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The Antigen Receptor as a Driver of B-Cell Lymphoma Development and Evolution

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Abstract

The expression of a functional antigen receptor is necessary for cell survival of normal B lymphocytes and most B-cell neoplasms alike. When the genetic modifications of the B-cell receptor locus fail to produce a functional antigen receptor or result in deleterious mutations of a previously expressed receptor, the affected B cell will undergo apoptosis. The three physiological mechanisms that generate the B-cell receptor, VDJ recombination, somatic hypermutation, and class switch recombination, can induce double-strand DNA breaks and can specifically contribute to lymphomagenesis. On the other hand, the B-cell receptor activation and signaling pathways, which provide strong survival and proliferation signals to normal B cells, can support the growth and evolution of malignant lymphocytes. As a result, an otherwise structurally normal B-cell receptor can behave, from the functional perspective, as a true oncogene. In this chapter, we provide an in-depth discussion of the most recently discovered recurrent mechanisms involving the B-cell receptor in lymphoma pathogenesis. The discussion is structured around two major topics: (1) the genetic mechanisms that create a functional antigen receptor and their errors leading to oncogenic events, and (2) the pathogenic activation of the B-cell receptor signaling cascade. Finally, we will briefly comment on novel emerging therapies targeting the B-cell receptor at different levels.

Keywords: lymphoma, B-cell receptor, activation-induced deaminase (AID), somatic hypermutation, class switch recombination, lymphomagenesis, pathogenesis, oncogenesis

1. Introduction

The immune system has evolved with the primary purpose of eliminating or at least controlling invading pathogens. In contrast to innate immunity, the adaptive immune system relies

for this task on recognition of the pathogen through antigen-specific receptors. In the case of B cells, these receptors are membrane-bound or soluble immunoglobulins that engage soluble or surface-bound antigens.

Hallmarks of the adaptive immune system related to the B-cell receptor are: (1) continuous presence of an extremely broad repertoire of antigen receptors; (2) rapid activation and expansion of cells whose particular receptors recognize a given antigen, and (3) maintenance of a memory of every immune response that has taken place in order to react even more efficaciously upon re-exposure to the evoking antigen [1].

The immune system has, therefore, developed unique molecular mechanisms to generate virtually unlimited numbers of antigen receptors with different specificities. These mechanisms are V, D, and J recombination of immunoglobulin gene segments, class switch recombination, and somatic hypermutation (SHM). Since these events involve genome editing, they entail intrinsic oncogenic risk [2].

The expression of a functional B-cell receptor (BCR) on the cell surface after successful completion of VDJ recombination distinguishes precursor from mature B cells, and correspondingly precursor cell from mature B-cell lymphomas.

Upon antigen recognition, B cells can undergo antibody affinity maturation through SHM, a genetic mechanism that permits antibody diversification. SHM is mediated by activation-induced deaminase (AID), an enzyme physiologically expressed in the germinal center. AID converts C:G base pairs in immunoglobulin genes into U:G mismatches. Repair of these mutations creates almost random point mutations [2–4].

Signals generated by the BCR govern the development, function, and survival of normal B cells. However, its ability to efficiently activate anti-apoptotic and proliferation pathways can be adopted by malignant B-cell, and even become essential for their survival [5].

In the current chapter, the discussion is structured around two major pathogenic mechanisms: (1) genetic mechanisms that create a functional antigen receptor and their errors leading to oncogenic events, and (2) pathogenic activation of the B-cell receptor signaling cascade.

2. Major B-cell receptor–related lymphomagenic mechanisms

2.1. Genetic mechanisms that create a functional antigen receptor and their errors leading to oncogenic events

Three unique genetic mechanisms operate sequentially in various stages of B-cell development to generate a functional antigen receptor: VDJ recombination, class switch recombination (CSR), and somatic hypermutation (SHM). Errors during these events may lead to lymphomagenesis.

2.1.1. V(D)J recombination

In the germ line DNA configuration, the antigen receptor gene loci contain discontinuous, non-functional V, D, and J segments. Committed B lymphocyte precursor cells create functional immunoglobulin heavy and light chain genes through VDJ recombination and VJ recombination, respectively [6]. The V(D)J recombination starts at the pro-B cell stage by activation of recombination-activating genes (RAG) 1 and 2. The first step is the DJ joining in the IgH locus followed by the joining of V segments to DJ, resulting in the rearrangement of the μ-chain (μH). The μH paired with a surrogate light chain (SLC) is expressed on the cell membrane as a part of a structure known as pre–B-cell receptor.

In pre-B cells, RAG1/2 expression results in the recombination of the kappa light chain. A successful rearrangement will induce RAG downregulation; otherwise, RAG will start a second rearrangement of the light chain [7].

During V(D)J recombination, a successful rearrangement of the heavy chain will suppress the rearrangement of the second allele, a process known as allelic exclusion. In the case of Ig-Kappa chains, if neither of both alleles generates a productive receptor the process will continue with the rearrangement of the Ig-Lambda locus [8].

