.; Wallet, M.A.; Mathews, C.E. Influence of PTPN22 Allotypes on Innate and Adaptive Immune Function in Health and Disease. *Front. Immunol.* **2021**, *12*, 636618. [[CrossRef](#)] [[PubMed](#)]
248. Tsubata, T. Role of inhibitory B cell co-receptors in B cell self-tolerance to non-protein antigens. *Immunol. Rev.* **2022**, *307*, 53–65. [[CrossRef](#)]
249. Tsubata, T. Ligand Recognition Determines the Role of Inhibitory B Cell Co-receptors in the Regulation of B Cell Homeostasis and Autoimmunity. *Front. Immunol.* **2018**, *9*, 2276. [[CrossRef](#)]
250. Akatsu, C.; Shinagawa, K.; Numoto, N.; Liu, Z.; Ucar, A.K.; Aslam, M.; Phoon, S.; Adachi, T.; Furukawa, K.; Ito, N.; et al. CD72 negatively regulates B lymphocyte responses to the lupus-related endogenous toll-like receptor 7 ligand Sm/RNP. *J. Exp. Med.* **2016**, *213*, 2691–2706. [[CrossRef](#)]
251. Li, D.H.; Winslow, M.M.; Cao, T.M.; Chen, A.H.; Davis, C.R.; Mellins, E.D.; Utz, P.J.; Crabtree, G.R.; Parnes, J.R. Modulation of peripheral B cell tolerance by CD72 in a murine model. *Arthritis Rheum.* **2008**, *58*, 3192–3204. [[CrossRef](#)] [[PubMed](#)]
252. Xu, M.; Hou, R.; Sato-Hayashizaki, A.; Man, R.; Zhu, C.; Wakabayashi, C.; Hirose, S.; Adachi, T.; Tsubata, T. Cd72(c) is a modifier gene that regulates Fas(lpr)-induced autoimmune disease. *J. Immunol.* **2013**, *190*, 5436–5445. [[CrossRef](#)] [[PubMed](#)]
253. Nakano, S.; Morimoto, S.; Suzuki, J.; Mitsuo, A.; Nakiri, Y.; Katagiri, A.; Nozawa, K.; Amano, H.; Tokano, Y.; Hashimoto, H.; et al. Down-regulation of CD72 and increased surface IgG on B cells in patients with lupus nephritis. *Autoimmunity* **2007**, *40*, 9–15. [[CrossRef](#)] [[PubMed](#)]
254. Asmiyou, A.; Bakr, A.M.; Shahin, D.A.; Wahba, Y. CD40 and CD72 expression and prognostic values among children with systemic lupus erythematosus: A case-control study. *Lupus* **2020**, *29*, 1270–1276. [[CrossRef](#)]
255. Hitomi, Y.; Tsuchiya, N.; Kawasaki, A.; Ohashi, J.; Suzuki, T.; Kyogoku, C.; Fukazawa, T.; Bejrachandra, S.; Siriboonrit, U.; Chandanayingyong, D.; et al. CD72 polymorphisms associated with alternative splicing modify susceptibility to human systemic lupus erythematosus through epistatic interaction with FCGR2B. *Hum. Mol. Genet.* **2004**, *13*, 2907–2917. [[CrossRef](#)]

256. Nitschke, L.; Carsetti, R.; Ocker, B.; Kohler, G.; Lamers, M.C. CD22 is a negative regulator of B-cell receptor signalling. *Curr. Biol.* **1997**, *7*, 133–143. [[CrossRef](#)]
257. Otipoby, K.L.; Andersson, K.B.; Draves, K.E.; Klaus, S.J.; Farr, A.G.; Kerner, J.D.; Perlmutter, R.M.; Law, C.L.; Clark, E.A. CD22 regulates thymus-independent responses and the lifespan of B cells. *Nature* **1996**, *384*, 634–637. [[CrossRef](#)]
258. Engel, P.; Wagner, N.; Miller, A.S.; Tedder, T.F. Identification of the ligand-binding domains of CD22, a member of the immunoglobulin superfamily that uniquely binds a sialic acid-dependent ligand. *J. Exp. Med.* **1995**, *181*, 1581–1586. [[CrossRef](#)]
259. Powell, L.D.; Sgroi, D.; Sjoberg, E.R.; Stamenkovic, I.; Varki, A. Natural ligands of the B cell adhesion molecule CD22 beta carry N-linked oligosaccharides with alpha-2,6-linked sialic acids that are required for recognition. *J. Biol. Chem.* **1993**, *268*, 7019–7027. [[CrossRef](#)]
260. Chen, J.; Wang, H.; Xu, W.P.; Wei, S.S.; Li, H.J.; Mei, Y.Q.; Li, Y.G.; Wang, Y.P. Besides an ITIM/SHP-1-dependent pathway, CD22 collaborates with Grb2 and plasma membrane calcium-ATPase in an ITIM/SHP-1-independent pathway of attenuation of Ca<sup>2+</sup>i signal in B cells. *Oncotarget* **2016**, *7*, 56129–56146. [[CrossRef](#)]
