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ADVANCED REVIEW

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Genetic obstacles to developing and tolerizing human B cells

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Abstract

Early in development, B cells explosively diversify B-cell receptors (BCRs) to recognize a wide variety of microbial antigens. A variety of developmental and tolerance checkpoints are subsequently deployed at later developmental stages to purge useless or potentially dangerous autoreactive B-cell clones. Once B cells recognize cognate antigens within secondary lymphoid tissues, their BCRs are genetically modified to increase the specificity and strength of antigen binding. Identification and investigation of monogenic inborn errors of immunity (IEI) diseases demonstrate which specific molecules and pathways are essential for developing well-tolerized human B cells. Although rare, IEI patients have provided important mechanistic insights into, and therapeutic clues for, patients afflicted with more common autoantibody associated autoimmune diseases like lupus, rheumatoid arthritis, and type 1 diabetes.

This article is categorized under:

Immune System Diseases > Stem Cells and Development > Genetics/Genomics/Epigenetics

KEYWORDS

B cell, germinal center, immune tolerance, inborn error of immunity

1 | INTRODUCTION

Among vertebrate receptor families, B-cell receptors (BCRs) bind the largest theoretic number and widest potential variety of ligands or antigens. In human bone marrow, every B-cell precursor self-organizes a unique BCR by pairing two immunoglobulin heavy (IgH) chains with two immunoglobulin light (IgL) chains. The distal ends of paired IgH and IgL mediate antigen recognition and are called antigen binding (Fab) domains. Fab diversification begins during early B-cell development through a series of highly orchestrated, yet ultimately arbitrary, genetic alterations to immunoglobulin encoding genes (*IGH* and *IGL*). Upon antigen recognition, *IGH* and *IGL* loci are further mutated within specialized structures called germinal centers (GCs). The GC reaction is an adaptation allowing mammals to compete on the same evolutionary time scale as microbial pathogens despite our slower replication and genomic mutation rates. In GCs, B cells are subjected to repetitive cycles of ever-increasing selective pressure which sharpens the affinity of the BCR for its cognate antigen. Once honed, affinity matured BCRs are expressed on the surface of memory B cells to conduct immune surveillance or are secreted by terminally differentiated plasma cells as immune protective, soluble immunoglobulins (antibodies).

Kim Nguyen, Nouf Alsaati, and Carole Le Coz contributed equally to this study.

The randomness harnessed to create broad BCR repertoires also produces defective out-of-frame IgH molecules that cannot be expressed and potentially dangerous in-frame BCRs that recognize self-proteins. As counter measures, quality control checkpoints are deployed at distinct B-cell developmental stages to either repair undesirable clones or cull unredeemable ones. Recognition of increased autoreactive B-cell frequencies in patients with complex autoimmune diseases demonstrates the clinical consequences of breeched tolerance checkpoints. Complementary analyses of B-cell development in patients with monogenic inborn errors of immunity (IEI) illuminate the essential molecular pathways that mediate self-reactive clone removal and immune protective clone survival (Box 1).

BOX 1 Recent advances in genomic technology have propelled the inborn errors of immunity (IEI) field forward

Twenty-five years ago, less than 50 distinct IEI disorders were recognized. Currently the International Union of Immunological Societies recognizes approximately 450 IEI diseases and most are caused by defects in single genes (Bousfiha et al., 2020). Explosive discoveries in the IEI field were driven forward by the wide adoption of three genetic technologies/resources: (1) universal T-cell excision circle (TREC)-based severe combined immune deficiency (SCID) newborn screening permitted early and broad detection of T-cell deficient patients (Kwan et al., 2014); (2) widely available, high-throughput whole exome (WES) and whole genome sequencing (WGS) allowed for rapid, unbiased genetic analyses (Chinn et al., 2020); (3) large, publicly available WES and WGS databases of ancestrally diverse, unaffected adults like the Exome Aggregation Consortium (ExAC) database and the Genome Aggregation Database (gnomAD) enabled investigators and clinical immunologists to disregard common genetic variants and focus on rare variants more likely to be disease causing (Karczewski et al., 2017, 2020).

2 | NAÏVE B-CELL DEVELOPMENT

2.1 | The pre-BCR developmental checkpoint; only in-frame IgH shall pass

Two characteristics define B lineage cells: rearranged(ing) immunoglobulin genes and CD19 expression. Pro-B cells are the earliest hematopoietic precursor to meet both criteria. Although pro-B cells do not yet express a BCR, their Ig heavy chain (*IGH*) loci are under active rearrangement by a multienzyme complex, VDJ recombinase (Figures 1 and 2, ①) (Allman et al., 1999). VDJ recombination proceeds through an orderly series of steps: (1) double-stranded DNA break introduction at the inner edges of arbitrarily chosen variable (V), diversity (D), and joining (J) gene segments, (2) excision of intervening genomic DNA, (3) joining blunt cut ends to create a hairpin loop, (4) cutting the hairpin loop to create palindromic (P) sequences, (5) addition of random new (N)-nucleotides and finally, (6) joint ligation (Agrawal & Schatz, 1997; Davis et al., 1980; Gilfillan et al., 1993; Moshous et al., 2001; Tonegawa et al., 1978; Weigert et al., 1980).

IGH diversity generated during early B-cell development is a product of the number of V (∼40), D (23), and J (6) Ig heavy gene segments on human chromosome 14, their semi-random selection by VDJ recombinase, and the arbitrary addition of N-nucleotides between VD and DJ joints (Figure 1a) (Matsuda & Honjo, 1996). Based on these inputs, humans can create on the order of $\sim 5 \times 10^{10}$ possible unique *IGH* transcripts. Since the number of added N-nucleotides is random and only one of three reading frames are correct, 2/3 of rearranged *IGH* transcripts encode a useless, out-of-frame IgH (Figure 1b). Also, because all unused D segments are expelled from the genome as episomes during primary recombination, there is only one *IGH* rearrangement opportunity per chromosome. Accordingly, pro-B cells failing to generate an in-frame IgH on their first try will attempt rearrangement of their second *IGH* locus with the same odds of success. Thus ∼45% $(2/3 - (2/3 \times 1/3))$ of human pro-B cells fail to generate an in-frame heavy chain.

The pre-BCR provides developing pre-B cells a Fab-independent mechanism to determine if their IgH is in or out-of-frame. The pre-BCR is comprised of two identical rearranged IgH molecules paired with two non-rearranged "surrogate" light chains (SLC) (Figure 1a) and utilizes the same signaling apparatus as the BCR (Bankovich et al., 2007; Löffert et al., 1996). Unlike BCRs, which only signal when antigen is bound, pre-BCRs cluster and signal constitutively due to attractive SLC/SLC interactions. After signaling, the pre-BCR is internalized and never expressed again. Pro-cells

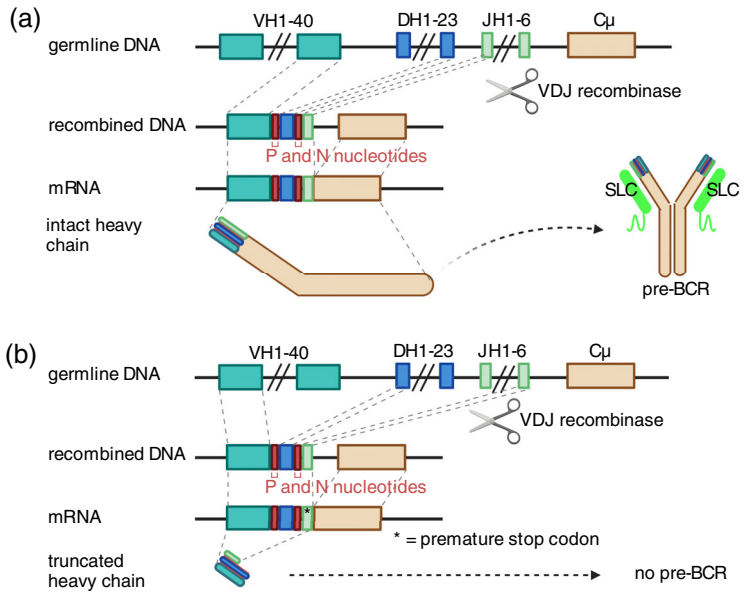

FIGURE 1 Immunoglobulin heavy chain (IgH) locus recombination. (a) V, D, and J gene segment recombination with P and N nucleotide additions (red) that maintain the translated reading frame are depicted. Full length, in-frame IgH supports surrogate light chains (SLC). (b) P and N nucleotides producing an out of frame, truncated IgH is depicted it cannot support SLC

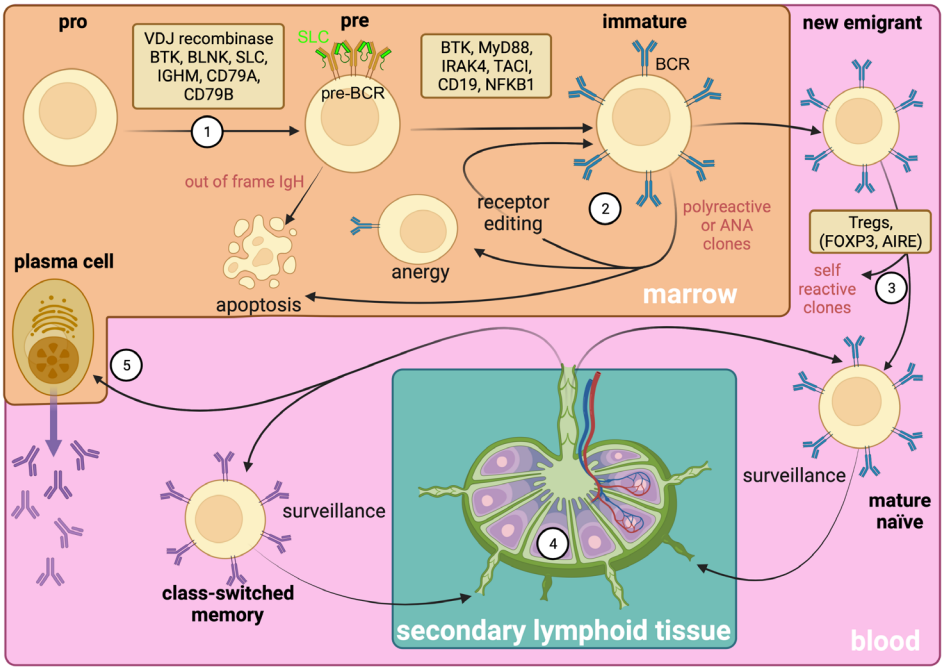

FIGURE 2 The arc of human B-cell development from pro-B cells to terminally differentiated plasma cells. The sites and stages where ① the pre-B-cell developmental checkpoint, ② central B-cell tolerance checkpoint, ③ peripheral B-cell tolerance checkpoint, ④ clonal redemption, and ⑤ antibody generation occur are displayed. Inborn errors of immunity-associated molecules essential for checkpoint function are listed. ANA, anti-nuclear; IgH, immunoglobulin heavy chain; SLC, surrogate light chain; Tregs, T regulatory cells

unable to express in-frame IgH lack the necessary scaffolding to support surface SLC expression, do not signal, and die via apoptosis (Figure 2, ①).