V(D)J recombination can be divided into two phases: the cleavage phase and the joining phase. In the cleavage phase, RAG1/2 creates double-strand breaks (DSB) at recombination signal sequences (RSS), which are located at the start of each antigen receptor gene segment. RSS is composed by a heptamer, a spacer sequence (12–23 nucleotides) and a nonamer sequence. RAG acts on RSS by introducing a nick between the coding sequence and the heptamer [9]. At each of the two remaining ends, called the coding ends, the two strands of DNA are joined to form a hairpin structure. The Artemis nuclease nicks the hairpin, whose ends are then joined by non-homologous end joining (NHEJ) [10]. The recombination process activates the DNA damage response (DDR), a system that detects any signal of DNA damage. The action of DDR may result in DNA repair or induction of apoptosis [11].

2.1.2. Class switch recombination

Class switch recombination (CSR) is a process that replaces the default Cμ exons with exons from a downstream constant chain (Cα, Cε, or Cγ), resulting in a change from IgM expressed by naïve B cells to expression of one of the downstream isotypes IgA, IgG, IgE.

CSR occurs by intrachromosomal deletion and recombination events between two different switch (S) regions localized upstream of each constant region in the IgH locus. S regions are GC-rich with a high frequency of the WGCW (A/T-G-G-A/T) motif, which is a target of activation-induced deaminase (AID) activity. CSR has two phases: (1) the break at the donor and acceptor S regions, and (2) the ligation process between distal breaks [12].

The recombination is initiated by AID, an enzyme that deaminates cytosines into uracil at the donor and acceptor S regions. Subsequently, the base excision repair (BER) pathway creates a single strand break (SSB) that is processed to double strand breaks (DSB) by mismatch repair

(MMR). After the formation of DSBs in the S regions (donor and acceptor), these S regions are recombined by non-homologous end joining (NHEJ) [13].

During normal B-cell development, the DNA repair pathways (BER and MMR) reduce the effect of off-target AID activity. However, several external factors like cellular stress, hypoxia, and viral infections; or intrinsic factors such as alterations in repair pathways may change the outcome of AID-induced lesions [14].

2.1.3. V(D)J recombination, class switch recombination, and neoplastic transformation

One evident deviation of the normal V(D)J recombination and CSR processes is the possibility of rearrangements between segments belonging to different genes. In fact, reciprocal chromosomal translocations are the most common recurrent genetic anomalies in lymphoid malignancies and the newly formed junctions generated in most human lymphoid translocations have the canonical features of NHEJ [15].

One paradigmatic example is follicular (FL), a lymphoid neoplasm characterized by the t(14;18)(q32;q21) translocation that juxtaposes the anti-apoptotic proto-oncogene BCL2 to the immunoglobulin heavy chain locus [16]. The functional result of this translocation is constitutive transcriptional upregulation of BCL2. Although this translocation is considered the founding event in FL pathogenesis, t(14;18)-positive B cells can be detected in many healthy individuals [17]. Therefore, this genetic event alone seems insufficient to cause lymphoma.

The t(11;14)(q13;q32) translocation, a hallmark of mantle cell lymphoma (MCL), results in the overexpression of cyclin D1 and also appears to be a V(D)J-mediated translocation [18]. As in FL, the sole constitutive overexpression of this cell cycle regulator is insufficient to explain malignant transformation.

Whereas the t(14;18) or t(11;14) translocations result from a mistake during V(D)J recombination, some translocations involve the IgH class switch regions in a failed CSR event. Translocations at the IgH class switch regions seem to depend on AID activity and commonly involve c-MYC and BCL-6 [19]. BCL6 is the most commonly rearranged gene in activated B cell (ABC) diffuse large B-cell lymphoma (DLBCL) and c-MYC rearrangements can be observed in Burkitt lymphoma (BL) and DLBCL.

BCL6 is a proto-oncogene encoding a transcriptional repressor expressed during B cell differentiation in germinal centers. A block in the normal downregulation of BCL6, through its translocation with more than 20 possible partner genes, might favor differentiation arrest, continuous cell proliferation, survival, and genetic instability [20]. BCL6 also suppresses the activity of the tumor suppressor gene TP53, which allows BCL6-expressing cells to escape apoptosis [21].

The c-MYC gene at 8q24 is involved in three translocations observed in DLBCL, most commonly t(8;14) (q24;q32), and less often t(2;8) (p12;q24) and t(8;22) (q24;q11) [21]. In the t(8;14) (q24;q32) translocation, also observed in BL, the gene segments from the IgH locus are joined with various regions around and within the c-MYC proto-oncogene [22]. As a result, IgH regulatory elements are misplaced upstream, of the c-MYC proto-oncogene [23].

Four recurrent translocations, t(1;14)(p22;q32), t(3;14)(p14.1;q32), t(11;18)(q21;q21), and t(14;18)(q32;q21), have been described in marginal zone B-cell lymphomas of MALT type. The two latter translocations involve the MALT1 gene. These translocations seem to occur as a result of illegitimate V(D)J-mediated recombination [22, 24].