261. Coughlin, S.; Noviski, M.; Mueller, J.L.; Chuwonpad, A.; Raschke, W.C.; Weiss, A.; Zikherman, J. An extracatalytic function of CD45 in B cells is mediated by CD22. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E6515–E6524. [[CrossRef](#)] [[PubMed](#)]
262. O’Keefe, T.L.; Williams, G.T.; Davies, S.L.; Neuberger, M.S. Hyperresponsive B cells in CD22-deficient mice. *Science* **1996**, *274*, 798–801. [[CrossRef](#)] [[PubMed](#)]
263. Jellusova, J.; Wellmann, U.; Amann, K.; Winkler, T.H.; Nitschke, L. CD22 x Siglec-G double-deficient mice have massively increased B1 cell numbers and develop systemic autoimmunity. *J. Immunol.* **2010**, *184*, 3618–3627. [[CrossRef](#)] [[PubMed](#)]
264. Hatta, Y.; Tsuchiya, N.; Matsushita, M.; Shiota, M.; Hagiwara, K.; Tokunaga, K. Identification of the gene variations in human CD22. *Immunogenetics* **1999**, *49*, 280–286. [[CrossRef](#)]
265. Ding, C.; Liu, Y.; Wang, Y.; Park, B.K.; Wang, C.Y.; Zheng, P.; Liu, Y. SiglecG limits the size of B1a B cell lineage by down-regulating NFkappaB activation. *PLoS ONE* **2007**, *2*, e997. [[CrossRef](#)]
266. Hoffmann, A.; Kerr, S.; Jellusova, J.; Zhang, J.; Weisel, F.; Wellmann, U.; Winkler, T.H.; Kneitz, B.; Crocker, P.R.; Nitschke, L. Siglec-G is a B1 cell-inhibitory receptor that controls expansion and calcium signaling of the B1 cell population. *Nat. Immunol.* **2007**, *8*, 695–704. [[CrossRef](#)]
267. Duong, B.H.; Tian, H.; Ota, T.; Completo, G.; Han, S.; Vela, J.L.; Ota, M.; Kubitz, M.; Bovin, N.; Paulson, J.C.; et al. Decoration of T-independent antigen with ligands for CD22 and Siglec-G can suppress immunity and induce B cell tolerance in vivo. *J. Exp. Med.* **2010**, *207*, 173–187. [[CrossRef](#)]
268. Bökers, S.; Ubat, A.; Daniel, C.; Amann, K.; Smith, K.G.; Espéli, M.; Nitschke, L. Siglec-G deficiency leads to more severe collagen-induced arthritis and earlier onset of lupus-like symptoms in MRL/lpr mice. *J. Immunol.* **2014**, *192*, 2994–3002. [[CrossRef](#)]
269. Müller, J.; Lunz, B.; Schwab, I.; Acs, A.; Nimmerjahn, F.; Daniel, C.; Nitschke, L. Siglec-G Deficiency Leads to Autoimmunity in Aging C57BL/6 Mice. *J. Immunol.* **2015**, *195*, 51–60. [[CrossRef](#)]
270. Alborzian Deh Sheikh, A.; Gomaa, S.; Li, X.; Routledge, M.; Saigoh, K.; Numoto, N.; Angata, T.; Hitomi, Y.; Takematsu, H.; Tsuiji, M.; et al. A Guillain-Barre syndrome-associated SIGLEC10 rare variant impairs its recognition of gangliosides. *J. Autoimmun.* **2021**, *116*, 102571. [[CrossRef](#)]
271. Bewarder, N.; Weinrich, V.; Budde, P.; Hartmann, D.; Flaswinkel, H.; Reth, M.; Frey, J. In vivo and in vitro specificity of protein tyrosine kinases for immunoglobulin G receptor (FcgammaRII) phosphorylation. *Mol. Cell. Biol.* **1996**, *16*, 4735–4743. [[CrossRef](#)] [[PubMed](#)]
272. Nishizumi, H.; Horikawa, K.; Mlinaric-Rascan, I.; Yamamoto, T. A double-edged kinase Lyn: A positive and negative regulator for antigen receptor-mediated signals. *J. Exp. Med.* **1998**, *187*, 1343–1348. [[CrossRef](#)] [[PubMed](#)]
273. Bolland, S.; Ravetch, J.V. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. *Immunity* **2000**, *13*, 277–285. [[CrossRef](#)]
274. Li, F.; Smith, P.; Ravetch, J.V. Inhibitory Fcgamma receptor is required for the maintenance of tolerance through distinct mechanisms. *J. Immunol.* **2014**, *192*, 3021–3028. [[CrossRef](#)] [[PubMed](#)]
275. Takai, T.; Ono, M.; Hikida, M.; Ohmori, H.; Ravetch, J.V. Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice. *Nature* **1996**, *379*, 346–349. [[CrossRef](#)] [[PubMed](#)]