Although ~55% of healthy donor pro-B cells advance through the pre-BCR developmental checkpoint into the immature stage, virtually zero immature B cells are formed in patients unable to generate in-frame IgH due to inherited

defects in VDJ recombinase, including RAG1, RAG2, Artemis, Cernunnos, DNA ligase IV, and DNAPKcs deficiencies (Figure 2, ①; Table 1) (Buck, Malivert, et al., 2006; Buck, Moshous, et al., 2006; Corneo et al., 2001; Moshous et al., 2001; Schwarz et al., 1996; van der Burg et al., 2008). Since VDJ recombinase also mediates T-cell receptor (TCR) rearrangement, patients with VDJ recombinase defects also lack T lymphocytes and present with severe combined immune deficiency (SCID). SCID patients succumb to opportunistic infections early in life unless they can be rapidly identified (Kwan et al., 2014) and treated with hematopoietic stem cell transplantation (HSCT) (Pai et al., 2014) or potentially gene therapy (Fischer & Hacein-Bey-Abina, 2020).

Monogenic causes of isolated B-cell aplasia, historically called congenital agammaglobulinemia, have also been identified. Affected patients lack components of the pre-BCR (IGHM, SLC) (Minegishi et al., 1998; Yel et al., 1996) or the downstream signaling apparatus (BTK, CD79A, CD79B, BLNK, PIK3CD, PIK3R1, LRRC8A) (Figure 2, ①; Table 1) (Bruton, 1952; Deau et al., 2014; Ferrari et al., 2007; Minegishi, Coustan-Smith, et al., 1999; Minegishi, Rohrer, et al., 1999; Sawada et al., 2003; Swan et al., 2019). B-cell aplasia can also be caused by mutations in key transcription factors that drive the pre-B cell transcriptional program. For instance, mutation of TCF3 (Boisson et al., 2013)—which drives SLC expression—or haploinsufficiency of PU.1 (Le Coz et al., 2021)—which drives CD79B, IGHM, and BTK expression—also arrest B-cell lymphopoiesis by affecting pre-BCR assembling and signaling between the pro- and pre-B cell stages. Regardless of genetic cause, B-cell aplasia is associated with recurrent sino-pulmonary infections preventable with lifelong immunoglobulin G replacement therapy (IRT) or, in certain circumstances, HSCT (Sun et al., 2021). Despite IRT B-cell aplasia patients remain at higher risk of enteric infections, inflammatory bowel disease, gastrointestinal malignancies, and enteroviral meningoencephalitis potentially because IRT products do not replace luminal IgA (Barmettler et al., 2017; van der Meer et al., 1993; Winkelstein et al., 2006).

2.2 | A central B-cell tolerance checkpoint tames polyreactive and anti-nuclear clones

After passing through the pre-B cell developmental checkpoint, VDJ recombinase begins arbitrarily joining V and J *IGL* gene segments to form a light chain. In humans there are two *IGL* loci per chromosome (κ and λ), and Igκ locus rearrangement precedes Igλ locus rearrangement. *IGL* recombination continues until pairs of in-frame IgH and IgL chains are co-expressed as a BCR on the surface of an immature B cell. Due to the unbiased nature of V(D)J recombination, the majority (55%–75%) of early immature B cells display self-reactive BCRs; ∼50% promiscuously bind multiple dissimilar antigens including DNA, insulin, and lipopolysaccharide (i.e., polyreactive BCRs) and 20% recognize nuclear antigens (Wardemann et al., 2003). Without mitigation, these self-reactive clones pose a significant risk of autoantibody-mediated autoimmune diseases. Fortunately, a central B-cell tolerance checkpoint between the pre- and immature B cell stages identifies, and counter selects especially autoreactive clones before marrow egress (Figure 2, ②). When new emigrant B cells do enter healthy donor peripheral blood, only ∼5% express polyreactive BCRs and fewer still recognize anti-nuclear antigens (C. Chen et al., 1995; Wardemann et al., 2003).

Most self-reactive cells identified by the central B-cell tolerance checkpoint are not destroyed but instead attempt to change their BCR reactivity by receptor editing (Figure 2, ②). (Casellas et al., 2001; Melamed et al., 1998; Prak & Weigert, 1995). Unlike IgH loci, which excise all unused D segments from their genome during V(D)J recombination, IgL loci lack D segments and VDJ recombinase will attempt to join remaining unused V and J gene segments distal to the original VJ joint. Secondary IgL recombination continues until a BCR with acceptable reactivity can be expressed or all available *Igκ* and *Igλ* loci gene segments are exhausted. The few immature B cells unable to tolerize their BCRs via receptor editing are clonally deleted or enter anergy, an unresponsive state.

Autoreactive new emigrant B cells are consistently found at high frequencies in the blood of lupus, type 1 diabetes, systemic sclerosis, myasthenia gravis, neuromyelitis optica, and rheumatoid arthritis patients (Chamberlain et al., 2015; Cotzomi et al., 2019; Glauzy et al., 2021; Lee et al., 2016; Samuels et al., 2005; Yurasov et al., 2005). These observations suggest defective central B-cell tolerance contributes to many common autoimmune diseases but does not explain how the checkpoint identifies problematic cells in healthy donors. More specific clues about the molecular basis of central tolerance have come from studying patients with rare genetic diseases of immunity. For instance, 40% of the very few new emigrant B cells produced by BTK-deficient patients are polyreactive, indicating a role for BCR signal strength in sensing polyreactivity (Ng et al., 2004). Similarly, central B-cell tolerance and BCR signal strength are altered by a single nucleotide polymorphism (SNP) in the gene encoding protein tyrosine phosphatase PTPN22 (Menard, Saadoun, et al., 2011; Schickel et al., 2016). Genome wide association studies have found this *PTPN22* SNP to be highly enriched in type 1 diabetes, rheumatoid arthritis, and multiple sclerosis (MS) patients (Bottini & Peterson, 2014). Increased

TABLE 1 Monogenic inborn errors of immunity discussed in this review

Protein (gene)	Mode of inheritance	Immune defect(s)	Symptoms	Treatment(s)
Severe combined immunodeficiency				
RAG1 (*RAG1*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections	HSCT
RAG2 (*RAG2*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections	HSCT
Artemis (*DCLRE1C*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections, radiosensitivity	HSCT
Cernunnos (*NHEJ1*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections, radiosensitivity	HSCT
DNA ligase IV (*LIG4*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections, radiosensitivity	HSCT
DNAPKcs (*PRKDC*)	AR	T- and B-cell aplasia	Opportunistic and sinopulmonary infections, radiosensitivity	HSCT
ADA (*ADA*)	AR	T-, B-, and NK-cell depletion	Opportunistic and sinopulmonary infections	HSCT; enzyme replacement and gene therapy
Isolated B cell aplasia (agammaglobulinemia)				
IGHM (*IGHM*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
λ5 (*IGLL1*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
BTK (*BTK*)	XL	B-cell aplasia	Sinopulmonary and gastrointestinal infections, enteroviral encephalitis	IRT
CD79A (*CD79A*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
CD79B (*CD79B*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
BLNK (*BLNK*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
PIK3CD (*PIK3CD*)	AR	B-cell aplasia	Sinopulmonary infections, autoimmune thrombocytopenia, enterocolitis	IRT
PIK3R1 (*PIK3R1*)	AR	B-cell aplasia	Sinopulmonary, meningoencephalitis, and gastrointestinal infections	IRT
LRRC8A (*LRRC8A*)	AD	B-cell aplasia	Sinopulmonary infections	IRT
TCF3 (*TCF3*)	AD	B-cell aplasia	Sinopulmonary infections, enteroviral encephalitis	IRT
PU.1 (*SPI1*)	AD	B-cell aplasia, cDC deficiency	Sinopulmonary infections, enteroviral encephalitis	IRT
Innate immune deficiencies				
MyD88 (*MYD88*)	AR	Defect in B-cell tolerance	Deep pyogenic bacterial infections (cellulitis, sepsis, meningitis, osteomyelitis)	Prophylactic antibiotics, IRT
IRAK4 (*IRAK4*)	AR	Defect in B-cell tolerance	Deep pyogenic bacterial infections (cellulitis, sepsis, meningitis, osteomyelitis)	Prophylactic antibiotics, IRT

(Continues)

TABLE 1 (Continued)

Protein (gene)	Mode of inheritance	Immune defect(s)	Symptoms	Treatment(s)
Common variable immune deficiencies				
TACI (*TNFRSF13B*)	AD or AR	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections, lymphoid hyperplasia, autoimmune disease	IRT
NFKB1 (*NFKB1*)	AD	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections, lymphoid hyperplasia, autoimmune disease	IRT
CD21 (*CD21*)	AR	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections	IRT
BACH2 (*BACH2*)	AD	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections, IBD, chronic lung disease	IRT
CD19 (*CD19*)	AR	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections	IRT
PLCG2 (*PLCG2*)	AD	B-cell activation defect, CSM B-cell deficiency	Sinopulmonary infections, cold urticaria	IRT
Immune regulatory diseases				
FOXP3 (*FOXP3*)	XL	Treg deficiency	Enteropathy, autoimmune disease, eczema	HSCT, immune modulatory therapy
AIRE (*AIRE*)	AR	Aberrant Treg TCR repertoire	CMC, polyendocrinopathy	Antifungals, hormonal replacement
Hyper IgM syndromes				
AID (*AID*)	AR	Impaired CSR and SHM	Sinopulmonary infections, lymphoid hyperplasia, autoimmune disease	IRT
UNG (*UNG*)	AR	Impaired CSR and SHM	Sinopulmonary infections	IRT
CD40L (*CD40LG*)	XL	Impaired CSR and SHM	Opportunistic and sinopulmonary infections	IRT, HSCT
CD40 (*CD40*)	AR	Impaired CSR and SHM	Opportunistic and sinopulmonary infections	IRT, HSCT
Hyper IgE syndromes				
IL-21 (*IL21*)	AR	Impaired CSR and SHM	Opportunistic and sinopulmonary infections, early-onset IBD	IRT
IL-21R (*IL21R*)	AR	Impaired CSR and SHM	Opportunistic, sinopulmonary, and gastrointestinal infections; cholangitis	IRT, HSCT?
STAT3 (*STAT3*)	AD	Impaired CSR and SHM	Severe eczema, bacterial skin abscesses and pneumonias, CMC	Prophylactic antibiotics and antifungals, IRT

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; cDC, conventional dendritic cells; CMC, chronic mucocutaneous candidiasis; CSM, class-switched memory; CSR, class-switch recombination; HSCT, hematopoietic stem cell transplant; IBD, inflammatory bowel disease; IRT, immunoglobulin replacement therapy; SHM, somatic hypermutation; Treg, T regulatory cell; XL, X-linked.

frequencies of anti-nuclear, new emigrant B cells in MyD88 and IRAK4-deficient patients (∼20%) also suggest one or more innate receptors utilizing these intracellular signaling molecules sense nuclear-antigen binding BCRs (Figure 2, ②; Table 1) (Isnardi et al., 2008). Endosomal toll-like receptors (TLR) 7 and/or 9, which both utilize MyD88/IRAK4 signaling and recognize nucleic acids, may help B cells to "sense" if their internalized BCRs are bound to exogenous chromosomal DNA (Chaturvedi et al., 2008; Leadbetter et al., 2002). Notably, TLR7 and TLR9 have been implicated in anti-nuclear antibody driven murine lupus models (Christensen et al., 2006). Finally, the receptor TACI (TNFRSF13B), which potentiates both BCR and TLR7/9 responses, plays a predictably essential role in central B-cell tolerance. TACI-mutated common variable immunodeficiency (CVID) patients display increased frequencies of polyreactive (∼30%) and anti-nuclear (∼15%) new emigrant B cells and secrete a variety of pathogenic autoantibodies (Romberg et al., 2013, 2015). Sadly, CVID B-cell activation defects resulting from mutations in TACI, NFKB1, CD21, BACH2, CD19, and

PLCG2 also prevent affected patients from mounting protective antibody responses to vaccines, requiring lifelong IRT (Table 1) (Afzali et al., 2017; Fliegauf et al., 2015; Ombrello et al., 2012; Perkins et al., 2017; Thiel et al., 2012; van Zelm et al., 2006).