2.1.4. Somatic hypermutation (SHM)

Somatic hypermutation (SHM) is the biological underlying mechanism for the generation of the secondary antibody repertoire. AID is the single enzyme that is responsible for the initiation of this process [25].
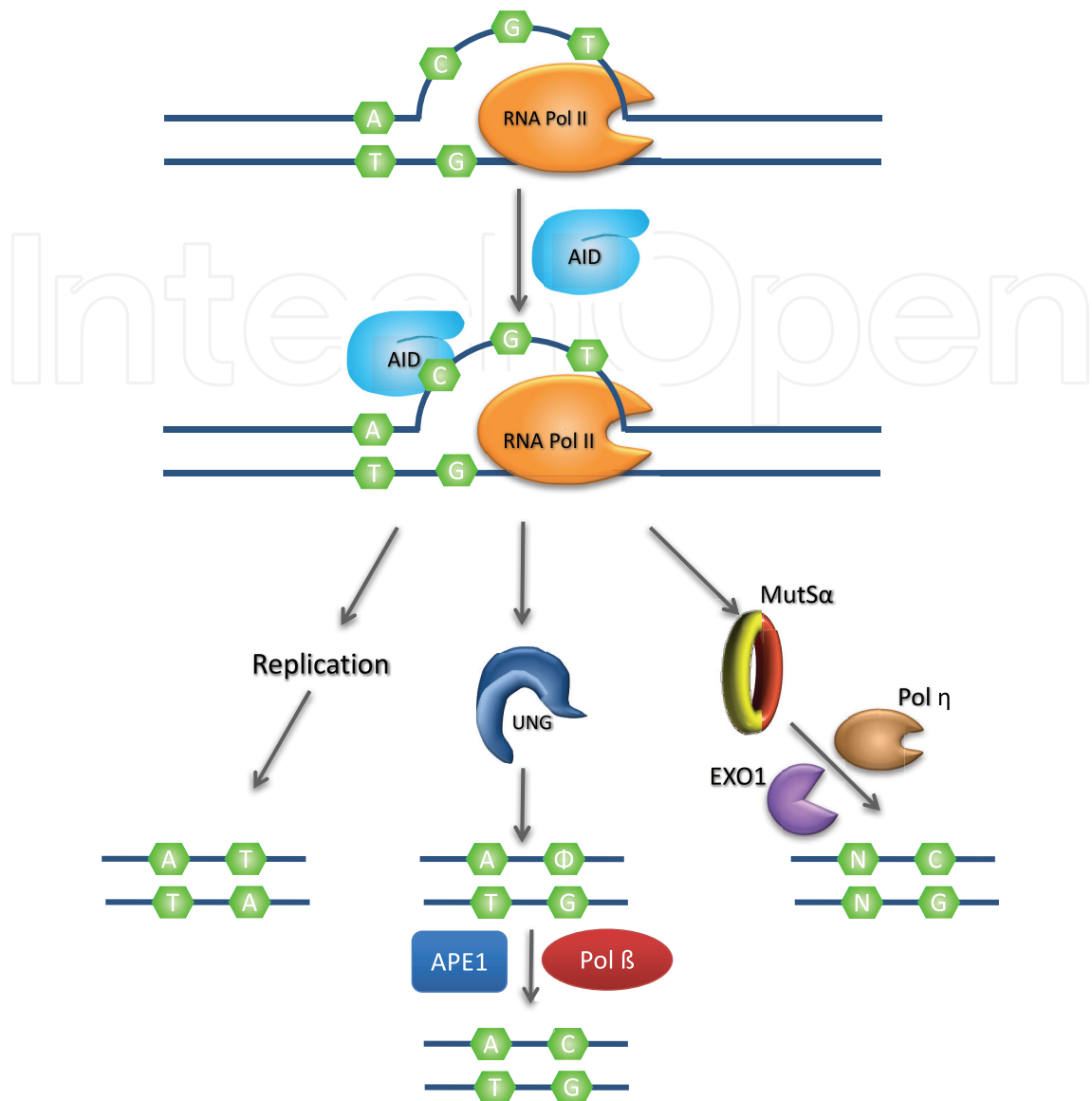
SHM is a post-rearrangement diversification process that introduces point mutations in the variable regions of the Ig loci, which can alter the antibody binding to its cognate antigen. AID acts enzymatically as a cytosine deaminase that converts cytosine to uracil. Uracil is mutagenic when paired with guanosine, this U:G mismatch triggers error-prone DNA repair in B cells. SHM results in a mutation rate of circa 1 mutation/1000 bp per cell generation. This mutation frequency is a million-fold higher than spontaneous mutation rate in somatic cells [26]. Highly selected antibodies with neutralizing activity against influenza virus can accumulate 30–40 mutations, and broadly neutralizing antibodies against HIV more than 100 mutations [27, 28].

AID acts on a single strand, thus its activity is probably generated during at transcription bubbles (**Figure 1**). Once AID produced deamination of dC to dU the error-prone processing begins. First AID-catalyzed uracils in the DNA are recognized by either the uracil-DNA glycosylase (UNG)—triggering the base excision repair (BER) pathway—or by the mismatch recognition heterodimer MutSα—initiating the mismatch repair (MMR) pathway. In BER, UNG binds to the U:G mispair and produces an abasic site, then this site is cleaved by the apurinic/apyrimidinic endonuclease (APE1), which removes the abasic site nucleotide and the DNA polymerase Polβ resynthesizes the DNA strand [29]. In the MMR pathway, the proteins MSH2 and MSH6 bind to the U:G mismatch and recruit DNA Polη, a low fidelity polymerase, that introduces error during nucleotide synthesis [30].