276. Mackay, M.; Stanevsky, A.; Wang, T.; Aranow, C.; Li, M.; Koenig, S.; Ravetch, J.V.; Diamond, B. Selective dysregulation of the FcgammaIIb receptor on memory B cells in SLE. *J. Exp. Med.* **2006**, *203*, 2157–2164. [[CrossRef](#)]
277. Smith, K.G.; Clatworthy, M.R. FcgammaRIIB in autoimmunity and infection: Evolutionary and therapeutic implications. *Nat. Rev. Immunol.* **2010**, *10*, 328–343. [[CrossRef](#)]
278. Clatworthy, M.R.; Willcocks, L.; Urban, B.; Langhorne, J.; Williams, T.N.; Peshu, N.; Watkins, N.A.; Floto, R.A.; Smith, K.G. Systemic lupus erythematosus-associated defects in the inhibitory receptor FcgammaRIIb reduce susceptibility to malaria. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 7169–7174. [[CrossRef](#)]
279. Crute, B.W.; Sheraden, R.; Ott, V.L.; Harley, I.T.W.; Getahun, A.; Cambier, J.C. Inhibitory Receptor Trap: A Platform for Discovery of Inhibitory Receptors That Utilize Inositol Lipid and Phosphotyrosine Phosphatase Effectors. *Front. Immunol.* **2020**, *11*, 592329. [[CrossRef](#)]
280. Losing, M.; Goldbeck, I.; Manno, B.; Oellerich, T.; Schnyder, T.; Bohnenberger, H.; Stork, B.; Urlaub, H.; Batista, F.D.; Wienands, J.; et al. The Dok-3/Grb2 protein signal module attenuates Lyn kinase-dependent activation of Syk kinase in B cell antigen receptor microclusters. *J. Biol. Chem.* **2013**, *288*, 2303–2313. [[CrossRef](#)]

281. Manno, B.; Oellerich, T.; Schnyder, T.; Corso, J.; Losing, M.; Neumann, K.; Urlaub, H.; Batista, F.D.; Engelke, M.; Wienands, J. The Dok-3/Grb2 adaptor module promotes inducible association of the lipid phosphatase SHIP with the BCR in a coreceptor-independent manner. *Eur. J. Immunol.* **2016**, *46*, 2520–2530. [[CrossRef](#)] [[PubMed](#)]
282. Mukherjee, O.; Weingarten, L.; Padberg, I.; Pracht, C.; Sinha, R.; Hochdorfer, T.; Kuppig, S.; Backofen, R.; Reth, M.; Huber, M. The SH2-domain of SHIP1 interacts with the SHIP1 C-terminus: Impact on SHIP1/Ig-alpha interaction. *Biochim. Biophys. Acta* **2012**, *1823*, 206–214. [[CrossRef](#)] [[PubMed](#)]
283. Reth, M.; Gold, M.R. What goes up must come down: A tripartite Dok-3/Grb2/SHIP1 inhibitory module limits BCR signaling. *Eur. J. Immunol.* **2016**, *46*, 2507–2511. [[CrossRef](#)] [[PubMed](#)]
284. Kraus, M.; Saijo, K.; Torres, R.M.; Rajewsky, K. Ig-alpha cytoplasmic truncation renders immature B cells more sensitive to antigen contact. *Immunity* **1999**, *11*, 537–545. [[CrossRef](#)]
285. Torres, R.M.; Hafen, K. A negative regulatory role for Ig-alpha during B cell development. *Immunity* **1999**, *11*, 527–536. [[CrossRef](#)]
286. Getahun, A.; Beavers, N.A.; Larson, S.R.; Shlomchik, M.J.; Cambier, J.C. Continuous inhibitory signaling by both SHP-1 and SHIP-1 pathways is required to maintain unresponsiveness of anergic B cells. *J. Exp. Med.* **2016**, *213*, 751–769. [[CrossRef](#)]
287. O'Neill, S.K.; Getahun, A.; Gauld, S.B.; Merrell, K.T.; Tamir, I.; Smith, M.J.; Dal Porto, J.M.; Li, Q.Z.; Cambier, J.C. Monophosphorylation of CD79a and CD79b ITAM motifs initiates a SHIP-1 phosphatase-mediated inhibitory signaling cascade required for B cell anergy. *Immunity* **2011**, *35*, 746–756. [[CrossRef](#)] [[PubMed](#)]
288. Reichlin, A.; Gazumyan, A.; Nagaoka, H.; Kirsch, K.H.; Kraus, M.; Rajewsky, K.; Nussenzweig, M.C. A B cell receptor with two Igalph cytoplasmic domains supports development of mature but anergic B cells. *J. Exp. Med.* **2004**, *199*, 855–865. [[CrossRef](#)]
289. Napirei, M.; Karsunky, H.; Zevnik, B.; Stephan, H.; Mannherz, H.G.; Möröy, T. Features of systemic lupus erythematosus in Dnase1-deficient mice. *Nat. Genet.* **2000**, *25*, 177–181. [[CrossRef](#)]