2.3 | T cells patrol a peripheral B-cell tolerance checkpoint

Even when central B-cell tolerance is intact, ~40% of new emigrant B cells recognize self-antigens (Wardemann et al., 2003). In healthy controls, the frequency of self-reactive clones drops to 20% during maturation in the periphery, indicating the presence of a peripheral B-cell tolerance checkpoint (Figure 2, ③). Although the anatomic site(s) and molecular mechanism are unknown, several lines of evidence suggest antigen-specific T lymphocytes are important participants in the peripheral tolerance checkpoint. For instance, CD3-deficient SCID patients, who possess B cells but not T cells, demonstrate normal central but breeched peripheral B-cell tolerance (Sng et al., 2019). More specifically, FOXP3 expressing T regulatory cells (Tregs) play irreplaceable roles in tolerizing peripheral B cells as demonstrated by FOXP3-deficient patients who lack Tregs and AIRE-deficient patients with aberrantly selected Treg TCR repertoires (Table 1) (Kinnunen, Chamberlain, Morbach, Choi, et al., 2013; Sng et al., 2019). Similar patterns of tolerance are observed in many MS patients, suggesting underlying T cell dysfunction promotes the formation of MS-associated anti-CNS antibodies (Kinnunen, Chamberlain, Morbach, Cantaert, et al., 2013). The mechanism by which Tregs eliminate self-reactive B cells is currently unknown but may involve additional cell types and/or positive selection (J. W. Chen et al., 2021).

3 | DEVELOPMENTAL TRAJECTORIES OF ANTIGEN EXPERIENCED B CELLS

3.1 | B cells find purpose (and antigens) in lymphoid follicles

Mature naïve and memory B cells continuously circulate through the body search of their antigen. They often encounter it in the secondary lymphoid structures (lymph nodes, spleen, or tonsils) draining inflamed tissues. (Figure 2, ④) Antigens are concentrated by follicular dendritic cells (FDCs), conventional dendritic cells (cDCs), and subcapsular macrophages (Batista & Harwood, 2009; Gonzalez et al., 2010; Phan et al., 2007; Qi et al., 2006). FDCs, cDCs, and subcapsular sinus macrophages decorate their surfaces with large unprocessed "native" antigens accessible to BCRs. cDCs, but not FDC, also continuously internalize native antigens for fragmentation, major histocompatibility receptor two (MHCII) loading, and presentation to TCRs. DC-activated B and T lymphocytes physically interact, proliferate, and together form a spherical collection called a secondary follicle (Crotty, 2019). As it grows, resting B cells are pushed outward to form a follicular mantle. Remaining in the interior is the GC, a temporary structure comprised of a light zone where T follicular helper cells (Tfh) interact with antigen-presenting B cells (centrocytes), and a dark zone containing rapidly proliferating B cells (centroblasts) (Figure 3). In addition to lymphocytes, GC light zones contain a lattice of FDCs (Fang et al., 1998). Since FDCs are stromal, not hematopoietic cells (Jarjour et al., 2014), they cannot directly present processed antigens to Tfh cells but instead must relinquish their native antigens to antigen-specific centrocytes (Figure 3, ①) to process and present via MHCII. This unusual arrangement, wherein centrocytes act as exclusive antigen presenters to Tfh cells, enforces BCR reactivity and affinity as the primary determinates of GC fate.

Early in a GC reaction, centrocytes that can present antigen to Tfh cells are rewarded with a co-stimulatory ligand CD40L and activating cytokines (IL-4 and IL-21), whereas centrocytes that cannot present antigen go unrewarded and die from neglect (Figure 3, ②) (Victora et al., 2010; Victora & Nussenzweig, 2012). If activated in the light zone, centrocytes transit to the dark zone where they proliferate as centroblasts (Figure 3, ③). After multiple cell divisions, centroblasts upregulate the cellular machinery needed for somatic hypermutation (SHM), namely activation-induced cytidine deaminase (AID), uracil-DNA glycosolase (UNG), and apurinic/apyrimidinic endonuclease I (Rush et al., 2005). The tripartite enzymatic complex alters BCR reactivity by introducing point mutations at random cytosine residues in rearranged *IGH* and *IGL* genes. Upon return to the light zone, centrocytes downregulate AID and compete to bind antigens with their newly mutated BCRs (Figure 3, ①). The clones expressing the highest affinity BCRs are rewarded for presenting the most antigen to Tfh cells and reenter the dark zone to proliferate and somatically mutate further (Figure 3, ②). Successive cycles of light and dark zone re-entry drive a process called affinity maturation wherein

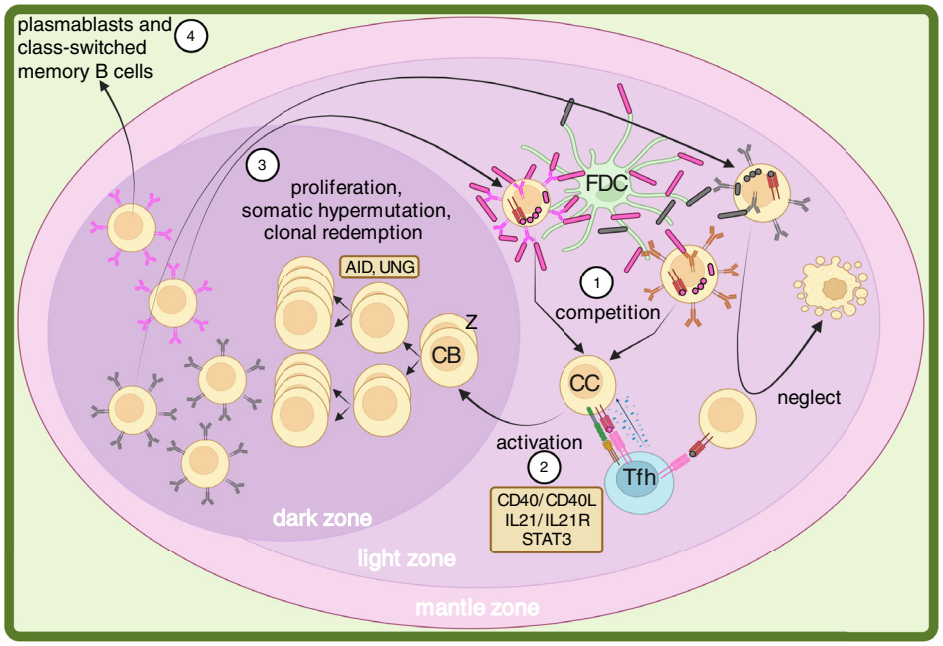

FIGURE 3 Germinal center reactions comprise cycles of competition, reward, proliferation and mutation. ① Centrocytes (CC) in the light zone compete for native antigens to process and ② present to T follicular helper cells (Tfh). CCs presenting antigen are activated and pass into the dark zone as centroblasts (CB). ③ CBs proliferate, somatically mutate their immunoglobulin gene loci and class-switch before returning to the light zone as CCs to compete for antigens again. ④ Highly activated CBs leave the germinal center to become either memory B cells or marrow-homing plasmablasts. FDC, follicular dendritic cell

BCRs preferentially accumulate amino acid substitutions at CDRs that increase antigen binding specificity and strength (Gitlin et al., 2014).

During the initial T-cell/B-cell interaction and prior to GC formation, AID also introduces double stranded breaks in the rearranged immunoglobulin gene fragment encoding the constant region (Fc) (Roco et al., 2019). The Fc of a secreted antibody dictates if it will multimerize, where it is transported, and what immune effector cells bind to it (Nimmerjahn & Ravetch, 2008). During break repair, the default constant gene fragment encoding IgM may be replaced with a constant gene fragment encoding IgG, IgA, or IgE isotypes (Nagaoka et al., 2002). The isotype selected during switching appears to be guided by the GC cytokine milieu. For instance, IL-4, which is associated with parasitic infections and atopic disease, makes the Fc epsilon locus available to AID, resulting in increased switching to IgE (Gowthaman et al., 2019; Vijayanand et al., 2012). In contrast, IL-21 is a broad negative regulator of IgE class-switch recombination (CSR) (Yang et al., 2020). Upon generating high-affinity class-switched BCRs, centroblasts begin differentiating into memory B cells or marrow-homing plasmablasts (Figure 3, ④). Upon reaching specialized niches in bone marrow, plasmablasts terminally differentiate into long-lived plasma cells that produce massive quantities of clonal antibodies for cellular export rather than for cell-surface expression. Once distributed systemically, antibodies bind and eliminate the antigens that originally spurred their creation (Figure 2, ⑤) (Zhang et al., 2013). Without antigens, GC dynamics cannot be sustained and the GC architecture involutes. Importantly, many memory B and T cells arising from GCs survive and constantly surveil secondary lymphoid tissues for their antigen (Figure 2, ④). Upon antigen re-exposure these cells can quickly reform antigen-specific GCs in the same or different secondary lymphoid tissues and rapidly clear subsequent infections (Bende et al., 2007).

The molecular complexity of GC reactions is well highlighted by patients with a group of genetic disorders called hyper IgM (HIGM) syndromes. HIGM can be caused by deficiencies of the CS) and SHM apparatus including AID, UNG, CD40L, and its receptor CD40 (Figure 3, ② and ③; Table 1). (Ferrari et al., 2001; Imai et al., 2003; Revy et al., 2000). To compensate for their inability to produce affinity maturated, class-switched antibodies, HIGM B cells oversecrete unmutated, low-affinity IgM that cannot protect against sinopulmonary infections. Low-affinity antibodies from AID-deficient patients and CVID patients also are unable to eliminate the antigens driving GC reactions (Cantaert et al., 2016; Romberg et al., 2019) or prevent CVID-associated endotoxemia, a condition favoring Tfh cell development (Le Coz et al., 2019). These forces culminate to drive fulminant follicular hyperplasia and clinically significant

lymphadenopathy. Other immunodeficient patients with defects in IL-21, its receptor (IL-21R), or an associated downstream signaling molecule (STAT3) do not generate high-affinity antibodies of any isotype and hypersecrete IgE due to Fc epsilon biased class-switching (Kotlarz et al., 2013; Minegishi et al., 2007; Salzer et al., 2014).