The processing of uracils by BER and MMR may result in different outcomes. The introduced uracils may (1) be replaced by another nucleotide, (2) expose DNA to further mutations in its vicinity like mutations at A:T pairs or (3) can be converted into DNA DSBs. The latter seems to be necessary for CSR.

Because of its mutagenic potential, SHM has multiple layers of regulation and competition between alternative pathways that define the level of SHM [31]. There is also increasing evidence that epigenetic factors, such as DNA methylation and post-translational histone modifications play major roles in regulating SHM [32]. Its implications in lymphoma development remain elusive.

When SHM affect off-target genes, it is referred to as aberrant SHM. Aberrant SHM can be mainly detected in FL, BL, DLBCL, and CLL [33–35]. This topic has been extensively reviewed elsewhere [36–39].

Figure 1. Molecular mechanism of somatic hypermutation (SHM). AID requires a single strand to initiate the SHM process. Transcription by RNA polymerase II (RNA Pol II) exposes the single-stranded DNA template for AID. AID deaminates a cytosine to create an uracil, which can then be processed by different pathways. Replication over the uracil results in C to T or G to A transition mutations. Processing by uracil DNA glycosylase (UNG) generates an abasic site (Φ) that is cleaved by the apurinic/apyrimidinic endonuclease (APE1), which removes this site and then Polβ resynthesizes the DNA. Recognition of the U-G mismatch by MutSα (represented by a torus shape) followed by the action of Exo1 and Polη spreads mutations (indicated as "N") to surrounding A-T nucleotides. UNG and Msh2/Msh6 can also act in the context of high fidelity base excision repair (BER) and mismatch repair (MMR) pathways, which results in error-free repair.

We have recently described that, in IgM expressing FL, the mutation load of the Ig genes can be described as a function of the AID expression level. In contrast, in FL cases that underwent class switch recombination (i.e., IgG expressing lymphomas) AID expression and SHM of immunoglobulin genes are dissociated [40, 41]. The distinctive patterns induced by SHM may also have implications for the clinical evolution of the disease [42].

AID expression is detected in a tumor subset in the peripheral blood of CLL patients [43, 44]. These cases display the dissociation between CSR and SHM, an observation that resembles our findings in FL. Our data also suggest that functional AID expression in CLL correlates with a distinctive genomic landscape and disease evolution [45].

Analysis of whole genome and whole exome sequencing data classified by the trinucleotide context of single nucleotide variants in so-called mutation signatures can help to elucidate underlying mutagenic mechanisms in tumor samples [46]. Our data indicate that the mutational landscape of both CLL and FL seems to be strongly shaped by AID activity. In FL, AID-induced mutations are mainly restricted to canonical AID hotspots and CpG methylation-dependent mutagenesis sites. In strong contrast, both canonical and non-canonical AID motifs seem to contribute to the mutational landscape of CLL [47].

SHM may not only contribute to lymphomagenesis by acting on oncogenes and proto-oncogenes, but also may provide adaptive advantages. As suggested by our data, BCR editing through SHM may allow FL cells to escape from immunosurveillance [48–50].
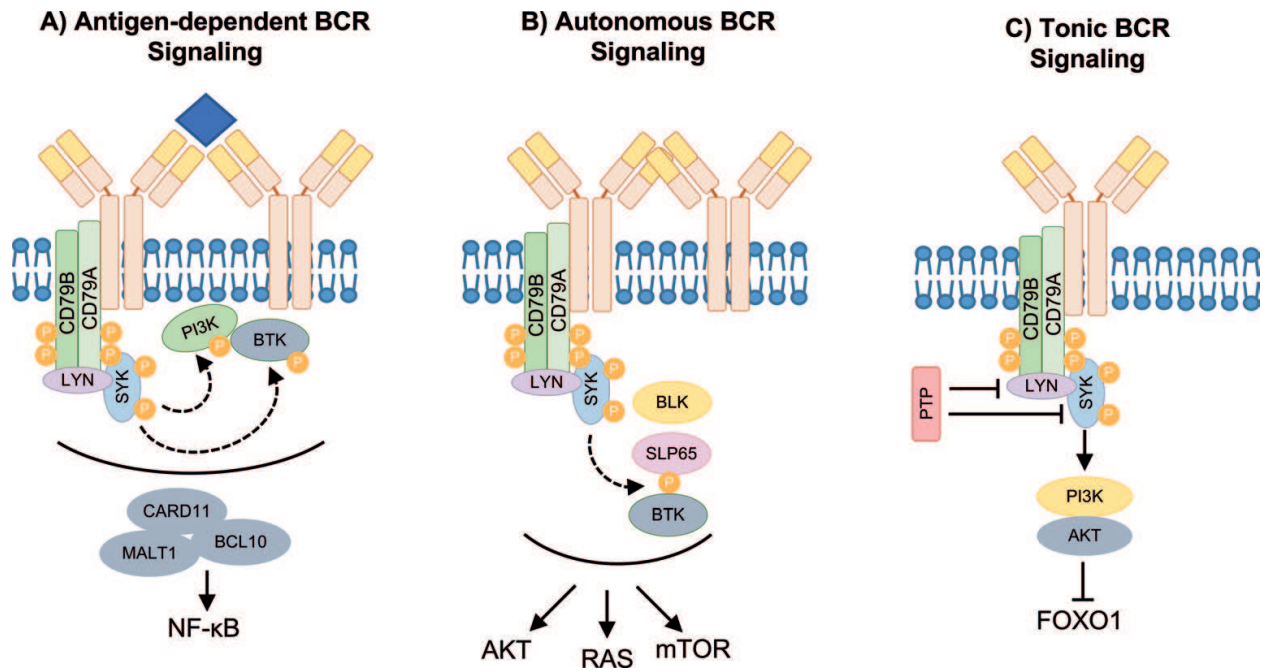
2.2. Pathogenic activation of the B-cell receptor signaling cascade