290. Yasutomo, K.; Horiuchi, T.; Kagami, S.; Tsukamoto, H.; Hashimura, C.; Urushihara, M.; Kuroda, Y. Mutation of DNASE1 in people with systemic lupus erythematosus. *Nat. Genet.* **2001**, *28*, 313–314. [[CrossRef](#)]
291. Hakkim, A.; Fürnrohr, B.G.; Amann, K.; Laube, B.; Abed, U.A.; Brinkmann, V.; Herrmann, M.; Voll, R.E.; Zychlinsky, A. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 9813–9818. [[CrossRef](#)] [[PubMed](#)]
292. Graham, R.R.; Kozyrev, S.V.; Baechler, E.C.; Reddy, M.V.; Plenge, R.M.; Bauer, J.W.; Ortmann, W.A.; Koeuth, T.; González Escribano, M.F.; The Argentine and Spanish Collaborative Groups; et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat. Genet.* **2006**, *38*, 550–555. [[CrossRef](#)] [[PubMed](#)]
293. García-Ortiz, H.; Velázquez-Cruz, R.; Espinosa-Rosales, F.; Jiménez-Morales, S.; Baca, V.; Orozco, L. Association of TLR7 copy number variation with susceptibility to childhood-onset systemic lupus erythematosus in Mexican population. *Ann. Rheum. Dis.* **2010**, *69*, 1861–1865. [[CrossRef](#)]
294. dos Santos, B.P.; Valverde, J.V.; Rohr, P.; Monticelo, O.A.; Brenol, J.C.; Xavier, R.M.; Chies, J.A. TLR7/8/9 polymorphisms and their associations in systemic lupus erythematosus patients from southern Brazil. *Lupus* **2012**, *21*, 302–309. [[CrossRef](#)]
295. Wang, C.M.; Chang, S.W.; Wu, Y.J.; Lin, J.C.; Ho, H.H.; Chou, T.C.; Yang, B.; Wu, J.; Chen, J.Y. Genetic variations in Toll-like receptors (TLRs 3/7/8) are associated with systemic lupus erythematosus in a Taiwanese population. *Sci. Rep.* **2014**, *4*, 3792. [[CrossRef](#)] [[PubMed](#)]
296. Mohan, C.; Putterman, C. Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. *Nat. Rev. Nephrol.* **2015**, *11*, 329–341. [[CrossRef](#)]
297. Davis, M.L.R.; LeVan, T.D.; Yu, F.; Sayles, H.; Sokolove, J.; Robinson, W.; Michaud, K.; Thiele, G.M.; Mikuls, T.R. Associations of toll-like receptor (TLR)-4 single nucleotide polymorphisms and rheumatoid arthritis disease progression: An observational cohort study. *Int. Immunopharmacol.* **2015**, *24*, 346–352. [[CrossRef](#)]
298. Lee, Y.H.; Choi, S.J.; Ji, J.D.; Song, G.G. Overall and cause-specific mortality in systemic lupus erythematosus: An updated meta-analysis. *Lupus* **2016**, *25*, 727–734. [[CrossRef](#)]
299. Deng, G.M.; Nilsson, I.M.; Verdrengh, M.; Collins, L.V.; Tarkowski, A. Intra-articularly localized bacterial DNA containing CpG motifs induces arthritis. *Nat. Med.* **1999**, *5*, 702–705. [[CrossRef](#)]
300. Kerfoot, S.M.; Long, E.M.; Hickey, M.J.; Andonegui, G.; Lapointe, B.M.; Zano, R.C.; Bonder, C.; James, W.G.; Robbins, S.M.; Kubes, P. TLR4 contributes to disease-inducing mechanisms resulting in central nervous system autoimmune disease. *J. Immunol.* **2004**, *173*, 7070–7077. [[CrossRef](#)]
301. Pisitkun, P.; Deane, J.A.; Difilippantonio, M.J.; Tarasenko, T.; Satterthwaite, A.B.; Bolland, S. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science* **2006**, *312*, 1669–1672. [[CrossRef](#)] [[PubMed](#)]
302. Subramanian, S.; Tus, K.; Li, Q.Z.; Wang, A.; Tian, X.H.; Zhou, J.; Liang, C.; Bartov, G.; McDaniel, L.D.; Zhou, X.J.; et al. A Tlr7 translocation accelerates systemic autoimmunity in murine lupus. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 9970–9975. [[CrossRef](#)]
303. Berland, R.; Fernandez, L.; Kari, E.; Han, J.H.; Lomakin, I.; Akira, S.; Wortis, H.H.; Kearney, J.F.; Ucci, A.A.; Imanishi-Kari, T. Toll-like receptor 7-dependent loss of B cell tolerance in pathogenic autoantibody knockin mice. *Immunity* **2006**, *25*, 429–440. [[CrossRef](#)] [[PubMed](#)]