3.2 | Somatic hypermutation offers autoreactive B cells a final chance at redemption

Autoreactive BCRs are permitted in the naïve B-cell pool of healthy donors but are rarely allowed to terminally differentiate into antibody producing plasma cells or class-switched memory B cells. For instance, many healthy donor naïve B cells utilize the germline *VH4-34* gene segment in their rearranged *IGH* loci even though antibodies encoded by it recognize the erythrocytic i-antigen and cause autoimmune hemolytic anemia (Potter et al., 2002). In contrast, post-GC healthy donor class-switched memory B cells rarely utilize *VH4-34* and those that do overwhelmingly express IgH somatically mutated to alter i-antigen recognition (Reed et al., 2016). Hence, the same GC enzymatic machinery increasing a BCR's affinity for an exogenous antigen also appears to preferentially decrease its affinity for self. This tolerogenic phenomenon, called clonal redemption, has been experimentally demonstrated in immunized transgenic mice and healthy humans (Sabouri et al., 2014). In these models, the introduction of tolerizing mutations that negate self-antigen recognition clearly appear before affinity maturation. How mutation placement order and location are regulated is unknown. The clinical consequences of failed clonal redemption are more clear and well demonstrated by CVID patients with autoimmune hemolytic anemia and immune thrombocytopenia (Romberg & Lawrence, 2019). Due to CVID-associated defects upregulating AID, these patients' memory B cells are highly enriched in *VH4-34* expressing clones that lack tolerizing somatic mutations (Romberg et al., 2019). The frequent episodes of autoimmune hemolytic anemia experienced by AID-deficient patients may occur by a similar mechanism (Cantaert et al., 2016). Notably, overly exuberant B-cell activation and AID induction caused by CD40L overexpression may also break B-cell tolerance as demonstrated by female lupus patients (Lu et al., 2007) and a male patient with a poly-autoimmunity syndrome caused by chromosomal duplication of the CD40L gene (Table 1) (Le Coz et al., 2018). Unregulated placement of somatic hypermutations in *IGH* and *IGL*, as seen in highly mutated, lupus associated, anti-nuclear antibodies can push GC B cells toward pathology rather than clonal redemption (Mietzner et al., 2008; Wellmann et al., 2005).

4 | B-CELL TOLERANCE RESTORING THERAPIES THAT WORK, MIGHT WORK, AND DO NOT

Although restoring B-cell lymphopoiesis in an infant with SCID (Pai et al., 2014) or B-cell aplasia (Le Coz et al., 2021; Sun et al., 2021) can be achieved directly with HSCT, restoring B-cell tolerance in patients with genetically complex autoimmune diseases requires a more nuanced approach. Most autoantibody-mediated diseases have been treated with B-depleting therapies with mixed results (Kaegi et al., 2019). Most popular of these treatments is rituximab, which targets CD20. Since autoantibody producing plasma cells do not express CD20, rituximab may work by depleting the ranks of naïve and memory B cells from which new plasma cells are formed. Unfortunately, B-cell depletion does not appear to "reset" or normalize central B-cell tolerance, a concept specifically tested in type 1 diabetes patients (Chamberlain et al., 2015). Several months after rituximab treatment, the frequency of reappearing autoreactive new emigrant B cells in rituximab treated diabetics remained stubbornly high. Related studies have demonstrated that methotrexate and anti-tumor necrosis factor α treatment do not change rheumatoid arthritis patients' high frequencies of autoreactive mature naïve B-cells (Menard, Samuels, et al., 2011). Thus disease-associated central tolerance defects are not inflammatory epiphenomena but rather appear to be B-cell intrinsic and likely genetically hardwired.

In contrast to B-cell depletion, gene therapy may offer opportunities to restore B-cell tolerance in patients with specific genetic tolerance defects. For instance, the central B-cell tolerance breeches observed in adenosine deaminase (ADA) deficient SCID patients were largely reversed by restoring ADA expression in autologous hematopoietic stem cells using a retroviral vector (Table 1) (Sauer et al., 2012). A different tolerogenic approach that may have broader therapeutic applications is Treg-cell-based therapy (Raffin et al., 2020). Currently in development to treat a variety of autoimmune conditions including type 1 diabetes (Bluestone et al., 2015; Dong et al., 2021), graft versus host disease (Trzonkowski et al., 2009), and solid-organ transplant rejection (Chandran et al., 2017; Todo et al., 2016), Treg-cell-based therapies may also restore breeches in peripheral B-cell tolerance and even compensate for upstream central B-cell tolerance defects. Since the specific mechanisms by which Tregs counter select autoreactive peripheral B cells

remains undetermined, it is unclear if Treg repertoires would need tailor engineering for each patient to specifically purge autoreactive clones without affecting pathogen recognizing B cells.

5 | CONCLUSION

A broad BCR repertoire that does not react to self-antigens but can neutralize a variety of foreign antigens is a biologic marvel and the lynchpin of global vaccine efforts. Creating these BCRs requires complex systems positioned throughout B-cell development that explosively diversify and meticulously refine receptor/ligand interactions throughout B-cell development. Although monogenic diseases of the immune system have illuminated many of the molecules and pathways required for development and maintenance of well-tolerized B cells, the mutations causing these diseases are rare and do not explain the rising global prevalence of autoantibody-mediated diseases. Genome wide association studies suggest that the confluence of common genetic variations, like certain MHC haplotypes or SNPs in cell-signal tuning genes, may explain a proportion of disease susceptibilities (Caliskan et al., 2021; Su et al., 2020). Large societal shifts in diet, exercise, and/or microbiome may also alter autoimmune disease risk (Cekanaviciute et al., 2017; Greiling et al., 2018; Manfredo Vieira et al., 2018; Paun et al., 2019; Pianta et al., 2017; Thorburn et al., 2014).

Since autoantibody-mediated autoimmune diseases can negatively affect survival, it is reasonable to ask why autoreactive immunoglobulin gene segments like *VH4-34* remain in the human genome over evolutionary time. A likely explanation is that the pathogens neutralized by *VH4-34* encoded antibodies have exerted greater negative selective pressure on our species than autoimmune disease have. In contrast, counter selection of polyreactive B cells by the central tolerance checkpoint has been identified as a major obstacle to developing a human immunodeficiency virus (HIV-1) vaccine (Haynes et al., 2005, 2012; Mouquet et al., 2010). Interestingly, HIV-1 infection rates are disproportionately low among lupus patients (Mody et al., 2014) and at least one HIV-1 infected woman with lupus has been identified with polyreactive, broadly neutralizing, anti-HIV-1 antibodies (Bonsignori et al., 2014). Finally, it may be a mistake to assume that all autoantibodies we generate are deleterious; some may promote health. Aducanumab, a fully human anti-amyloid monoclonal antibody approved to treat Alzheimer's disease, was developed by screening memory B cells from cognitively normal elderly individuals for reactivity against amyloid plaques (Sevigny et al., 2016). Adjusting our intellectual framework toward searching for diseases that autoantibodies *prevent*, rather than cause, may spur additional therapeutic discoveries.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AUTHOR CONTRIBUTIONS

Kim Nguyen: Data curation (equal); writing – original draft (equal). **Nouf Alsaati:** Conceptualization (equal); writing – original draft (equal). **Carole Le Coz:** Conceptualization (equal). **Neil Romberg:** Conceptualization (equal); supervision (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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RELATED WIREs ARTICLE

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FURTHER READING

Immunodeficiency search (https://www.immunodeficiencysearch.com) is an excellent, up to date, online reference for practicing (and aspiring) clinical immunologists.

REFERENCES

Afzali, B., Grönholm, J., Vandrovcova, J., O'Brien, C., Sun, H.-W., Vanderleyden, I., Davis, F. P., Khoder, A., Zhang, Y., Hegazy, A. N., Villarino, A. V., Palmer, I. W., Kaufman, J., Watts, N. R., Kazemian, M., Kamenyeva, O., Keith, J., Sayed, A., Kasperaviciute, D., ... Laurence, A. D. J. (2017). BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. *Nature Immunology*, *18*(7), 813–823. https://doi.org/10.1038/ni.3753

Agrawal, A., & Schatz, D. G. (1997). RAG1 and RAG2 form a stable postcleavage synaptic complex with DNA containing signal ends in V(D) J recombination. *Cell*, *89*(1), 43–53. https://doi.org/10.1016/S0092-8674(00)80181-6

Allman, D., Li, J., & Hardy, R. R. (1999). Commitment to the B lymphoid lineage occurs before DH-JH recombination. *Journal of Experimental Medicine*, *189*(4), 735–740. https://doi.org/10.1084/jem.189.4.735

Bankovich, A. J., Raunser, S., Juo, Z. S., Walz, T., Davis, M. M., & Garcia, K. C. (2007). Structural insight into pre-B cell receptor function. *Science*, *316*(5822), 291–294. https://doi.org/10.1126/science.1139412

Barmettler, S., Otani, I. M., Minhas, J., Abraham, R. S., Chang, Y., Dorsey, M. J., Ballas, Z. K., Bonilla, F. A., Ochs, H. D., & Walter, J. E. (2017). Gastrointestinal manifestations in X-linked agammaglobulinemia. *Journal of Clinical Immunology*, *37*(3), 287–294. https://doi.org/10.1007/s10875-017-0374-x

Batista, F. D., & Harwood, N. E. (2009). The who, how and where of antigen presentation to B cells. *Nature Reviews Immunology*, *9*(1), 15–27. https://doi.org/10.1038/nri2454

Bende, R. J., van Maldegem, F., Triesscheijn, M., Wormhoudt, T. A. M., Guijt, R., & van Noesel, C. J. M. (2007). Germinal centers in human lymph nodes contain reactivated memory B cells. *The Journal of Experimental Medicine*, *204*(11), 2655–2665. https://doi.org/10.1084/jem.20071006

Bluestone, J. A., Buckner, J. H., Fitch, M., Gitelman, S. E., Gupta, S., Hellerstein, M. K., Herold, K. C., Lares, A., Lee, M. R., Li, K., Liu, W., Long, S. A., Masiello, L. M., Nguyen, V., Putnam, A. L., Rieck, M., Sayre, P. H., & Tang, Q. (2015). Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Science Translational Medicine*, *7*(315), 315ra189. https://doi.org/10.1126/scitranslmed.aad4134

Boisson, B., Wang, Y.-D., Bosompem, A., Ma, C. S., Lim, A., Kochetkov, T., Tangye, S. G., Casanova, J.-L., & Conley, M. E. (2013). A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR(−) B cells. *Journal of Clinical Investigation*, *123*(11), 4781–4785. https://doi.org/10.1172/JCI71927

Bonsignori, M., Wiehe, K., Grimm, S. K., Lynch, R., Yang, G., Kozink, D. M., Perrin, F., Cooper, A. J., Hwang, K.-K., Chen, X., Liu, M., McKee, K., Parks, R. J., Eudailey, J., Wang, M., Clowse, M., Criscione-Schreiber, L. G., Moody, M. A., Ackerman, M. E., ... Haynes, B. F. (2014). An autoreactive antibody from an SLE/HIV-1 individual broadly neutralizes HIV-1. *Journal of Clinical Investigation*, *124*(4), 1835–1843. https://doi.org/10.1172/JCI73441

Bottini, N., & Peterson, E. J. (2014). Tyrosine phosphatase PTPN22: Multifunctional regulator of immune signaling, development, and disease. *Annual Review of Immunology*, *32*(1), 83–119. https://doi.org/10.1146/annurev-immunol-032713-120249

Bousfiha, A., Jeddane, L., Picard, C., Al-Herz, W., Ailal, F., Chatila, T., Cunningham-Rundles, C., Etzioni, A., Franco, J. L., Holland, S. M., Klein, C., Morio, T., Ochs, H. D., Oksenhendler, E., Puck, J., Torgerson, T. R., Casanova, J.-L., Sullivan, K. E., & Tangye, S. G. (2020). Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. *Journal of Clinical Immunology*, *40*(1), 66–81. https://doi.org/10.1007/s10875-020-00758-x

Bruton, O. C. (1952). Agammaglobulinemia. *Pediatrics*, *9*(6), 722–728.

