Chapter 9
Chromosomal Translocations in B Cell Lymphomas

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Contents

Abstract B cell lymphomas represent a diverse group of biologically and clinically distinct neoplasms, encompassing over 40 subtypes that derive from the malignant transformation of mature B cells, most commonly at the germinal centre (GC) stage of differentiation. Analogous to most cancer types, these tumours are caused by alterations of oncogenes and tumour suppressor genes, some of which have

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specific roles in GC development. This chapter will focus on the mechanisms and consequences of chromosomal translocations and other genetic lesions involved in the pathogenesis of the most common types of mature B cell lymphomas, including Mantle Cell Lymphoma, Follicular Lymphoma, Diffuse Large B Cell Lymphoma, and Burkitt Lymphoma.

Keywords Germinal centre • Lymphoma • Genetic lesions • BCL6 • Immunoglobulin remodelling

9.1 Introduction

This chapter will focus on the role of chromosomal translocations and other mechanisms of genetic lesion in the pathogenesis of the most common and well-characterized types of B cell lymphoma (BCL), including Mantle Cell Lymphoma (MCL), Follicular Lymphoma (FL), Diffuse Large B Cell Lymphoma (DLBCL), and Burkitt Lymphoma (BL). Two additional common lymphoid malignancies, Chronic Lymphocytic Leukaemia (CLL) and Hodgkin Lymphoma (HL), will not be discussed in this chapter since either they lack recurrent chromosomal translocations (CLL) or their genome is still incompletely characterized (HL). Emphasis will be placed on the mechanisms of genetic lesions and the function of the involved genes in the context of normal B cell biology.

9.2 Cell of Origin of B Cell Lymphomas

Knowledge of the unique events that take place in the cell of origin of BCL is essential for understanding the mechanisms that are involved in the generation of chromosomal translocations and other BCL-associated genetic lesions. Most BCLs develop from the malignant expansion of mature B cells, and with the exception of MCL, arise from B cells that are arrested at various stages during their transit through a particular structure known as the germinal centre (GC). The GC is a specialized environment that forms in peripheral lymphoid organs when mature,

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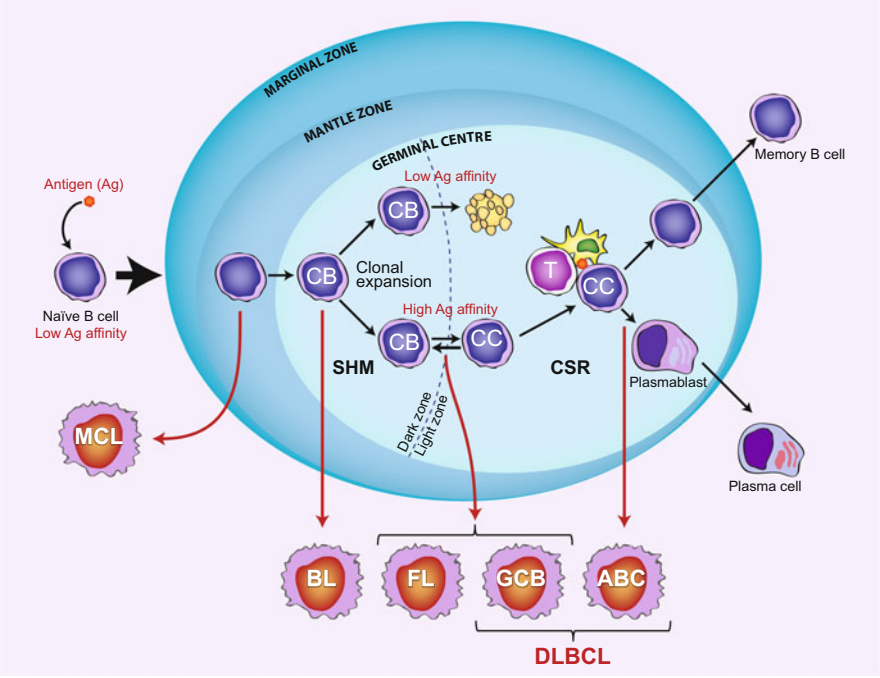