304. Fairhurst, A.M.; Hwang, S.H.; Wang, A.; Tian, X.H.; Boudreaux, C.; Zhou, X.J.; Casco, J.; Li, Q.Z.; Connolly, J.E.; Wakeland, E.K. Yaa autoimmune phenotypes are conferred by overexpression of TLR7. *Eur. J. Immunol.* **2008**, *38*, 1971–1978. [[CrossRef](#)] [[PubMed](#)]

305. Alzabin, S.; Kong, P.; Medghalchi, M.; Palfreeman, A.; Williams, R.; Sacre, S. Investigation of the role of endosomal Toll-like receptors in murine collagen-induced arthritis reveals a potential role for TLR7 in disease maintenance. *Arthritis Res. Ther.* **2012**, *14*, R142. [[CrossRef](#)] [[PubMed](#)]
306. Walsh, E.R.; Pisitkun, P.; Voynova, E.; Deane, J.A.; Scott, B.L.; Caspi, R.R.; Bolland, S. Dual signaling by innate and adaptive immune receptors is required for TLR7-induced B-cell-mediated autoimmunity. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 16276–16281. [[CrossRef](#)] [[PubMed](#)]
307. Tran, N.L.; Manzin-Lorenzi, C.; Santiago-Raber, M.L. Toll-like receptor 8 deletion accelerates autoimmunity in a mouse model of lupus through a Toll-like receptor 7-dependent mechanism. *Immunology* **2015**, *145*, 60–70. [[CrossRef](#)]
308. Brown, G.J.; Cañete, P.F.; Wang, H.; Medhavy, A.; Bones, J.; Roco, J.A.; He, Y.; Qin, Y.; Cappello, J.; Ellyard, J.I.; et al. TLR7 gain-of-function genetic variation causes human lupus. *Nature* **2022**, *605*, 349–356. [[CrossRef](#)]
309. Jenks, S.A.; Cashman, K.S.; Zumaquero, E.; Marigorta, U.M.; Patel, A.V.; Wang, X.; Tomar, D.; Woodruff, M.C.; Simon, Z.; Bugrovsky, R.; et al. Distinct Effector B Cells Induced by Unregulated Toll-like Receptor 7 Contribute to Pathogenic Responses in Systemic Lupus Erythematosus. *Immunity* **2018**, *49*, 725–739.e726. [[CrossRef](#)]
310. Souyris, M.; Cenac, C.; Azar, P.; Daviaud, D.; Canivet, A.; Grunenwald, S.; Pienkowski, C.; Chaumeil, J.; Mejía, J.E.; Guéry, J.C. TLR7 escapes X chromosome inactivation in immune cells. *Sci. Immunol.* **2018**, *3*. [[CrossRef](#)]
311. Margery-Muir, A.A.; Bundell, C.; Nelson, D.; Groth, D.M.; Wetherall, J.D. Gender balance in patients with systemic lupus erythematosus. *Autoimmun. Rev.* **2017**, *16*, 258–268. [[CrossRef](#)] [[PubMed](#)]
312. Christensen, S.R.; Kashgarian, M.; Alexopoulou, L.; Flavell, R.A.; Akira, S.; Shlomchik, M.J. Toll-like receptor 9 controls anti-DNA autoantibody production in murine lupus. *J. Exp. Med.* **2005**, *202*, 321–331. [[CrossRef](#)]
313. Christensen, S.R.; Shupe, J.; Nickerson, K.; Kashgarian, M.; Flavell, R.A.; Shlomchik, M.J. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity* **2006**, *25*, 417–428. [[CrossRef](#)] [[PubMed](#)]
314. Desnues, B.; Macedo, A.B.; Roussel-Queval, A.; Bonnardel, J.; Henri, S.; Demaria, O.; Alexopoulou, L. TLR8 on dendritic cells and TLR9 on B cells restrain TLR7-mediated spontaneous autoimmunity in C57BL/6 mice. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 1497–1502. [[CrossRef](#)] [[PubMed](#)]
315. Jackson, S.W.; Scharping, N.E.; Kolhatkar, N.S.; Khim, S.; Schwartz, M.A.; Li, Q.Z.; Hudkins, K.L.; Alpers, C.E.; Liggitt, D.; Rawlings, D.J. Opposing impact of B cell-intrinsic TLR7 and TLR9 signals on autoantibody repertoire and systemic inflammation. *J. Immunol.* **2014**, *192*, 4525–4532. [[PubMed](#)]
316. Umiker, B.R.; Andersson, S.; Fernandez, L.; Korgaokar, P.; Larbi, A.; Pilichowska, M.; Weinkauff, C.C.; Wortis, H.H.; Kearney, J.F.; Imanishi-Kari, T. Dosage of X-linked Toll-like receptor 8 determines gender differences in the development of systemic lupus erythematosus. *Eur. J. Immunol.* **2014**, *44*, 1503–1516. [[CrossRef](#)]