Buck, D., Malivert, L., de Chasseval, R., Barraud, A., Fondanèche, M.-C., Sanal, O., Plebani, A., Stéphan, J.-L., Hufnagel, M., le Deist, F., Fischer, A., Durandy, A., de Villartay, J.-P., & Revy, P. (2006). Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. *Cell*, *124*(2), 287–299. https://doi.org/10.1016/j.cell.2005.12.030

Buck, D., Moshous, D., de Chasseval, R., Ma, Y., le Deist, F., Cavazzana-Calvo, M., Fischer, A., Casanova, J.-L., Lieber, M. R., & de Villartay, J.-P. (2006). Severe combined immunodeficiency and microcephaly in siblings with hypomorphic mutations in DNA ligase IV. *European Journal of Immunology*, *36*(1), 224–235. https://doi.org/10.1002/eji.200535401

Caliskan, M., Brown, C. D., & Maranville, J. C. (2021). A catalog of GWAS fine-mapping efforts in autoimmune disease. *The American Journal of Human Genetics*, *108*(4), 549–563. https://doi.org/10.1016/j.ajhg.2021.03.009

Cantaert, T., Schickel, J.-N., Bannock, J. M., Ng, Y.-S., Massad, C., Delmotte, F. R., Yamakawa, N., Glauzy, S., Chamberlain, N., Kinnunen, T., Menard, L., Lavoie, A., Walter, J. E., Notarangelo, L. D., Bruneau, J., Al-Herz, W., Kilic, S. S., Ochs, H. D., Cunningham-Rundles, C., ... Meffre, E. (2016). Decreased somatic hypermutation induces an impaired peripheral B cell tolerance checkpoint. *Journal of Clinical Investigation*, *126*(11), 4289–4302. https://doi.org/10.1172/JCI84645

Casellas, R., Shih, T.-A. Y., Kleinewietfeld, M., Rakonjac, J., Nemazee, D., Rajewsky, K., & Nussenzweig, M. C. (2001). Contribution of receptor editing to the antibody repertoire. *Science*, *291*(5508), 1541–1544. https://doi.org/10.1126/science.1056600

Cekanaviciute, E., Yoo, B. B., Runia, T. F., Debelius, J. W., Singh, S., Nelson, C. A., Kanner, R., Bencosme, Y., Lee, Y. K., Hauser, S. L., Crabtree-Hartman, E., Sand, I. K., Gacias, M., Zhu, Y., Casaccia, P., Cree, B. A. C., Knight, R., Mazmanian, S. K., & Baranzini, S. E. (2017). Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(40), 10713–10718. https://doi.org/10.1073/pnas.1711235114

Chamberlain, N., Massad, C., Oe, T., Cantaert, T., Herold, K. C., Meffre, E., & the Type 1 Diabetes TrialNet Pathway to Prevention Study Group. (2015). Rituximab does not reset defective early B cell tolerance checkpoints. *Journal of Clinical Investigation*, *126*(1), 282–287. https://doi.org/10.1172/JCI83840

Chandran, S., Tang, Q., Sarwal, M., Laszik, Z. G., Putnam, A. L., Lee, K., Leung, J., Nguyen, V., Sigdel, T., Tavares, E. C., Yang, J. Y. C., Hellerstein, M., Fitch, M., Bluestone, J. A., & Vincenti, F. (2017). Polyclonal regulatory T cell therapy for control of inflammation in kidney transplants. *American Journal of Transplantation*, *17*(11), 2945–2954. https://doi.org/10.1111/ajt.14415

Chaturvedi, A., Dorward, D., & Pierce, S. K. (2008). The B cell receptor governs the subcellular location of toll-like receptor 9 leading to hyperresponses to DNA-containing antigens. *Immunity*, *28*(6), 799–809. https://doi.org/10.1016/j.immuni.2008.03.019

Chen, C., Nagy, Z., Radic, M. Z., Hardy, R. R., Huszar, D., Camper, S. A., & Weigert, M. (1995). The site and stage of anti-DNA B-cell deletion. *Nature*, *373*(6511), 252–255. https://doi.org/10.1038/373252a0

Chen, J. W., Schickel, J.-N., Tsakiris, N., Sng, J., Arbogast, F., Bouis, D., Parisi, D., Gera, R., Boeckers, J. M., Delmotte, F. R., Veselits, M., Schuetz, C., Jacobsen, E.-M., Posovszky, C., Schulz, A. S., Schwarz, K., Clark, M. R., Menard, L., & Meffre, E. (2021). Positive and negative selection shape the human naïve B cell repertoire. *Journal of Clinical Investigation*, *132*, e150985. https://doi.org/10.1172/JCI150985

Chinn, I. K., Chan, A. Y., Chen, K., Chou, J., Dorsey, M. J., Hajjar, J., Jongco, A. M., Keller, M. D., Kobrynski, L. J., Kumanovics, A., Lawrence, M. G., Leiding, J. W., Lugar, P. L., Orange, J. S., Patel, K., Platt, C. D., Puck, J. M., Raje, N., Romberg, N., … Walter, J. E. (2020). Diagnostic interpretation of genetic studies in patients with primary immunodeficiency diseases: A working group report of the Primary Immunodeficiency Diseases Committee of the American Academy of Allergy, Asthma & Immunology. *Journal of Allergy and Clinical Immunology*, *145*(1), 46–69. https://doi.org/10.1016/j.jaci.2019.09.009

Christensen, S. R., Shupe, J., Nickerson, K., Kashgarian, M., Flavell, R. A., & Shlomchik, M. J. (2006). Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity*, *25*(3), 417–428. https://doi.org/10.1016/j.immuni.2006.07.013

Corneo, B., Moshous, D., Güngör, T., Wulffraat, N., Philippet, P., Deist, F. L., Fischer, A., & de Villartay, J.-P. (2001). Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B–severe combined immune deficiency or Omenn syndrome. *Blood*, *97*(9), 2772–2776. https://doi.org/10.1182/blood.V97.9.2772

Cotzomi, E., Stathopoulos, P., Lee, C. S., Ritchie, A. M., Soltys, J. N., Delmotte, F. R., Oe, T., Sng, J., Jiang, R., Ma, A. K., Vander Heiden, J. A., Kleinstein, S. H., Levy, M., Bennett, J. L., Meffre, E., & O'Connor, K. C. (2019). Early B cell tolerance defects in neuromyelitis optica favour anti-AQP4 autoantibody production. *Brain*, *142*(6), 1598–1615. https://doi.org/10.1093/brain/awz106

Crotty, S. (2019). T follicular helper cell biology: A decade of discovery and diseases. *Immunity*, *50*(5), 1132–1148. https://doi.org/10.1016/j.immuni.2019.04.011

Davis, M. M., Calame, K., Early, P. W., Livant, D. L., Joho, R., Weissman, I. L., & Hood, L. (1980). An immunoglobulin heavy-chain gene is formed by at least two recombinational events. *Nature*, *283*(5749), 733–739. https://doi.org/10.1038/283733a0

Deau, M.-C., Heurtier, L., Frange, P., Suarez, F., Bole-Feysot, C., Nitschke, P., Cavazzana, M., Picard, C., Durandy, A., Fischer, A., & Kracker, S. (2014). A human immunodeficiency caused by mutations in the PIK3R1 gene. *Journal of Clinical Investigation*, *124*(9), 3923–3928. https://doi.org/10.1172/JCI75746

Dong, S., Hiam-Galvez, K. J., Mowery, C. T., Herold, K. C., Gitelman, S. E., Esensten, J. H., Liu, W., Lares, A. P., Leinbach, A. S., Lee, M., Nguyen, V., Tamaki, S. J., Tamaki, W., Tamaki, C. M., Mehdizadeh, M., Putnam, A. L., Spitzer, M. H., Ye, C. J., Tang, Q., & Bluestone, J. A. (2021). The effect of low-dose IL-2 and Treg adoptive cell therapy in patients with type 1 diabetes. *JCI Insight*, *6*(18), e147474. https://doi.org/10.1172/jci.insight.147474

Fang, Y., Xu, C., Fu, Y. X., Holers, V. M., & Molina, H. (1998). Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response. *Journal of Immunology (Baltimore, Md.: 1950)*, *160*(11), 5273–5279.

Ferrari, S., Giliani, S., Insalaco, A., Al-Ghonaium, A., Soresina, A. R., Loubser, M., Avanzini, M. A., Marconi, M., Badolato, R., Ugazio, A. G., Levy, Y., Catalan, N., Durandy, A., Tbakhi, A., Notarangelo, L. D., & Plebani, A. (2001). Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(22), 12614–12619. https://doi.org/10.1073/pnas.221456898

Ferrari, S., Lougaris, V., Caraffi, S., Zuntini, R., Yang, J., Soresina, A., Meini, A., Cazzola, G., Rossi, C., Reth, M., & Plebani, A. (2007). Mutations of the Igβ gene cause agammaglobulinemia in man. *Journal of Experimental Medicine*, *204*(9), 2047–2051. https://doi.org/10.1084/jem.20070264

Fischer, A., & Hacein-Bey-Abina, S. (2020). Gene therapy for severe combined immunodeficiencies and beyond. *Journal of Experimental Medicine*, *217*(2), e20190607. https://doi.org/10.1084/jem.20190607

Fliegauf, M., Bryant, V. L., Frede, N., Slade, C., Woon, S.-T., Lehnert, K., Winzer, S., Bulashevska, A., Scerri, T., Leung, E., Jordan, A., Keller, B., de Vries, E., Cao, H., Yang, F., Schäffer, A. A., Warnatz, K., Browett, P., Douglass, J., … Grimbacher, B. (2015). Haploinsufficiency of the NF-κB1 subunit p50 in common variable immunodeficiency. *American Journal of Human Genetics*, *97*(3), 389–403. https://doi.org/10.1016/j.ajhg.2015.07.008

Gilfillan, S., Dierich, A., Lemeur, M., Benoist, C., & Mathis, D. (1993). Mice lacking TdT: Mature animals with an immature lymphocyte repertoire. *Science*, *261*(5125), 1175–1178. https://doi.org/10.1126/science.8356452

Gitlin, A. D., Shulman, Z., & Nussenzweig, M. C. (2014). Clonal selection in the germinal centre by regulated proliferation and hypermutation. *Nature*, *509*(7502), 637–640. https://doi.org/10.1038/nature13300

Glauzy, S., Olson, B., May, C. K., Parisi, D., Massad, C., Hansen, J. E., Ryu, C., Herzog, E. L., & Meffre, E. (2021). Defective early B cell tolerance checkpoints in patients with systemic sclerosis allow the production of self antigen-specific clones. *Arthritis & Rheumatology*, *74*, 307–317. https://doi.org/10.1002/art.41927

Gonzalez, S. F., Lukacs-Kornek, V., Kuligowski, M. P., Pitcher, L. A., Degn, S. E., Kim, Y.-A., Cloninger, M. J., Martinez-Pomares, L., Gordon, S., Turley, S. J., & Carroll, M. C. (2010). Capture of influenza by medullary dendritic cells via SIGN-R1 is essential for humoral immunity in draining lymph nodes. *Nature Immunology*, *11*(5), 427–434. https://doi.org/10.1038/ni.1856