Fig. 9.1 The germinal centre reaction and lymphomagenesis. Schematic representation of a lymphoid follicle illustrating the germinal centre, the mantle zone, and the surrounding marginal zone. Upon encounter with a T-cell dependent antigen, naïve B cells undergo rapid proliferation and differentiate into centroblasts (CB) in the dark zone of the GC, where they also modify their *IG* genes by the process of SHM. CBs then transition into centrocytes (CC) in the light zone, where their encounter the antigen again, now presented by FDC, and, based on affinity for the antigen, are either selected to differentiate into plasma cells or memory B cells, re-enter the DZ, or be eliminated by apoptosis. In the light zone, CCs also undergo CSR. With the exception of mantle cell lymphoma (MCL), most BCL derive from cells that have experienced the GC reaction (*arrows*). FL, follicular lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B cell lymphoma (*GCB* germinal centre B cell-like, *ABC* activated B cell-like)

naive B cells encounter a foreign antigen for the first time, in the context of signals delivered by CD4+ T cells and antigen-presenting cells (APC) (Fig. 9.1) [1–3].

GCs are characterized by two histologically and functionally well-defined zones: the dark zone (DZ), which consists of rapidly proliferating centroblasts (CBs) (doubling time 6–12 h), and the light zone (LZ), which is composed of more quiescent cells called centrocytes (CCs), surrounded by a network of follicular dendritic cells (FDC) and Tfh cells [4, 5]. In the DZ, the process of somatic hypermutation (SHM) modifies the variable region of the immunoglobulin (*IG*) genes, which encodes for the antigen-binding portion of the antibody, by introducing mostly point mutations that will change its affinity for the antigen [3, 6]. Following SHM in the DZ, CBs move to the LZ, where they compete for limited amount of antigen presented by FDCs. Based on the affinity of their B cell receptor (BCR) for the antigen, CCs will

then be selected to differentiate into memory B cells and plasma cells [3, 7] or, depending on stimulation by a variety of different signals, re-enter the DZ. In the GC, CCs also undergo class-switch recombination (CSR) [8], a DNA remodelling event that confers distinct effector functions to antibodies with identical specificities [9]. Both SHM and CSR represent B cell-specific functions that modify the genome of B cells via mechanisms involving single- or double-strand breaks, and both depend on the function of the activation-induced cytidine deaminase (AICDA/AID) enzyme [10, 11].

A master regulator of the GC reaction is the transcriptional repressor BCL6; this protein is specifically expressed in the GC and is an essential requirement for GC formation, as documented in vivo by mouse models where deletion of the *BCL6* gene was associated to the complete absence of these structures in response to antigenic stimulation [12–14]. BCL6 modulates the expression of numerous genes involved in BCR and CD40 signalling [15, 16], T-cell mediated B cell activation [15], apoptosis [15, 17], sensing and response to DNA damage [18–21], signalling pathways triggered by various cytokines and chemokines (e.g., interferon and TGFB1) [15, 17], and terminal B cell differentiation [22, 23]. BCL6 is therefore a central player in sustaining the proliferative nature of CBs, while allowing the execution of specific DNA remodelling processes (SHM and CSR) without eliciting responses to DNA damage. Furthermore, BCL6 suppresses a variety of signalling pathways that could lead to premature activation and differentiation before the selection of cells producing high-affinity antibodies. Once these processes are completed, multiple signals, including engagement of the BCR by the antigen and activation of the CD40 receptor by the CD40 ligand expressed on CD4+ T-cells, will induce the activation of different pathways and ultimately lead to downregulation of BCL6 at both the translational and transcriptional level, thus restoring the ability of the B cell to become activated and differentiate.

This simplified overview of the GC reaction is important to introduce two major concepts that are critical for the understanding of B cell lymphomagenesis: (i) as an irreversible marker of transit through the GC, the presence of somatically mutated *IG* genes in these tumours documented that the majority of BCLs, with the exception of most MCL cases, derive from the clonal expansion of GC-experienced B cells [24]; (ii) mistakes occurring during SHM and CSR are responsible for the generation of genetic alterations associated with BCL, including chromosomal translocations and aberrant somatic hypermutation (ASHM).