317. Nündel, K.; Green, N.M.; Shaffer, A.L.; Moody, K.L.; Busto, P.; Eilat, D.; Miyake, K.; Oropallo, M.A.; Cancro, M.P.; Marshak-Rothstein, A. Cell-intrinsic expression of TLR9 in autoreactive B cells constrains BCR/TLR7-dependent responses. *J. Immunol.* **2015**, *194*, 2504–2512. [[CrossRef](#)]
318. Tilstra, J.S.; John, S.; Gordon, R.A.; Leibler, C.; Kashgarian, M.; Bastacky, S.; Nickerson, K.M.; Shlomchik, M.J. B cell-intrinsic TLR9 expression is protective in murine lupus. *J. Clin. Investig.* **2020**, *130*, 3172–3187. [[CrossRef](#)]
319. Sieber, J.; Daridon, C.; Fleischer, S.J.; Fleischer, V.; Hiepe, F.; Alexander, T.; Heine, G.; Burmester, G.R.; Fillatreau, S.; Dörner, T. Active systemic lupus erythematosus is associated with a reduced cytokine production by B cells in response to TLR9 stimulation. *Arthritis Res. Ther.* **2014**, *16*, 477. [[CrossRef](#)]
320. Gies, V.; Schickel, J.N.; Jung, S.; Joubin, A.; Glauzy, S.; Knapp, A.M.; Soley, A.; Poindron, V.; Guffroy, A.; Choi, J.Y.; et al. Impaired TLR9 responses in B cells from patients with systemic lupus erythematosus. *JCI Insight* **2018**, *3*, e96795.
321. Kim, Y.M.; Brinkmann, M.M.; Paquet, M.E.; Ploegh, H.L. UNC93B1 delivers nucleotide-sensing toll-like receptors to endolysosomes. *Nature* **2008**, *452*, 234–238. [[CrossRef](#)] [[PubMed](#)]
322. Fukui, R.; Saitoh, S.; Kanno, A.; Onji, M.; Shibata, T.; Ito, A.; Onji, M.; Matsumoto, M.; Akira, S.; Yoshida, N.; et al. UNC93B1 restricts systemic lethal inflammation by orchestrating Toll-like receptor 7 and 9 trafficking. *Immunity* **2011**, *35*, 69–81. [[CrossRef](#)] [[PubMed](#)]
323. Majer, O.; Liu, B.; Woo, B.J.; Kreuk, L.S.M.; Van Dis, E.; Barton, G.M. Release from UNC93B1 reinforces the compartmentalized activation of select TLRs. *Nature* **2019**, *575*, 371–374. [[CrossRef](#)]
324. De Nardo, D. Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine* **2015**, *74*, 181–189. [[CrossRef](#)]
325. Bernasconi, N.L.; Onai, N.; Lanzavecchia, A. A role for Toll-like receptors in acquired immunity: Up-regulation of TLR9 by BCR triggering in naive B cells and constitutive expression in memory B cells. *Blood* **2003**, *101*, 4500–4504. [[CrossRef](#)] [[PubMed](#)]
326. Busconi, L.; Bauer, J.W.; Tumang, J.R.; Laws, A.; Perkins-Mesires, K.; Tabor, A.S.; Lau, C.; Corley, R.B.; Rothstein, T.L.; Lund, F.E.; et al. Functional outcome of B cell activation by chromatin immune complex engagement of the B cell receptor and TLR9. *J. Immunol.* **2007**, *179*, 7397–7405. [[CrossRef](#)]
327. Chaturvedi, A.; Dorward, D.; Pierce, S.K. The B cell receptor governs the subcellular location of Toll-like receptor 9 leading to hyperresponses to DNA-containing antigens. *Immunity* **2008**, *28*, 799–809. [[CrossRef](#)] [[PubMed](#)]
328. Otipoby, K.L.; Waisman, A.; Derudder, E.; Srinivasan, L.; Franklin, A.; Rajewsky, K. The B-cell antigen receptor integrates adaptive and innate immune signals. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 12145–12150. [[CrossRef](#)]

329. Schweighoffer, E.; Nys, J.; Vanes, L.; Smithers, N.; Tybulewicz, V.L.J. TLR4 signals in B lymphocytes are transduced via the B cell antigen receptor and SYK. *J. Exp. Med.* **2017**, *214*, 1269–1280. [\[CrossRef\]](#)
330. Iwata, S.; Yamaoka, K.; Nihiro, H.; Nakano, K.; Wang, S.P.; Akashi, K.; Tanaka, Y. Amplification of Toll-like receptor-mediated signaling through spleen tyrosine kinase in human B-cell activation. *J. Allergy Clin. Immunol.* **2012**, *129*, 1594–1601.e1592. [\[CrossRef\]](#)