Gowthaman, U., Chen, J. S., Zhang, B., Flynn, W. F., Lu, Y., Song, W., Joseph, J., Gertie, J. A., Xu, L., Collet, M. A., Grassmann, J. D. S., Simoneau, T., Chiang, D., Berin, M. C., Craft, J. E., Weinstein, J. S., Williams, A., & Eisenbarth, S. C. (2019). Identification of a T

follicular helper cell subset that drives anaphylactic IgE. *Science (New York, N.Y.)*, *365*(6456), eaaw6433. https://doi.org/10.1126/science.aaw6433

Greiling, T. M., Dehner, C., Chen, X., Hughes, K., Iñiguez, A. J., Boccitto, M., Ruiz, D. Z., Renfroe, S. C., Vieira, S. M., Ruff, W. E., Sim, S., Kriegel, C., Glanternik, J., Chen, X., Girardi, M., Degnan, P., Costenbader, K. H., Goodman, A. L., Wolin, S. L., & Kriegel, M. A. (2018). Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. *Science Translational Medicine*, *10*(434), eaan2306. https://doi.org/10.1126/scitranslmed.aan2306

Haynes, B. F., Fleming, J., St. Clair, E. W., Katinger, H., Stiegler, G., Kunert, R., Robinson, J., Scearce, R. M., Plonk, K., Staats, H. F., Ortel, T. L., Liao, H.-X., & Alam, S. M. (2005). Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science*, *308*(5730), 1906–1908. https://doi.org/10.1126/science.1111781

Haynes, B. F., Kelsoe, G., Harrison, S. C., & Kepler, T. B. (2012). B-cell-lineage immunogen design in vaccine development with HIV-1 as a case study. *Nature Biotechnology*, *30*(5), 423–433. https://doi.org/10.1038/nbt.2197

Imai, K., Slupphaug, G., Lee, W.-I., Revy, P., Nonoyama, S., Catalan, N., Yel, L., Forveille, M., Kavli, B., Krokan, H. E., Ochs, H. D., Fischer, A., & Durandy, A. (2003). Human uracil–DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. *Nature Immunology*, *4*(10), 1023–1028. https://doi.org/10.1038/ni974

Isnardi, I., Ng, Y.-S., Srdanovic, I., Motaghedi, R., Rudchenko, S., von Bernuth, H., Zhang, S.-Y., Puel, A., Jouanguy, E., Picard, C., Garty, B.-Z., Camcioglu, Y., Doffinger, R., Kumararatne, D., Davies, G., Gallin, J. I., Haraguchi, S., Day, N. K., Casanova, J.-L., & Meffre, E. (2008). IRAK-4- and MyD88-dependent pathways are essential for the removal of developing autoreactive B cells in humans. *Immunity*, *29*(5), 746–757. https://doi.org/10.1016/j.immuni.2008.09.015

Jarjour, M., Jorquera, A., Mondor, I., Wienert, S., Narang, P., Coles, M. C., Klauschen, F., & Bajénoff, M. (2014). Fate mapping reveals origin and dynamics of lymph node follicular dendritic cells. *Journal of Experimental Medicine*, *211*(6), 1109–1122. https://doi.org/10.1084/jem.20132409

Kaegi, C., Wuest, B., Schreiner, J., Steiner, U. C., Vultaggio, A., Matucci, A., Crowley, C., & Boyman, O. (2019). Systematic review of safety and efficacy of rituximab in treating immune-mediated disorders. *Frontiers in Immunology*, *10*, 1990. https://doi.org/10.3389/fimmu.2019.01990

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alföldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, *581*(7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Karczewski, K. J., Weisburd, B., Thomas, B., Solomonson, M., Ruderfer, D. M., Kavanagh, D., Hamamsy, T., Lek, M., Samocha, K. E., Cummings, B. B., Birnbaum, D., The Exome Aggregation Consortium, Daly, M. J., & MacArthur, D. G. (2017). The ExAC browser: Displaying reference data information from over 60 000 exomes. *Nucleic Acids Research*, *45*(D1), D840–D845. https://doi.org/10.1093/nar/gkw971

Kinnunen, T., Chamberlain, N., Morbach, H., Cantaert, T., Lynch, M., Preston-Hurlburt, P., Herold, K. C., Hafler, D. A., O'Connor, K. C., & Meffre, E. (2013). Specific peripheral B cell tolerance defects in patients with multiple sclerosis. *Journal of Clinical Investigation*, *123*(6), 2737–2741. https://doi.org/10.1172/JCI68775

Kinnunen, T., Chamberlain, N., Morbach, H., Choi, J., Kim, S., Craft, J., Mayer, L., Cancrini, C., Passerini, L., Bacchetta, R., Ochs, H. D., Torgerson, T. R., & Meffre, E. (2013). Accumulation of peripheral autoreactive B cells in the absence of functional human regulatory T cells. *Blood*, *121*(9), 1595–1603. https://doi.org/10.1182/blood-2012-09-457465

Kotlarz, D., Ziętara, N., Uzel, G., Weidemann, T., Braun, C. J., Diestelhorst, J., Krawitz, P. M., Robinson, P. N., Hecht, J., Puchałka, J., Gertz, E. M., Schäffer, A. A., Lawrence, M. G., Kardava, L., Pfeifer, D., Baumann, U., Pfister, E.-D., Hanson, E. P., Schambach, A., … Klein, C. (2013). Loss-of-function mutations in the IL-21 receptor gene cause a primary immunodeficiency syndrome. *The Journal of Experimental Medicine*, *210*(3), 433–443. https://doi.org/10.1084/jem.20111229

Kwan, A., Abraham, R. S., Currier, R., Brower, A., Andruszewski, K., Abbott, J. K., Baker, M., Ballow, M., Bartoshesky, L. E., Bonilla, F. A., Brokopp, C., Brooks, E., Caggana, M., Celestin, J., Church, J. A., Comeau, A. M., Connelly, J. A., Cowan, M. J., Cunningham-Rundles, C., … Puck, J. M. (2014). Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA*, *312*(7), 729–738. https://doi.org/10.1001/jama.2014.9132

Le Coz, C., Bengsch, B., Khanna, C., Trofa, M., Ohtani, T., Nolan, B. E., Henrickson, S. E., Lambert, M. P., Kim, T. O., Despotovic, J. M., Feldman, S., Fadugba, O. O., Takach, P., Ruffner, M., Jyonouchi, S., Heimall, J., Sullivan, K. E., Wherry, E. J., & Romberg, N. (2019). Common variable immunodeficiency-associated endotoxemia promotes early commitment to the T follicular lineage. *The Journal of Allergy and Clinical Immunology*, *144*(6), 1660–1673. https://doi.org/10.1016/j.jaci.2019.08.007

Le Coz, C., Nguyen, D. N., Su, C., Nolan, B. E., Albrecht, A. V., Xhani, S., Sun, D., Demaree, B., Pillarisetti, P., Khanna, C., Wright, F., Chen, P. A., Yoon, S., Stiegler, A. L., Maurer, K., Garifallou, J. P., Rymaszewski, A., Kroft, S. H., Olson, T. S., … Romberg, N. (2021). Constrained chromatin accessibility in PU.1-mutated agammaglobulinemia patients. *Journal of Experimental Medicine*, *218*(7), e20201750. https://doi.org/10.1084/jem.20201750

Le Coz, C., Trofa, M., Syrett, C. M., Martin, A., Jyonouchi, H., Jyonouchi, S., Anguera, M. C., & Romberg, N. (2018). CD40LG duplication-associated autoimmune disease is silenced by nonrandom X-chromosome inactivation. *The Journal of Allergy and Clinical Immunology*, *141*(6), 2308–2311.e7. https://doi.org/10.1016/j.jaci.2018.02.010

Leadbetter, E. A., Rifkin, I. R., Hohlbaum, A. M., Beaudette, B. C., Shlomchik, M. J., & Marshak-Rothstein, A. (2002). Chromatin–IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature*, *416*(6881), 603–607. https://doi.org/10.1038/416603a

Lee, J., Stathopoulos, P., Gupta, S., Bannock, J. M., Barohn, R. J., Cotzomi, E., Dimachkie, M. M., Jacobson, L., Lee, C. S., Morbach, H., Querol, L., Shan, J., Vander Heiden, J. A., Waters, P., Vincent, A., Nowak, R. J., & O'Connor, K. C. (2016). Compromised fidelity of B-cell tolerance checkpoints in AChR and MuSK myasthenia gravis. *Annals of Clinical and Translational Neurology*, *3*(6), 443–454. https://doi.org/10.1002/acn3.311

Löffert, D., Ehlich, A., Müller, W., & Rajewsky, K. (1996). Surrogate light chain expression is required to establish immunoglobulin heavy chain allelic exclusion during early B cell development. *Immunity*, *4*(2), 133–144. https://doi.org/10.1016/S1074-7613(00)80678-0

Lu, Q., Wu, A., Tesmer, L., Ray, D., Yousif, N., & Richardson, B. (2007). Demethylation of *CD40LG* on the inactive X in T cells from women with lupus. *The Journal of Immunology*, *179*(9), 6352–6358. https://doi.org/10.4049/jimmunol.179.9.6352

Manfredo Vieira, S., Hiltensperger, M., Kumar, V., Zegarra-Ruiz, D., Dehner, C., Khan, N., Costa, F. R. C., Tiniakou, E., Greiling, T., Ruff, W., Barbieri, A., Kriegel, C., Mehta, S. S., Knight, J. R., Jain, D., Goodman, A. L., & Kriegel, M. A. (2018). Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science*, *359*(6380), 1156–1161. https://doi.org/10.1126/science.aar7201

Matsuda, F., & Honjo, T. (1996). Organization of the human immunoglobulin heavy-chain locus. In *Advances in immunology* (Vol. 62, pp. 1–29). Elsevier. https://doi.org/10.1016/S0065-2776(08)60426-5

Melamed, D., Benschop, R. J., Cambier, J. C., & Nemazee, D. (1998). Developmental regulation of B lymphocyte immune tolerance compartmentalizes clonal selection from receptor selection. *Cell*, *92*(2), 173–182. https://doi.org/10.1016/S0092-8674(00)80912-5

Menard, L., Saadoun, D., Isnardi, I., Ng, Y.-S., Meyers, G., Massad, C., Price, C., Abraham, C., Motaghedi, R., Buckner, J. H., Gregersen, P. K., & Meffre, E. (2011). The PTPN22 allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans. *Journal of Clinical Investigation*, *121*(9), 3635–3644. https://doi.org/10.1172/JCI45790

Menard, L., Samuels, J., Ng, Y.-S., & Meffre, E. (2011). Inflammation-independent defective early B cell tolerance checkpoints in rheumatoid arthritis. *Arthritis and Rheumatism*, *63*(5), 1237–1245. https://doi.org/10.1002/art.30164

Mietzner, B., Tsuiji, M., Scheid, J., Velinzon, K., Tiller, T., Abraham, K., Gonzalez, J. B., Pascual, V., Stichweh, D., Wardemann, H., & Nussenzweig, M. C. (2008). Autoreactive IgG memory antibodies in patients with systemic lupus erythematosus arise from nonreactive and polyreactive precursors. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(28), 9727–9732. https://doi.org/10.1073/pnas.0803644105

Minegishi, Y., Coustan-Smith, E., Rapalus, L., Ersoy, F., Campana, D., & Conley, M. E. (1999). Mutations in Igα (CD79a) result in a complete block in B-cell development. *Journal of Clinical Investigation*, *104*(8), 1115–1121. https://doi.org/10.1172/JCI7696