9.3 Mechanisms of Genetic Lesions in B Cell Lymphomas

9.3.1 Chromosomal Translocations

In B cell malignancies, chromosomal translocations occur at least in part as a consequence of mistakes in *IG* gene modification processes, and can thus be distinguished into three groups based on the structural features of the chromosomal breakpoint: (i) translocations due to errors occurring during the RAG-mediated

V(D)J recombination process (e.g. translocations involving *IGH* and *CCND1* in MCL [25] and translocations involving *IGH* and *BCL2* in FL) [26, 27]; (ii) translocations due to errors in the AICDA/AID -dependent CSR process (e.g., those involving the *IG* genes and *MYC* in sporadic BL) [26]; and (iii) translocations occurring as by-products of DNA breaks generated during the AICDA/AID-mediated SHM process (e.g., those joining the *IG* and *MYC* loci in endemic BL) [26]. Importantly, deletion of AICDA/AID in lymphoma-prone mouse models was shown to prevent both the occurrence of *IGH*/*MYC* translocations in normal B cells undergoing CSR [28, 29] and the development of GC-type lymphomas [30, 31], documenting the involvement and requirement of *IG* gene remodelling mechanisms in the pathogenesis of BCL.

In most chromosomal translocations associated with BCL, and in contrast with translocations associated with acute leukaemias, the coding domain of the involved proto-oncogene is left unaltered by the translocation, and no gene fusion is generated. Instead, heterologous regulatory sequences derived from the partner chromosome are juxtaposed in proximity of the oncogene, leading to deregulated expression of an intact protein. This process of proto-oncogene deregulation is defined as homotopic if a proto-oncogene whose expression is tightly regulated in the normal tumour counterpart becomes constitutively expressed in the lymphoma cell, and heterotopic if the proto-oncogene is not expressed in the putative normal counterpart of the tumour cell and undergoes ectopic expression in the lymphoma. In most types of BCL-associated translocations, the heterologous regulatory sequences responsible for proto-oncogene deregulation are derived from antigen receptor loci, which are expressed at high levels in the target tissue [26]. However, in certain translocations, such as the ones involving *BCL6* in DLBCL, different promoter regions from distinct chromosomal sites can be found juxtaposed to the proto-oncogene in individual tumour cases, a concept known as "promiscuous" translocations [32–40].

Only few BCL associated chromosomal translocations juxtapose the coding regions of the two involved genes, forming a chimeric transcriptional unit that encodes for a novel fusion protein, an outcome typically observed in chromosomal translocations associated with acute leukaemia. Examples include the t(11;18)(q22.2;q21.3) found in mucosa associated lymphoid tissue (MALT) lymphoma and the t(2;5)(p23.2;q35.1) typical of anaplastic large cell lymphoma (ALCL). The molecular cloning of the genetic loci involved in most recurrent translocations has led to the identification of a number of proto-oncogenes involved in lymphomagenesis (Supplemental Table 9.1).

9.3.2 Gain-of-Function Mutations and Copy Number Gains

The biological properties of a proto-oncogene can be altered by two additional mechanisms, including somatic point mutations and copy number gains/amplifications. Genomic mutations in the coding and/or regulatory region of a proto-oncogene may lead to stabilization or constitutive activation of its protein product. CN gains and

Supplemental Table 9.1 Most common chromosomal translocations associated with major B-NHL types

B-NHL type	Chromosomal translocation	Frequency	Involved gene	Functional consequences	Postulated mechanism of transformation
MCL	t(11;14)(q13.3;q32.3)	>95 %	*CCND1*	Deregulated expression	Enhanced proliferation and growth
BL	t(8;14)(q24.2;q32.3)	80 %	*MYC*	Deregulated expression	Enhanced proliferation and growth, aberrant DNA replication
	t(2;8)(p12;q24.2)	15 %	*MYC*	”	”
	t(8;22)(q24.2;q11.2)	5 %	*MYC*	”	”
FL	t(14;18)(q32.3;q21.3)	85 %	*BCL2*	Deregulated expression	Resistance to apoptosis
	t(2;18)(p12;q21.3)	rare	*BCL2*	”	”
	t(18;22)(q21.3;q11.2)	rare	*BCL2*	”	”
	t(3;various)(q27;various)	6–14 %	*BCL6*	”	Enhanced proliferation, impaired DNA damage responses, block of differentiation
MZL (MALT type)	t(11;18)(q22.2;q21.3)	60 %	*BIRC3*; *MALT1*	Fusion protein/transcriptional activation of BIRC3	Constitutive activation of the NF-κB signalling pathway
	t(1;14)(p22.3;q32.3)	4–9 %[a]	*BCL10*	Deregulated expression	Constitutive activation of the NF-κB signalling pathway
	t(14;18)(q32.3;q21.3)	7–38 %[a]	*MALT1*	Deregulated expression	Constitutive activation of the NF-κB signalling pathway
	t(3;14)(p13;q32.3)	5–20 %[a]	*FOXP1*	Deregulated expression	Unclear (transcription factor)