331. Kremlitzka, M.; Mácsik-Valent, B.; Erdei, A. Syk is indispensable for CpG-induced activation and differentiation of human B cells. *Cell. Mol. Life Sci.* **2015**, *72*, 2223–2236. [\[CrossRef\]](#) [\[PubMed\]](#)
332. Jefferies, C.A.; Doyle, S.; Brunner, C.; Dunne, A.; Brint, E.; Wietek, C.; Walch, E.; Wirth, T.; O'Neill, L.A. Bruton's tyrosine kinase is a Toll/interleukin-1 receptor domain-binding protein that participates in nuclear factor kappaB activation by Toll-like receptor 4. *J. Biol. Chem.* **2003**, *278*, 26258–26264. [\[CrossRef\]](#)
333. Gray, P.; Dunne, A.; Brikos, C.; Jefferies, C.A.; Doyle, S.L.; O'Neill, L.A. MyD88 adapter-like (Mal) is phosphorylated by Bruton's tyrosine kinase during TLR2 and TLR4 signal transduction. *J. Biol. Chem.* **2006**, *281*, 10489–10495. [\[CrossRef\]](#) [\[PubMed\]](#)
334. Lee, K.G.; Xu, S.; Wong, E.T.; Tergaonkar, V.; Lam, K.P. Bruton's tyrosine kinase separately regulates NFkappaB p65RelA activation and cytokine interleukin (IL)-10/IL-12 production in TLR9-stimulated B Cells. *J. Biol. Chem.* **2008**, *283*, 11189–11198. [\[CrossRef\]](#) [\[PubMed\]](#)
335. Kenny, E.F.; Quinn, S.R.; Doyle, S.L.; Vink, P.M.; van Eenennaam, H.; O'Neill, L.A. Bruton's tyrosine kinase mediates the synergistic signalling between TLR9 and the B cell receptor by regulating calcium and calmodulin. *PLoS ONE* **2013**, *8*, e74103. [\[CrossRef\]](#)
336. Wu, Y.Y.; Kumar, R.; Haque, M.S.; Castillejo-López, C.; Alarcón-Riquelme, M.E. BANK1 controls CpG-induced IL-6 secretion via a p38 and MNK1/2/eIF4E translation initiation pathway. *J. Immunol.* **2013**, *191*, 6110–6116.
337. Wu, Y.Y.; Kumar, R.; Iida, R.; Bagavant, H.; Alarcón-Riquelme, M.E. BANK1 Regulates IgG Production in a Lupus Model by Controlling TLR7-Dependent STAT1 Activation. *PLoS ONE* **2016**, *11*, e0156302. [\[CrossRef\]](#)
338. Ni, M.; MacFarlane, A.W.t.; Toft, M.; Lowell, C.A.; Campbell, K.S.; Hamerman, J.A. B-cell adaptor for PI3K (BCAP) negatively regulates Toll-like receptor signaling through activation of PI3K. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 267–272. [\[CrossRef\]](#)
339. Troutman, T.D.; Hu, W.; Fulenchek, S.; Yamazaki, T.; Kurosaki, T.; Bazan, J.F.; Pasare, C. Role for B-cell adaptor for PI3K (BCAP) as a signaling adapter linking Toll-like receptors (TLRs) to serine/threonine kinases PI3K/Akt. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 273–278. [\[CrossRef\]](#)
340. Szili, D.; Bankó, Z.; Tóth, E.A.; Nagy, G.; Rojkovich, B.; Gáti, T.; Simon, M.; Hérincs, Z.; Sármay, G. TGFβ activated kinase 1 (TAK1) at the crossroad of B cell receptor and Toll-like receptor 9 signaling pathways in human B cells. *PLoS ONE* **2014**, *9*, e96381. [\[CrossRef\]](#)
341. Jabara, H.H.; McDonald, D.R.; Janssen, E.; Massaad, M.J.; Ramesh, N.; Borzutzky, A.; Rauter, I.; Benson, H.; Schneider, L.; Baxi, S.; et al. DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. *Nat. Immunol.* **2012**, *13*, 612–620. [\[CrossRef\]](#)
342. Rönnblom, L.; Alm, G.V. A pivotal role for the natural interferon alpha-producing cells (plasmacytoid dendritic cells) in the pathogenesis of lupus. *J. Exp. Med.* **2001**, *194*, F59–F63. [\[CrossRef\]](#)
343. Bekeredjian-Ding, I.B.; Wagner, M.; Hornung, V.; Giese, T.; Schnurr, M.; Endres, S.; Hartmann, G. Plasmacytoid dendritic cells control TLR7 sensitivity of naive B cells via type I IFN. *J. Immunol.* **2005**, *174*, 4043–4050. [\[CrossRef\]](#)