Antibody molecules, when expressed on the cell surface, constitute the binding moiety of a molecular complex known as B-cell antigen receptor (BCR). Signals from the BCR regulate the development and function of B cells. However, the ability of the BCR signaling pathway to induce cell survival and proliferation could be adopted and distorted by malignant cells.

The BCR immunoglobulin consists of a heavy chain and a light chain, whereas its precursor, the pre-BCR, consists of a heavy chain and a surrogate light chain. The transmembrane domain of the heavy chains anchors the BCR to the cell membrane, where each BCR molecule associates with the signaling subunit. The signaling subunit is constituted by a heterodimer of Igα (CD79A) and Igβ (CD79B) [51]. Within their cytoplasmic tails, Igα and Igβ harbor 2 conserved tyrosine residues as part of a 26 amino acid-long sequence, also referred to as an immunoreceptor tyrosine-based activation motif (ITAM) [52]. Phosphorylation of ITAM through kinases, such as Lck/Yes-related novel protein tyrosine kinase (LYN), B-lymphoid kinase (BLK), or spleen tyrosine kinase (SYK), marks the first step in signal transduction from the BCR to the nucleus [53]. SYK in conjunction with PI3K recruits Burton's tyrosine kinase (BTK). Upon activation of the BCR pathway, BTK binds to PIP3 and attaches to the plasma membrane [54]. These events contribute to BCR-induced calcium release, cell proliferation, and activation of the NF-κB pathway (**Figure 2A**) [55].

In pre-B cells, the BCR signaling cascade is activated through autonomous signaling, a mechanism that relies on the structural conformation of the pre-BCR which is constituted by a heavy chain and a surrogate light chain [56, 57]. While pre-B cells rely on autonomous BCR signaling, immature and mature B-cells receive two types of signals from their BCRs: the antigen-dependent, and the antigen-independent "tonic" signals. The antigen-dependent signal is generated by binding of an external antigen to the BCR and results in the clustering and

Figure 2. BCR signals generated in malignant and normal B cells. (A) Tonic signaling: random and transient disruptions in the equilibrium between positive regulators of BCR signaling, such as the CD79a/CD79b heterodimer, LYN and SYK, and negative regulators, such as the various phosphatases (PTP), could generate a tonic antigen-independent BCR signal characterized by increased activity of the PI3K/AKT pathway. (B) Aggregation of neighboring BCRs in polyreactive receptors initiates a cell-autonomous BCR signal in the absence of an external antigen. (C) The binding of the cognate antigen induces aggregation of neighboring BCRs that initiate the classical antigen-dependent BCR signal (see text for details).

activation of a signaling complex that transmits the signal inside the cell. In contrast, the tonic signal occurs in the absence of external ligands (**Figure 2**) [58, 59].

Current evidence indicates that all three, tonic, autonomous, as well as antigen-dependent BCR signaling, are used by different B-cell lymphoid neoplasms. Activation may occur through physiological mechanisms such as antigen interaction or by pathological mechanisms such as mutations in genes acting downstream the signaling cascade. The relative contribution of these types of signals varies across different B-cell neoplasms and is currently subject to debate.

2.2.1. Antigen-driven BCR activation and lymphomagenesis

The hypothesis that antigenic stimulation can contribute to the development of B-cell malignancies was proposed over half a century ago [60]. There is growing indirect and direct evidence suggesting that antigen recognition may have a role in the pathogenesis of chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), marginal zone lymphoma (MZL) of the spleen, and MZL of mucosa-associated lymphoid tissue (MALT)-type.

Indirect evidence for the role of antigen stimulation includes the association between certain lymphoma subtypes and specific infections and autoimmune diseases, as well as the identification of an antigen selection footprint in the BCR; i.e., a bias in gene usage and positive

selection of somatic mutations in the complementarity determining regions [40, 42, 50, 61, 62]. More direct evidence for the role of antigen stimulation and BCR activation in lymphomagenesis is based on the identification of BCR reactivity toward foreign or auto-antigens, and the induction of intracellular BCR signaling in primary lymphoma cells in response to specific antigens [63–65].