DLBCL, GCB-type	t(8;14)(q24.2;q32.3)	10 %	*MYC*	Deregulated expression	Enhanced proliferation and growth, aberrant DNA replication
	t(14;18)(q32.3;q21.3)	30–40 %	*BCL2*	”	Resistance to apoptosis
	t(3;various) (q27;various)	15 %	*BCL6*	”	Enhanced proliferation, impaired DNA damage responses, block of differentiation
DLBCL, ABC-type	t(3;various) (q27;various)	25 %	*BCL6*	Deregulated expression	Enhanced proliferation, impaired DNA damage responses, block of differentiation
PMBCL	t(16; various) (p13; various)	38 %	*CIITA*	Disruption of CIITA function	Reduced tumour cell immunogenicity, downregulation of HLA class II protein
LPL	t(9;14)(p13.2;q32.3)	50 %	*PAX5*	Deregulated expression	Altered B-cell proliferation and differentiation

LPL lymphoplasmacytic lymphoma
[a]Depending on the involved site

amplifications typically result in the overexpression of an intact protein. Over the past few years, the use of next-generation sequencing technologies and high density genomic arrays have led to the identification of numerous recurrent targets of somatic mutations and CN changes that likely play central roles in transformation. These genes will be discussed in individual disease sections. Of note, point mutations of the *RAS* genes, a very frequent proto-oncogene alteration in human neoplasia, are rare in lymphomas [41]. Also, only a few genes have been identified so far as specific targets of amplification in BCLs, including *REL* and *BCL2* in DLBCL [42–45] and the genes encoding for the PD ligands in primary mediastinal B cell lymphoma (PMBCL)[46].

9.3.3 Deletions and Inactivating Mutations

Recent genomic efforts have uncovered several new candidate tumour suppressor genes that are lost in BCLs due to chromosomal deletions and/or deleterious mutations. Among these genes, *PRDM1* (also known as *BLIMP1*) on 6q21 is biallelically inactivated in ~25 % of ABC-DLBCL cases [47–49]; and *TNFAIP3*, the gene encoding for the negative NF-κB-regulator A20 on 6q23, is inactivated in ~30 % of ABC-DLBCL, as well as in PMBCL, marginal-zone lymphoma and HL [50–53]. Heterozygous mutations and deletions inactivating the acetyltransferase genes *CREBBP* and *EP300* are observed in a significant fraction of DLBCL and FL, supporting a haploinsufficient tumour suppressor role [54]. DLBCL and FL also carry loss-of-function mutations of *KMT2D*/*MLL2*, a gene encoding for a methyltransferase found mutated in multiple cancer types [55, 56]. More than half of all CLL cases are associated with CN losses encompassing the *DLEU2*/*miR15-a*/*16.1* cluster on 13q14.3 [57–59], while the *CDKN2A*/*CDKN2B* locus is targeted by focal homozygous deletions in a large proportion of transformed FL (tFL), Richter syndrome (RS) and ABC-DLBCL cases [60–62], and is epigenetically silenced in various MCL cases [63]. Loss of the *TP53* tumour suppressor gene, likely the most commonly mutated gene in human cancer [64], is observed at relatively low frequencies in BCL, where these lesions seem preferentially associated with specific disease subtypes, including BL and DLBCL derived from the transformation of FL or CLL [65, 66]. Analogous to other neoplasms, the mechanism of *TP53* inactivation in BCL entails point mutation of one allele and chromosomal deletion or mutation of the second allele.

9.3.4 Aberrant Somatic Hypermutation

In normal GC B cells, the process of SHM is tightly regulated, introducing mutations only in the rearranged *IG* variable sequences [67] as well as in the 5′ region of a few other loci, including *BCL6* and the *CD79* components of the B cell receptor

[68–70], although the functional role of mutations found in non-*IG* genes remains obscure. On the contrary, multiple mutational events have been found to affect numerous loci in over half of DLBCL cases [71] and, at lower frequencies, in other lymphoma types [72–76], as the result of a pathologic phenomenon called aberrant somatic hypermutation (ASHM). These mutations are typically distributed within ~2 Kb from the transcription initiation site [77] and, depending on the genomic configuration of the target gene, may affect both coding and non-coding regions, thus holding the potential to alter the function of the encoded protein and its transcriptional regulation. The target loci identified to date include several well-known proto-oncogenes, such as *PIM1*, *PAX5* and *MYC* [71]. However, the mechanism underlying ASHM and a comprehensive genome-wide characterization of its consequences are still incompletely defined.