344. Lau, C.M.; Broughton, C.; Tabor, A.S.; Akira, S.; Flavell, R.A.; Mamula, M.J.; Christensen, S.R.; Shlomchik, M.J.; Viglianti, G.A.; Rifkin, I.R.; et al. RNA-associated autoantigens activate B cells by combined B cell antigen receptor/Toll-like receptor 7 engagement. *J. Exp. Med.* **2005**, *202*, 1171–1177. [\[CrossRef\]](#)
345. Poovassery, J.S.; Vanden Bush, T.J.; Bishop, G.A. Antigen receptor signals rescue B cells from TLR tolerance. *J. Immunol.* **2009**, *183*, 2974–2983. [\[CrossRef\]](#)
346. Li, H.; Yang, Y.; Hong, W.; Huang, M.; Wu, M.; Zhao, X. Applications of genome editing technology in the targeted therapy of human diseases: Mechanisms, advances and prospects. *Signal Transduct. Target. Ther.* **2020**, *5*, 1. [\[CrossRef\]](#)
347. Medetgul-Ernar, K.; Davis, M.M. Standing on the shoulders of mice. *Immunity* **2022**, *55*, 1343–1353. [\[CrossRef\]](#)
348. Rip, J.; de Bruijn, M.J.W.; Kaptein, A.; Hendriks, R.W.; Corneth, O.B.J. Phosphoflow Protocol for Signaling Studies in Human and Murine B Cell Subpopulations. *J. Immunol.* **2020**, *204*, 2852–2863. [\[CrossRef\]](#)
349. Marsman, C.; Jorritsma, T.; ten Brinke, A.; van Ham, S.M. Flow Cytometric Methods for the Detection of Intracellular Signaling Proteins and Transcription Factors Reveal Heterogeneity in Differentiating Human B Cell Subsets. *Cells* **2020**, *9*, 2633. [\[CrossRef\]](#)
350. Csomos, K.; Ujhazi, B.; Blazso, P.; Herrera, J.L.; Tipton, C.M.; Kawai, T.; Gordon, S.; Ellison, M.; Wu, K.; Stowell, M.; et al. Partial RAG deficiency in humans induces dysregulated peripheral lymphocyte development and humoral tolerance defect with accumulation of T-bet(+) B cells. *Nat. Immunol.* **2022**, *23*, 1256–1272. [\[CrossRef\]](#)
351. Hoshino, A.; Boutboul, D.; Zhang, Y.; Kuehn, H.S.; Hadjadj, J.; Özdemir, N.; Celkan, T.; Walz, C.; Picard, C.; Lenoir, C.; et al. Gain-of-function IKZF1 variants in humans cause immune dysregulation associated with abnormal T/B cell late differentiation. *Sci. Immunol.* **2022**, *7*, eabi7160. [\[CrossRef\]](#)
352. Yazar, S.; Alquicira-Hernandez, J.; Wing, K.; Senabouth, A.; Gordon, M.G.; Andersen, S.; Lu, Q.; Rowson, A.; Taylor, T.R.P.; Clarke, L.; et al. Single-cell eQTL mapping identifies cell type-specific genetic control of autoimmune disease. *Science* **2022**, *376*, eabf3041. [\[CrossRef\]](#)

353. Chiou, J.; Geusz, R.J.; Okino, M.L.; Han, J.Y.; Miller, M.; Melton, R.; Beebe, E.; Benaglio, P.; Huang, S.; Korgaonkar, K.; et al. Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. *Nature* **2021**, *594*, 398–402. [[CrossRef](#)]
354. Farh, K.K.-H.; Marson, A.; Zhu, J.; Kleinewietfeld, M.; Housley, W.J.; Beik, S.; Shores, N.; Whitton, H.; Ryan, R.J.H.; Shishkin, A.A.; et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* **2015**, *518*, 337–343. [[CrossRef](#)]
355. Catalina, M.D.; Owen, K.A.; Labonte, A.C.; Grammer, A.C.; Lipsky, P.E. The pathogenesis of systemic lupus erythematosus: Harnessing big data to understand the molecular basis of lupus. *J. Autoimmun.* **2020**, *110*, 102359. [[CrossRef](#)]
356. Soskic, B.; Cano-Gamez, E.; Smyth, D.J.; Ambridge, K.; Ke, Z.; Matte, J.C.; Bossini-Castillo, L.; Kaplanis, J.; Ramirez-Navarro, L.; Lorenc, A.; et al. Immune disease risk variants regulate gene expression dynamics during CD4+ T cell activation. *Nat. Genet.* **2022**, *54*, 817–826. [[CrossRef](#)]
357. Foulquier, N.; Le Dantec, C.; Bettacchioli, E.; Jamin, C.; Consortium, P.C.; Consortium, P.F.C.; Alarcón-Riquelme, M.E.; Pers, J.-O. Machine learning identifies a common signature for anti-SSA/Ro60 antibody expression across autoimmune diseases. *Arthritis Rheumatol.* **2022**, *74*, 1706–1719. [[CrossRef](#)]