Although several bacterial and viral infections have been associated with the development different lymphoma types, direct demonstration of lymphoma development due to infectious agent-derived antigenic stimulation remains limited.

Helicobacter pylori infection is associated with gastric MZL of MALT-type. This association relies on epidemiological, biological, molecular, and clinical data [41, 66–70]. Indeed, since the initial evidence of the association between *H. pylori* infection with the development of gastric MALT lymphoma [67], *H. pylori* eradication has established as the first-line therapy for this lymphoma [71, 72]. It has been demonstrated that MALT lymphoma B cells exhibit polyreactive surface BCR immunoglobulins. Direct stimulation by specific alloantigens (including *H. pylori* sonicate) and autoantigens recognized by these surface antibodies leads to the proliferation of tumor cells [73]. *H. pylori* infection may also induce aberrant AID expression followed by accumulation of mutations in tumor-related genes, suggesting a link between BCR activation and AID expression [74]. Nevertheless, a direct link to the activation of the BCR signaling pathway remains elusive.

Chlamydia psittaci infection is associated with ocular adnexal extranodal marginal zone lymphomas (OAEMZLs) [75]. These neoplasms express a biased repertoire of mutated surface immunoglobulins suggesting, which suggests that antigen receptors have been subject to clonal selection. In OAEMZL patients, local monocytes and macrophages are the carriers of *Chlamydia psittaci*, and lymphomas seem to preferentially arise in organs primarily exposed to antigens [76].

Certain lymphomas, such as splenic marginal zone lymphoma (SMZL), are associated with *hepatitis C virus* (HCV) infection. Current evidence suggests that a subset of HCV-associated lymphomas originate from B cells that were initially activated by the HCV-E2 protein, suggesting that this subgroup of lymphomas arise as an expansion of HCV-reactive B cells [77]. Consistently, antiviral treatment results in complete responses in about 75% of HCV positive lymphoma patients, whereas no responses are seen in HCV negative patients [78]. Altogether, this data suggest that antigen-dependent BCR activation may be the driver of lymphomagenesis for some SMZL cases; and removal of the antigen can lead to clinical remission in these patients.

Several viral, bacterial, and fungal antigens may bind specific BCRs on chronic lymphocytic leukemia (CLL) cells [79–81]. Moreover, CLL cells in the lymph node contain increased levels of activated SYK and express genes upregulated in response to BCR activation [82]. In addition, the observation of a reversible down-modulation of surface IgM expression on CLL cells also supports the idea of chronic antigen stimulation [83].

In follicular lymphoma (FL), the BCR is characterized by abnormal N-linked glycosylation. The mannosylated variable regions of FL immunoglobulins bind to recombinant lectin

domains of the mannose receptor and dendritic-cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), which results in stimulation of FL cells [84]. It has also been demonstrated that V-region mannosylation conferred the ability of B cells to be activated by soluble bacterial lectins from common opportunistic pathogens such as *Pseudomonas aeruginosa* or *Burkholderia cenocepacia* while disrupting the initial receptor specificity for potential autoantigens [64].

The source of the antigen is not necessarily derived from an external pathogen as it has also been shown to derive from self-antigens. CLL BCRs can react with many different self-antigens, including antigens released by apoptotic cells [85, 86]. In addition, BCR derived from CLL patients can bind to a conserved epitope within the second framework region (FR2) of their own BCR [87]. About 26% of FL cases recognize autoantigens, and the interaction with certain self-antigens such as myoferlin can induce BCR-mediated signaling *in vitro* [65]. It has also been demonstrated that interaction of the BCR of ABC DLBCL with a self-antigen is essential for the survival of these lymphoma cells. This interaction may explain the microclusters observed in the plasma membrane of ABC DLBCL cells [5, 88].

2.2.2. Tonic B-cell receptor signaling and lymphomagenesis

The tonic B-cell receptor signaling (BCR) is thought to provide an antigen-independent constitutive baseline signal essential for B cell survival and development [58, 89]. Although the detailed molecular mechanisms regulating tonic signaling remain to be defined, current evidence highlights the central role of the SYK tyrosine kinase and the balance between BCR-associated SYK activation and protein tyrosine phosphatase (PTP)-mediated SYK inhibition [53, 90]. The tonic signaling transmitted via SYK appears to activate the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway [91]. The inhibition of the tonic BCR signal results in increased activation of FOXO1 and increased expression of its target genes, including the pro-apoptotic BCL2 family member, BCL2L11, and the cell-cycle inhibitor p27 [92].

Evidence about the use of tonic antigen-independent type of BCR signaling by malignant B cells is reported for Burkitt lymphoma (BL) and germinal center B diffuse large B-cell lymphoma (GCB-DLBCL) [93, 94].

In BL, PI3K signals promote the survival and proliferation of BL cells [95]. One study demonstrated by quantitative phosphoproteomics, in which phosphorylation events in tonic BCR signaling differ from those induced by BCR engagement in BL cells [96].