9.4 Molecular Pathogenesis of Common B Cell Lymphomas

9.4.1 Mantle Cell Lymphoma

Mantle cell lymphoma is a tumour of mature B cells expressing specific differentiation markers and characterized in most cases by unmutated *IGH* variable sequences, consistent with the derivation from naive, pre-GC peripheral B cells (Fig. 9.1). However, recent studies revealed the existence of cases that carry SHM-associated mutations (15–40 % of diagnoses), reflecting the influence of the GC environment.

MCL is characteristically associated with the t(11;14)(q13.3;q32.3) translocation, which juxtaposes the *IGH* gene to chromosomal region 11q13.3, containing the *CCND1* gene [25, 78, 79]. The translocation causes the heterotopic deregulation of cyclin D1, a member of the D-type G_1 cyclins that regulates the early phases of the cell cycle and is normally not expressed in resting B cells [80–82]. Another ~10 % of MCL patients over-express aberrant or shorter cyclin D1 transcripts resulting from secondary rearrangements, microdeletions or point mutations in the gene 3′ untranslated region [78, 83–85]. The tumourigenic role of cyclin D1 deregulation in human neoplasia is suggested by the ability of the overexpressed protein to transform cells in vitro and to induce B cell lymphomas in transgenic mice, although only when combined to other oncogenic alterations [86, 87]. Because of the elevated frequency and specificity of alterations, the ectopic expression of cyclin D1 in the tumour cells constitutes a standard immunohistochemical marker for MCL diagnosis [88].

Additional genetic alterations accompanying the t(11;14)(q13.3;q32.3) in MCL include deletions and mutations inactivating the *ATM* gene (~40 % of patients) [89], loss of *TP53* (20 %) [90], and inactivation of the *CDKN2A* gene by deletions, point mutations or promoter hypermethylation, more frequently observed in aggressive cases (67 %) [91]. Aggressive tumours are associated with mutations in *NOTCH1* (12 % of clinical samples) and *NOTCH2* (5 % of samples), which are mutually exclusive and are typically represented by frameshift or nonsense events leading to the loss

of the PEST sequences required for protein degradation and thus to stabilization of the NOTCH protein [92, 93]. Less common, yet recurrent and therefore presumably functionally relevant mutations involve *BIRC3*, the Toll-like receptor 2 (TLR2), the chromatin modifiers WHSC1 and KMT2D/MLL2, and the MEF2B transcription factor [92]. Finally, in a small number of cases, *BMI1* is amplified and/or overexpressed, possibly as an alternative mechanism to the loss of the *CDKN2A* cell cycle regulator gene [94].

9.4.2 Burkitt Lymphoma

BL derives from GC B cells displaying phenotypic and molecular features of transformed centroblasts, as documented by the presence of highly mutated *IG* variable sequences [95–97] and the expression of a distinct transcriptional signature [98, 99]. BL includes three clinical variants: sporadic BL (sBL), endemic BL (eBL) and HIV-associated BL, which is often diagnosed as a manifestation of AIDS [88].

The genetic hallmark of BL is a chromosomal translocation involving the *MYC* gene on chromosome 8q24.2 and one of the *IG* loci on the partner chromosome [100, 101], with *IGH* (14q32.3) being the most frequently involved (80 % of cases) and *IGK* (2p12) or *IGL* (22q11.2) being found in the remaining 20 % of cases [100–103]. These translocations show a high degree of molecular heterogeneity, since the breakpoints are located 5′ and centromeric to *MYC* in t(8;14), but map 3′ to *MYC* in t(2;8) and t(8;22) [100–104]. Further molecular heterogeneity derives from the breakpoint sites observed on chromosomes 8 and 14 in t(8;14): translocations of eBL tend to involve sequences at an undefined distance (>100 kb) 5′ to *MYC* on chromosome 8 and sequences within or in proximity to the Ig J_H region on chromosome 14 (Fig. 9.2) [105, 106]. In sBL, t(8;14) preferentially involves sequences within or immediately 5′ to *MYC* (<3 kb) on chromosome 8 and within the Ig switch regions on chromosome 14 (Fig. 9.2) [105, 106].