Minegishi, Y., Coustan-Smith, E., Wang, Y.-H., Cooper, M. D., Campana, D., & Conley, M. E. (1998). Mutations in the human λ5/14.1 gene result in B cell deficiency and agammaglobulinemia. *Journal of Experimental Medicine*, *187*(1), 71–77. https://doi.org/10.1084/jem.187.1.71

Minegishi, Y., Rohrer, J., Coustan-Smith, E., Lederman, H. M., Pappu, R., Campana, D., Chan, A. C., & Conley, M. E. (1999). An essential role for BLNK in human B cell development. *Science*, *286*(5446), 1954–1957. https://doi.org/10.1126/science.286.5446.1954

Minegishi, Y., Saito, M., Tsuchiya, S., Tsuge, I., Takada, H., Hara, T., Kawamura, N., Ariga, T., Pasic, S., Stojkovic, O., Metin, A., & Karasuyama, H. (2007). Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*, *448*(7157), 1058–1062. https://doi.org/10.1038/nature06096

Mody, G. M., Patel, N., Budhoo, A., & Dubula, T. (2014). Concomitant systemic lupus erythematosus and HIV: Case series and literature review. *Seminars in Arthritis and Rheumatism*, *44*(2), 186–194. https://doi.org/10.1016/j.semarthrit.2014.05.009

Moshous, D., Callebaut, I., de Chasseval, R., Corneo, B., Cavazzana-Calvo, M., Le Deist, F., Tezcan, I., Sanal, O., Bertrand, Y., Philippe, N., Fischer, A., & de Villartay, J.-P. (2001). Artemis, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immune deficiency. *Cell*, *105*(2), 177–186. https://doi.org/10.1016/S0092-8674(01)00309-9

Mouquet, H., Scheid, J. F., Zoller, M. J., Krogsgaard, M., Ott, R. G., Shukair, S., Artyomov, M. N., Pietzsch, J., Connors, M., Pereyra, F., Walker, B. D., Ho, D. D., Wilson, P. C., Seaman, M. S., Eisen, H. N., Chakraborty, A. K., Hope, T. J., Ravetch, J. V., Wardemann, H., & Nussenzweig, M. C. (2010). Polyreactivity increases the apparent affinity of anti-HIV antibodies by heteroligation. *Nature*, *467*(7315), 591–595. https://doi.org/10.1038/nature09385

Nagaoka, H., Muramatsu, M., Yamamura, N., Kinoshita, K., & Honjo, T. (2002). Activation-induced deaminase (AID)-directed hypermutation in the immunoglobulin Sμ region. *Journal of Experimental Medicine*, *195*(4), 529–534. https://doi.org/10.1084/jem.20012144

Ng, Y.-S., Wardemann, H., Chelnis, J., Cunningham-Rundles, C., & Meffre, E. (2004). Bruton's tyrosine kinase is essential for human B cell tolerance. *Journal of Experimental Medicine*, *200*(7), 927–934. https://doi.org/10.1084/jem.20040920

Nimmerjahn, F., & Ravetch, J. V. (2008). Fcγ receptors as regulators of immune responses. *Nature Reviews Immunology*, *8*(1), 34–47. https://doi.org/10.1038/nri2206

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., Romberg, N., Komarow, H., Aksentijevich, I., Kim, H. S., Ho, J., Cruse, G., Jung, M.-Y., Gilfillan, A. M., Metcalfe, D. D., … Milner, J. D. (2012). Cold urticaria, immunodeficiency, and autoimmunity related to *PLCG2* deletions. *New England Journal of Medicine*, *366*(4), 330–338. https://doi.org/10.1056/NEJMoa1102140

Pai, S.-Y., Logan, B. R., Griffith, L. M., Buckley, R. H., Parrott, R. E., Dvorak, C. C., Kapoor, N., Hanson, I. C., Filipovich, A. H., Jyonouchi, S., Sullivan, K. E., Small, T. N., Burroughs, L., Skoda-Smith, S., Haight, A. E., Grizzle, A., Pulsipher, M. A., Chan, K. W., Fuleihan, R. L., … O'Reilly, R. J. (2014). Transplantation outcomes for severe combined immunodeficiency, 2000–2009. *New England Journal of Medicine*, *371*(5), 434–446. https://doi.org/10.1056/NEJMoa1401177

Paun, A., Yau, C., Meshkibaf, S., Daigneault, M. C., Marandi, L., Mortin-Toth, S., Bar-Or, A., Allen-Vercoe, E., Poussier, P., & Danska, J. S. (2019). Association of HLA-dependent islet autoimmunity with systemic antibody responses to intestinal commensal bacteria in children. *Science Immunology*, *4*(32), eaau8125. https://doi.org/10.1126/sciimmunol.aau8125

Perkins, T., Rosenberg, J. M., Le Coz, C., Alaimo, J. T., Trofa, M., Mullegama, S. V., Antaya, R. J., Jyonouchi, S., Elsea, S. H., Utz, P. J., Meffre, E., & Romberg, N. (2017). Smith-Magenis syndrome patients often display antibody deficiency but not other immune pathologies. *The Journal of Allergy and Clinical Immunology: In Practice*, *5*(5), 1344–1350.e3. https://doi.org/10.1016/j.jaip.2017.01.028

Phan, T. G., Grigorova, I., Okada, T., & Cyster, J. G. (2007). Subcapsular encounter and complement-dependent transport of immune complexes by lymph node B cells. *Nature Immunology*, *8*(9), 992–1000. https://doi.org/10.1038/ni1494

Pianta, A., Arvikar, S. L., Strle, K., Drouin, E. E., Wang, Q., Costello, C. E., & Steere, A. C. (2017). Two rheumatoid arthritis-specific autoantigens correlate microbial immunity with autoimmune responses in joints. *Journal of Clinical Investigation*, *127*(8), 2946–2956. https://doi.org/10.1172/JCI93450

Potter, K. N., Hobby, P., Klijn, S., Stevenson, F. K., & Sutton, B. J. (2002). Evidence for involvement of a hydrophobic patch in framework region 1 of human V4-34-encoded Igs in recognition of the red blood cell I antigen. *The Journal of Immunology*, *169*(7), 3777–3782. https://doi.org/10.4049/jimmunol.169.7.3777

Prak, E. L., & Weigert, M. (1995). Light chain replacement: A new model for antibody gene rearrangement. *Journal of Experimental Medicine*, *182*(2), 541–548. https://doi.org/10.1084/jem.182.2.541

Qi, H., Egen, J. G., Huang, A. Y. C., & Germain, R. N. (2006). Extrafollicular activation of lymph node B cells by antigen-bearing dendritic cells. *Science*, *312*(5780), 1672–1676. https://doi.org/10.1126/science.1125703

Raffin, C., Vo, L. T., & Bluestone, J. A. (2020). Treg cell-based therapies: Challenges and perspectives. *Nature Reviews Immunology*, *20*(3), 158–172. https://doi.org/10.1038/s41577-019-0232-6

Reed, J. H., Jackson, J., Christ, D., & Goodnow, C. C. (2016). Clonal redemption of autoantibodies by somatic hypermutation away from self-reactivity during human immunization. *The Journal of Experimental Medicine*, *213*(7), 1255–1265. https://doi.org/10.1084/jem.20151978

Revy, P., Muto, T., Levy, Y., Geissmann, F., Plebani, A., Sanal, O., Catalan, N., Forveille, M., Dufourcq-Lagelouse, R., Gennery, A., Tezcan, I., Ersoy, F., Kayserili, H., Ugazio, A. G., Brousse, N., Muramatsu, M., Notarangelo, L. D., Kinoshita, K., Honjo, T., … Durandy, A. (2000). Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the hyper-IgM syndrome (HIGM2). *Cell*, *102*(5), 565–575. https://doi.org/10.1016/S0092-8674(00)00079-9

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., Vohra, H., Zhang, Y., Nowosad, C. R., Schiepers, A., Corcoran, L. M., Toellner, K.-M., Polo, J. M., Meyer-Hermann, M., Victora, G. D., & Vinuesa, C. G. (2019). Class-switch recombination occurs infrequently in germinal centers. *Immunity*, *51*(2), 337–350.e7. https://doi.org/10.1016/j.immuni.2019.07.001

Romberg, N., Chamberlain, N., Saadoun, D., Gentile, M., Kinnunen, T., Ng, Y. S., Virdee, M., Menard, L., Cantaert, T., Morbach, H., Rachid, R., Martinez-Pomar, N., Matamoros, N., Geha, R., Grimbacher, B., Cerutti, A., Cunningham-Rundles, C., & Meffre, E. (2013). CVID-associated TACI mutations affect autoreactive B cell selection and activation. *The Journal of Clinical Investigation*, *123*(10), 4283–4293. https://doi.org/10.1172/JCI69854

Romberg, N., & Lawrence, M. G. (2019). Birds of a feather: Common variable immune deficiencies. *Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology*, *123*(5), 461–467. https://doi.org/10.1016/j.anai.2019.07.027

Romberg, N., Le Coz, C., Glauzy, S., Schickel, J.-N., Trofa, M., Nolan, B. E., Paessler, M., Xu, M. L., Lambert, M. P., Lakhani, S. A., Khokha, M. K., Jyonouchi, S., Heimall, J., Takach, P., Maglione, P. J., Catanzaro, J., Hsu, F. I., Sullivan, K. E., Cunningham-Rundles, C., & Meffre, E. (2019). Patients with common variable immunodeficiency with autoimmune cytopenias exhibit hyperplastic yet inefficient germinal center responses. *The Journal of Allergy and Clinical Immunology*, *143*(1), 258–265. https://doi.org/10.1016/j.jaci.2018.06.012

Romberg, N., Virdee, M., Chamberlain, N., Oe, T., Schickel, J.-N., Perkins, T., Cantaert, T., Rachid, R., Rosengren, S., Palazzo, R., Geha, R., Cunningham-Rundles, C., & Meffre, E. (2015). TNF receptor superfamily member 13b (TNFRSF13B) hemizygosity reveals transmembrane activator and CAML interactor haploinsufficiency at later stages of B-cell development. *The Journal of Allergy and Clinical Immunology*, *136*(5), 1315–1325. https://doi.org/10.1016/j.jaci.2015.05.012

Rush, J. S., Liu, M., Odegard, V. H., Unniraman, S., & Schatz, D. G. (2005). Expression of activation-induced cytidine deaminase is regulated by cell division, providing a mechanistic basis for division-linked class switch recombination. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(37), 13242–13247. https://doi.org/10.1073/pnas.0502779102

Sabouri, Z., Schofield, P., Horikawa, K., Spierings, E., Kipling, D., Randall, K. L., Langley, D., Roome, B., Vazquez-Lombardi, R., Rouet, R., Hermes, J., Chan, T. D., Brink, R., Dunn-Walters, D. K., Christ, D., & Goodnow, C. C. (2014). Redemption of autoantibodies on anergic B cells by variable-region glycosylation and mutation away from self-reactivity. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(25), E2567–E2575. https://doi.org/10.1073/pnas.1406974111