In DLBCL, BCR signaling differs between the germinal center B-cell (GCB) subtype, which is insensitive to Bruton's tyrosine kinase inhibition by ibrutinib, and the activated B-cell (ABC) subtype [97]. As recently reported, the replacement of antigen-binding regions of the BCR has no effect on BCR signaling in GCB-DLBCL cell lines, which supports the hypothesis of the use of tonic BCR signaling by this DLBCL subtype [94]. Unlike antigen-driven BCR signaling, tonic BCR signaling requires specific phosphorylation of CD79A. This finding provides a rationale for the development of novel molecular targeted drugs for the treatment of DLBCL [94].

2.2.3. Autonomous signaling and lymphomagenesis

Autonomous antigen-independent, BCR signaling is a survival mechanism characteristic of the pre–B-cell receptor [57, 98]. However, immature and mature B cells with BCRs, that recognize multiple self-antigens, may also induce autonomous signaling and selective expansion of B cell in a manner comparable to the pre-BCR [56]. This functional similarity between autoreactive BCRs and the pre-BCR suggests that recognition of self-antigens might not only play a role in the positive selection of early B cells, but also could contribute to lymphomagenesis [87, 99–101].

Autonomous signaling has been proposed as a novel oncogenic mechanism in chronic lymphocytic leukemia (CLL) and diffuses large B-cell lymphoma (DLBCL) [87, 100, 101]. BCR, derived from both mutated and unmutated CLL cases, expressed in a cellular system designed to measure BCR signaling cascade activation, show signaling properties that are equivalent to those of the pre-BCR [87]. This striking signaling property is dependent on the antigen-binding site of the clonal BCR and an internal motif in framework region 2, a part of the structural BCR backbone [102].

The gene expression profile of activated B-cell (ABC) type of DLBCL resembles that of mature B cells upon stimulation via their B-cell receptor (BCR). In up to 30% of ABC DLBCL cases, this signature can be explained by gain-of-function mutations in CD79A, CD79B, or CARD11 [103]. However, in patients without CARD11 mutations activation of the BCR may occur through autonomous signaling. We have recently demonstrated the presence of autonomous BCR activity in 72% of non-GCB DLBCL, including primary mediastinal DLBCL [100, 101]. This finding may provide a complementary or alternative explanation to the characteristic gene expression signature of ABC DLBCL.

These findings in CLL and DLBCL support the concept of the BCR acting as a true oncogene, despite being structurally normal and solely characterized by this autonomous signaling property.

2.2.4. Mutations in the BCR signaling cascade

In addition to the natural activation, BCR signaling can be induced by acquired mutations.

Different ABC DLBCL cases carry diverse activating mutations in the BCR pathway (**Table 1**). Mutations of a critical tyrosine residue in the ITAM of CD79B increase the signaling response by interfering with activation of LYN. In this subset of ABC DLBCL cells, PI3K and BTK signaling remain essential for NF-κB activation [104]. About 10% of ABC DBCL cases show activating mutations of CARD11, a key protein that connects BCR activation to NF-κB signaling. This mutation is sufficient to intrinsically activate survival signaling in the malignant B cells and obviates the need for upstream BCR signaling [103]. Loss of function mutations in the tumor suppressor A20 contributes to NF-κB pro-survival signaling have also been described in ABC DLBCL and CLL cases [105, 106].

	Errors in VDJ recombination	Errors in class switch recombination	Resulting event
Mantle cell lymphoma	t(11;14)(q13;q32)		Cyclin D1 overexpression
Follicular lymphoma	t(14;18)(q32;q21)		BCL2 overexpression
Marginal zone lymphoma of MALT type	t(11;18)(q21;q21), t(14;18) (q32;q21)		MALT1 dysregulation
GCB-diffuse large B-cell lymphoma		t(8;14) (q24;q32), t(2;8) (p12;q24), t(8;22) (q24;q11)	c-MYC overexpression
ABC-diffuse large B-cell lymphoma		BCL6 rearrangement—multiple partner genes	BCL6 dysregulation
Burkitt lymphoma		t(8;14)(q24;q32)	c-MYC overexpression

Table 1. Recurrent translocations and their link to V(D)J recombination or class switch recombination in mature B-cell neoplasms.

Although germinal center B (GCB) DLBCL seems independent of BCR signaling, still may require intrinsic activation of the PI3K pathway (**Table 1**). Some germinal center B (GCB) DLBCLs display activating mutations in the PIK3CA domain of PI3K [107].

Another example of a transition from a dependence on extrinsic BCR activation to intrinsic activation has been described in MALT lymphomas (**Table 2**). In advanced cases, the t(11;18) chromosomal results in a fusion transcript of API2-MALT1 and the t(1;14) leads to overexpression of BCL10 under the control of the Ig heavy chain locus. Consequently, MALT1/BCL10/ CARD11 complex activates the classical NF-κB pathway (**Figure 2A**) [108].

Burkitt lymphoma (BL) seems dependent upon tonic BCR survival signaling through PI3K but not upon the NF-κB pathway. The hallmark of BL is a translocation of MYC to the Ig heavy chain locus. However, MYC has strong pro-apoptotic effects and requires activation of pro-survival signaling through the PI3K pathway. In BL activation of PI3K resembles the tonic signaling in normal resting B cells [95, 96]. Consistently, BL cells are sensitive to genetic knockdown of CD79A or SYK and pharmacologic inhibition of PI3K, however, are not affected by knockdown of BTK [95].