The different molecular architecture of these translocations is thought to reflect distinct mechanisms of *IG* gene remodelling involved in their generation, namely CSR in sBL and AIDS-BL and SHM in eBL [26].

All t(8;14), t(2;8) and t(8;22) lead to the ectopic expression of the MYC proto-oncogene [107–109], which is normally absent in the majority of proliferating GC B cells [1], where it is repressed by BCL6 [110]. Oncogenic activation of *MYC* in BL is mediated by at least three distinct mechanisms: (i) juxtaposition of the MYC coding sequences to heterologous enhancers derived from the *IG* loci [107–109]; (ii) point mutations in the gene 5′ regulatory sequences, which alter the responsiveness to cellular factors controlling its expression [111]; (iii) amino acid substitutions within the gene exon 2, encoding for the protein transactivation domain [112, 113]; these mutations can abolish the ability of RBL1/p107, a nuclear protein related to *RB1*, to suppress *MYC* activity [114], or can increase protein stability [115, 116].

MYC is a nuclear phosphoprotein that binds and transcriptionally regulates thousand of target genes with diverse roles in regulating cell growth by affecting DNA replication, energy metabolism, protein synthesis, and telomere elongation

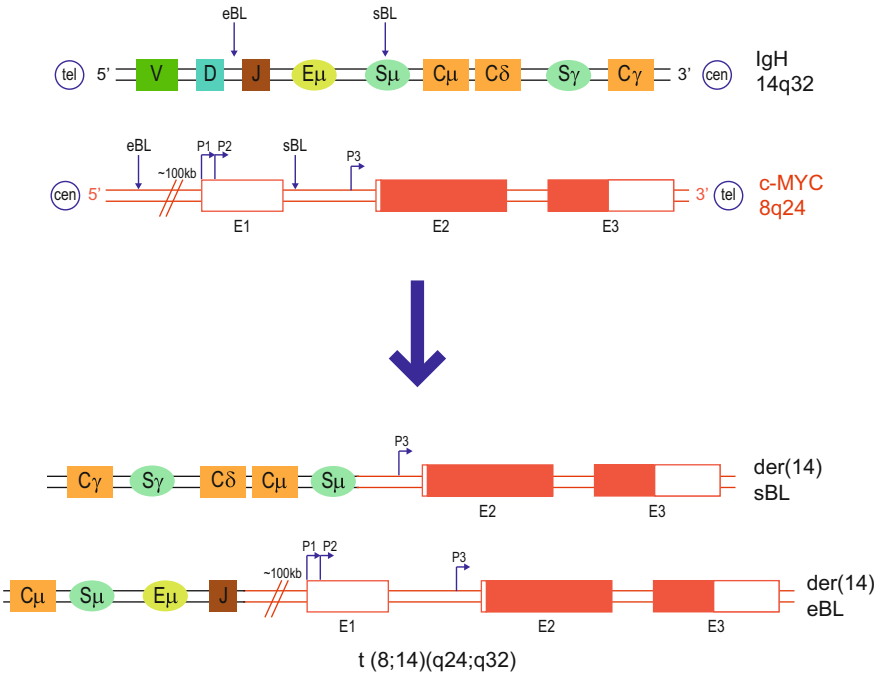

Fig. 9.2 Molecular anatomy of chromosomal translocations involving *MYC*. The *top panel* shows the genomic configuration of the germline *IGH* and *MYC* loci involved in the t(8;14) translocation (not in scale). Upon recombination, the *IGH* enhancer sequences are juxtaposed to the *MYC* coding region (*bottom panel*), causing deregulated expression of its protein product. Only one of the derivative chromosomes is shown. *TEL* telomeric end, *CEN* centromeric end

[117–119]. The deregulated expression of these functions is typically involved in malignant transformation. In addition, deregulated *MYC* expression is thought to cause genomic instability and, thus, contribute to tumour progression by facilitating the occurrence of additional genetic lesions [120]. Several transgenic mouse models of deregulated MYC expression have been generated and shown to develop aggressive B cell lymphomas with high penetrance and short latency [116, 121, 122]. In particular, the combination of deregulated expression of *MYC* and PI3K signalling activation in GC B cells leads to lymphomas recapitulating the features of human BL [123].