Salzer, E., Kansu, A., Sic, H., Májek, P., Ikincioğullari, A., Dogu, F. E., Prengemann, N. K., Santos-Valente, E., Pickl, W. F., Bilic, I., Ban, S. A., Kuloğlu, Z., Demir, A. M., Ensari, A., Colinge, J., Rizzi, M., Eibel, H., & Boztug, K. (2014). Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. *The Journal of Allergy and Clinical Immunology*, *133*(6), 1651–1659.e12. https://doi.org/10.1016/j.jaci.2014.02.034

Samuels, J., Ng, Y.-S., Coupillaud, C., Paget, D., & Meffre, E. (2005). Impaired early B cell tolerance in patients with rheumatoid arthritis. *Journal of Experimental Medicine*, *201*(10), 1659–1667. https://doi.org/10.1084/jem.20042321

Sauer, A. V., Morbach, H., Brigida, I., Ng, Y.-S., Aiuti, A., & Meffre, E. (2012). Defective B cell tolerance in adenosine deaminase deficiency is corrected by gene therapy. *Journal of Clinical Investigation*, *122*(6), 2141–2152. https://doi.org/10.1172/JCI61788

Sawada, A., Takihara, Y., Kim, J. Y., Matsuda-Hashii, Y., Tokimasa, S., Fujisaki, H., Kubota, K., Endo, H., Onodera, T., Ohta, H., Ozono, K., & Hara, J. (2003). A congenital mutation of the novel gene LRRC8 causes agammaglobulinemia in humans. *Journal of Clinical Investigation*, *112*(11), 1707–1713. https://doi.org/10.1172/JCI18937

Schickel, J.-N., Kuhny, M., Baldo, A., Bannock, J. M., Massad, C., Wang, H., Katz, N., Oe, T., Menard, L., Soulas-Sprauel, P., Strowig, T., Flavell, R., & Meffre, E. (2016). PTPN22 inhibition resets defective human central B cell tolerance. *Science Immunology*, *1*(1), aaf7153. https://doi.org/10.1126/sciimmunol.aaf7153

Schwarz, K., Gauss, G. H., Ludwig, L., Pannicke, U., Li, Z., Lindner, D., Friedrich, W., Seger, R. A., Hansen-Hagge, T. E., Desiderio, S., Lieber, M. R., & Bartram, C. R. (1996). RAG mutations in human B cell-negative SCID. *Science*, *274*(5284), 97–99. https://doi.org/10.1126/science.274.5284.97

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O'Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., … Sandrock, A. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*, *537*(7618), 50–56. https://doi.org/10.1038/nature19323

Sng, J., Ayoglu, B., Chen, J. W., Schickel, J.-N., Ferre, E. M. N., Glauzy, S., Romberg, N., Hoenig, M., Cunningham-Rundles, C., Utz, P. J., Lionakis, M. S., & Meffre, E. (2019). AIRE expression controls the peripheral selection of autoreactive B cells. *Science Immunology*, *4*(34), eaav6778. https://doi.org/10.1126/sciimmunol.aav6778

Su, C., Johnson, M. E., Torres, A., Thomas, R. M., Manduchi, E., Sharma, P., Mehra, P., Le Coz, C., Leonard, M. E., Lu, S., Hodge, K. M., Chesi, A., Pippin, J., Romberg, N., Grant, S. F. A., & Wells, A. D. (2020). Mapping effector genes at lupus GWAS loci using promoter capture-C in follicular helper T cells. *Nature Communications*, *11*(1), 3294. https://doi.org/10.1038/s41467-020-17089-5

Sun, D., Heimall, J. R., Greenhawt, M. J., Bunin, N. J., Shaker, M. S., & Romberg, N. (2021). Cost utility of lifelong immunoglobulin replacement therapy vs hematopoietic stem cell transplant to treat agammaglobulinemia. *JAMA Pediatrics*, *176*, 176–184. https://doi.org/10.1001/jamapediatrics.2021.4583

Swan, D. J., Aschenbrenner, D., Lamb, C. A., Chakraborty, K., Clark, J., Pandey, S., Engelhardt, K. R., Chen, R., Cavounidis, A., Ding, Y., Krasnogor, N., Carey, C. D., Acres, M., Needham, S., Cant, A. J., Arkwright, P. D., Chandra, A., Okkenhaug, K., Uhlig, H. H., & Hambleton, S. (2019). Immunodeficiency, autoimmune thrombocytopenia and enterocolitis caused by autosomal recessive deficiency of *PIK3CD*-encoded phosphoinositide 3-kinase δ. *Haematologica*, *104*(10), e483–e486. https://doi.org/10.3324/haematol.2018.208397

Thiel, J., Kimmig, L., Salzer, U., Grudzien, M., Lebrecht, D., Hagena, T., Draeger, R., Völxen, N., Bergbreiter, A., Jennings, S., Gutenberger, S., Aichem, A., Illges, H., Hannan, J. P., Kienzler, A.-K., Rizzi, M., Eibel, H., Peter, H.-H., Warnatz, K., … Schlesier, M. (2012). Genetic CD21 deficiency is associated with hypogammaglobulinemia. *Journal of Allergy and Clinical Immunology*, *129*(3), 801–810.e6. https://doi.org/10.1016/j.jaci.2011.09.027

Thorburn, A. N., Macia, L., & Mackay, C. R. (2014). Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity*, *40*(6), 833–842. https://doi.org/10.1016/j.immuni.2014.05.014

Todo, S., Yamashita, K., Goto, R., Zaitsu, M., Nagatsu, A., Oura, T., Watanabe, M., Aoyagi, T., Suzuki, T., Shimamura, T., Kamiyama, T., Sato, N., Sugita, J., Hatanaka, K., Bashuda, H., Habu, S., Demetris, A. J., & Okumura, K. (2016). A pilot study of operational tolerance with a regulatory T-cell-based cell therapy in living donor liver transplantation. *Hepatology*, *64*(2), 632–643. https://doi.org/10.1002/hep.28459

Tonegawa, S., Maxam, A. M., Tizard, R., Bernard, O., & Gilbert, W. (1978). Sequence of a mouse germ-line gene for a variable region of an immunoglobulin light chain. *Proceedings of the National Academy of Sciences of the United States of America*, *75*(3), 1485–1489. https://doi.org/10.1073/pnas.75.3.1485

Trzonkowski, P., Bieniaszewska, M., Juścińska, J., Dobyszuk, A., Krzystyniak, A., Marek, N., Myśliwska, J., & Hellmann, A. (2009). First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127− T regulatory cells. *Clinical Immunology*, *133*(1), 22–26. https://doi.org/10.1016/j.clim.2009.06.001

van der Burg, M., IJspeert, H., Verkaik, N. S., Turul, T., Wiegant, W. W., Morotomi-Yano, K., Mari, P.-O., Tezcan, I., Chen, D. J., Zdzienicka, M. Z., van Dongen, J. J. M., & van Gent, D. C. (2008). A DNA-PKcs mutation in a radiosensitive T–B– SCID patient inhibits Artemis activation and nonhomologous end-joining. *Journal of Clinical Investigation*, *119*, 91–98. https://doi.org/10.1172/JCI37141

van der Meer, J. W., Weening, R. S., Schellekens, P. T., van Munster, I. P., & Nagengast, F. M. (1993). Colorectal cancer in patients with X-linked agammaglobulinaemia. *Lancet (London, England)*, *341*(8858), 1439–1440. https://doi.org/10.1016/0140-6736(93)90883-i

van Zelm, M. C., Reisli, I., van der Burg, M., Castaño, D., van Noesel, C. J. M., van Tol, M. J. D., Woellner, C., Grimbacher, B., Patiño, P. J., van Dongen, J. J. M., & Franco, J. L. (2006). An antibody-deficiency syndrome due to mutations in the *CD19* gene. *New England Journal of Medicine*, *354*(18), 1901–1912. https://doi.org/10.1056/NEJMoa051568

Victora, G. D., & Nussenzweig, M. C. (2012). Germinal centers. *Annual Review of Immunology*, *30*, 429–457. https://doi.org/10.1146/annurev-immunol-020711-075032

Victora, G. D., Schwickert, T. A., Fooksman, D. R., Kamphorst, A. O., Meyer-Hermann, M., Dustin, M. L., & Nussenzweig, M. C. (2010). Germinal center dynamics revealed by multiphoton microscopy with a photoactivatable fluorescent reporter. *Cell*, *143*(4), 592–605. https://doi.org/10.1016/j.cell.2010.10.032

Vijayanand, P., Seumois, G., Simpson, L. J., Abdul-Wajid, S., Baumjohann, D., Panduro, M., Huang, X., Interlandi, J., Djuretic, I. M., Brown, D. R., Sharpe, A. H., Rao, A., & Ansel, K. M. (2012). Interleukin-4 production by follicular helper T cells requires the conserved Il4 enhancer hypersensitivity site V. *Immunity*, *36*(2), 175–187. https://doi.org/10.1016/j.immuni.2011.12.014

Wardemann, H., Yurasov, S., Schaefer, A., Young, J. W., Meffre, E., & Nussenzweig, M. C. (2003). Predominant autoantibody production by early human B cell precursors. *Science*, *301*(5638), 1374–1377. https://doi.org/10.1126/science.1086907

Weigert, M., Perry, R., Kelley, D., Hunkapiller, T., Schilling, J., & Hood, L. (1980). The joining of V and J gene segments creates antibody diversity. *Nature*, *283*(5746), 497–499. https://doi.org/10.1038/283497a0

Wellmann, U., Letz, M., Herrmann, M., Angermuller, S., Kalden, J. R., & Winkler, T. H. (2005). The evolution of human anti-double-stranded DNA autoantibodies. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(26), 9258–9263. https://doi.org/10.1073/pnas.0500132102

Winkelstein, J. A., Marino, M. C., Lederman, H. M., Jones, S. M., Sullivan, K., Burks, A. W., Conley, M. E., Cunningham-Rundles, C., & Ochs, H. D. (2006). X-linked agammaglobulinemia: Report on a United States registry of 201 patients. *Medicine*, *85*(4), 193–202. https://doi.org/10.1097/01.md.0000229482.27398.ad

Yang, Z., Wu, C.-A. M., Targ, S., & Allen, C. D. C. (2020). IL-21 is a broad negative regulator of IgE class switch recombination in mouse and human B cells. *The Journal of Experimental Medicine*, *217*(5), e20190472. https://doi.org/10.1084/jem.20190472

Yel, L., Minegishi, Y., Coustan-Smith, E., Buckley, R. H., Trübel, H., Pachman, L. M., Kitchingman, G. R., Campana, D., Rohrer, J., & Conley, M. E. (1996). Mutations in the mu heavy-chain gene in patients with agammaglobulinemia. *New England Journal of Medicine*, *335*(20), 1486–1493. https://doi.org/10.1056/NEJM199611143352003

Yurasov, S., Wardemann, H., Hammersen, J., Tsuiji, M., Meffre, E., Pascual, V., & Nussenzweig, M. C. (2005). Defective B cell tolerance checkpoints in systemic lupus erythematosus. *Journal of Experimental Medicine*, *201*(5), 703–711. https://doi.org/10.1084/jem.20042251

Zhang, Y., Meyer-Hermann, M., George, L. A., Figge, M. T., Khan, M., Goodall, M., Young, S. P., Reynolds, A., Falciani, F., Waisman, A., Notley, C. A., Ehrenstein, M. R., Kosco-Vilbois, M., & Toellner, K.-M. (2013). Germinal center B cells govern their own fate via antibody feedback. *The Journal of Experimental Medicine*, *210*(3), 457–464. https://doi.org/10.1084/jem.20120150

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