In follicular lymphoma, at least half of the patients show evidence of mutations in the interconnected BCR and CXCR4 signaling pathways such as mutations in CD79B, CARD11, CXCR4, SYK, BTK, and HVCN1 [3, 109]. Considering the unique characteristics of the BCR in this lymphoma type, such as high hypermutation rates, distinctive selection patterns, mannosylation of the antigen binding site and autoantigen binding, the understanding of the precise interplay between the tumor dependence on a functional BCR and the presence of this recurrent mutation requires further investigation [3, 40, 42, 48].

In CLL there is evidence for mutations in BTK and PLCγ2 that may confer resistance to BTK inhibition [110]. Despite the general consensus on the absence of somatic mutation on both CD79A and CD79B in CLL, one study has reported mutations in CD79B [111].

	Antigen-dependent BCR signaling	Tonic BCR signaling	Autonomous BCR signaling	Recurrent mutations in the signaling pathway
Chronic lymphocytic leukemia	++	+	+++	BTK, PLCγ2
Follicular lymphoma	+	−	−	CD79B, CARD11, CXCR4, SYK, BTK
Marginal zone lymphoma of MALT type	++	−	−	MALT1
GCB-diffuse large B-cell lymphoma	−	++	−	PI3K, PTEN
ABC-diffuse large B-cell lymphoma	−	+	++	ITAM, CARD11, NF-kB dependent
Burkitt lymphoma	−	++	−	NF-kB independent

The estimated relative contribution of antigen-dependent, tonic, and autonomous BCR signaling to the pathogenesis is represented as follows: [++] = major contribution, [+] = potential contribution, [−] = no evidence of contribution or minor contribution to pathogenesis.

Table 2. Pathogenic activation of the B-cell receptor signaling cascade.

3. Therapeutic implications

In malignancies, in which chromosomal translocations result in the constitutive overexpression of oncogenes, the use of targeted therapy in these oncogenes represents a very attractive concept. One example is venetoclax, a highly potent and selective oral BCL-2 antagonist. Venetoclax has proven to be highly active in patients with CLL, FL, and MCL [112].

The link between antigen-driven BCR activation and lymphomagenesis immediately suggest that the identification and elimination of the putative antigen could result in tumor regression. The induction of complete remission of gastric MZL by antibiotic therapy aimed to eradicate *H. pylori* represents a paradigmatic example of this idea [70]. However, the identification of cognate foreign antigens has been extremely difficult. Another therapeutic concept is the idea of disrupting the interaction of the BCR with its antigen by the generation of anti-idiotype antibodies. Despite promising results in early phase clinical trials, phase III studies failed to show a substantial benefit of this approach when used as consolidation therapy [49, 113].

The evident dependence of B-cell lymphomas on the BCR signaling pathway establishes BCR signaling blockade as a rational and disease-specific therapeutic approach. This strategy has the potential to block all three BCR signaling mechanisms: antigen-dependent signaling, tonic signaling, and autonomous signaling.

The BCR signal can be blocked by specific inhibitors of essential tyrosine kinases of the signaling cascade such as BTK [114] or SYK [115, 116], or by blocking integration point of signals originating from cell surface receptors. PI3Kδ represents one of this integration points and idelalisib, a small molecular PI3Kδ inhibitor has shown clinical efficacy in CLL and FL [117, 118].

Ibrutinib, a BTK inhibitor has demonstrated durable clinical responses in relapsed/refractory CLL patients, including those with the high-risk del(17p) cytogenetic abnormality. Durable clinical responses have also been demonstrated MCL and DLBCL [97, 114]. Several oral SYK inhibitors, including fostamatinib, entospletinib, and cerdulatinib, are being assessed in clinical trials [119].

All these new drugs share a pattern of response resulting in nodal reduction and increased lymphocytosis. This phenomenon may reflect unique properties such as micro-environment modulation, and activity on the proliferative pools existing in the bone marrow and lymph nodes [74, 120].

4. Conclusion and perspective

The understanding of lymphomagenesis remains essential for the development of novel therapeutic strategies. Both the errors in the genetic mechanisms that create a functional BCR and the pathogenic activation of the BCR signaling cascade have a clearly established role in B-cell lymphoma pathogenesis.

AID, an essential enzyme for the generation of the BCR, seems to play an important role in origin and progression of B-cell neoplasms. AID may also be involved in both mechanisms: the BCR origin and the BCR activation. Its study as a therapeutic target certainly deserves further research.

Novel technologies, such as next-generation sequencing, are helping to depict the complex genomic landscape of lymphoid malignancies. Recent developments, not only are enabling the identification of the underlying mutagenic mechanisms, but also the ongoing determination of "targetable" genetic aberrations is currently pushing forward the development of molecularly driven targeted therapeutics.

Current developments may change the natural history of this group of diseases in the near future. Nevertheless, further progress still depends on our ability to understand and integrate knowledge on the B-cell biology, the evolving tumor dynamics, clonal heterogeneity, and microenvironment interaction.

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