Genome sequencing has recently revealed additional oncogenic mechanisms that cooperate with MYC in the development of BL. Mutations affecting the genes encoding for the TCF3 transcription factor and for its negative regulator ID3 are frequently observed in all BL subtypes (10–25 % and 35–38 % of cases, respectively). These mutations trigger tonic (antigen-independent) BCR signalling and promote cell survival through activation of the PI3K signalling pathway (Fig. 9.3) [124].

TCF3 can also transactivate *CCND3*, promoting cell-cycle progression, while in 38 % of sBL, mutations within the carboxyl terminus domain of CCND3 stabilize the protein leading to higher expression levels. Other recurrent alterations associated

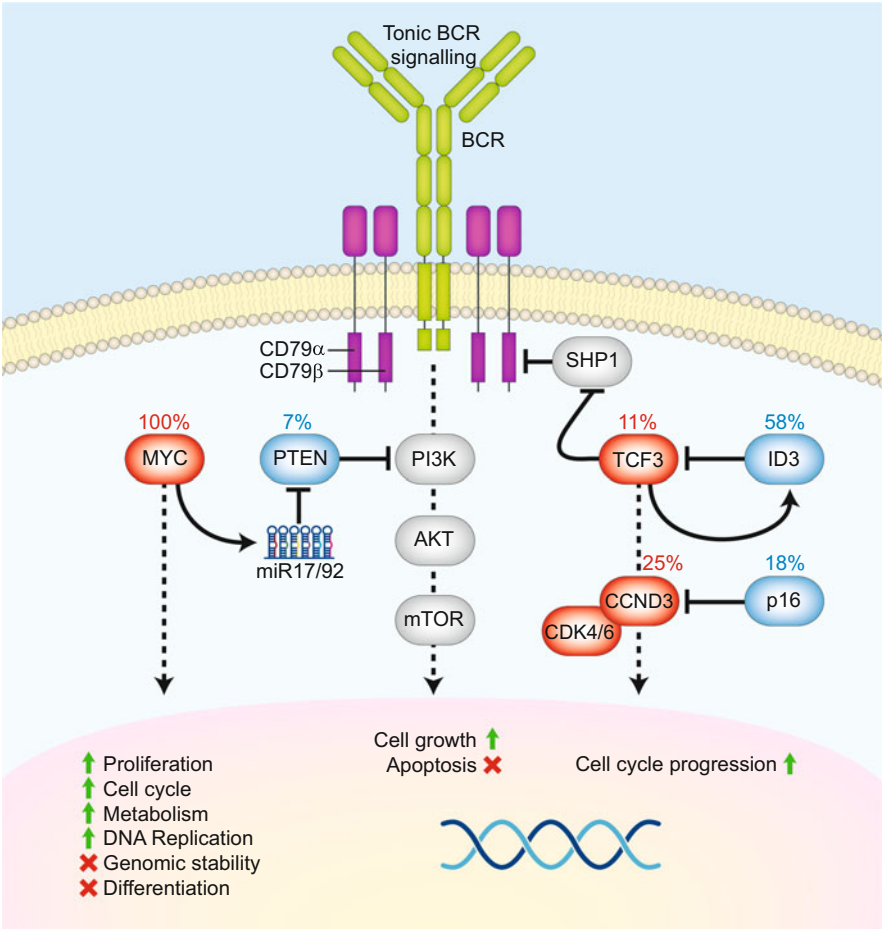

Fig. 9.3 Molecular basis of BL pathogenesis. Pathways affected by genetic aberrations in BL. Proteins in red are encoded by genes targeted by translocations (*MYC*) or activating mutations, and Proteins in blue denote genes targeted by inactivating events

with BL include *TP53* loss by mutation and/or deletion (35 % of both sBL and eBL cases) [65], *CDKN2B* inactivation by deletion or hypermethylation (17 % of samples) [125], and 6q deletions (~30 % of cases, independent of the clinical variant) [126]. Finally, one contributing factor to the development of BL is monoclonal EBV infection, present in virtually all cases of eBL and in ~30 % of sBL and AIDS-BL [127–130]. However, BL cells lack the expression of both EBV transforming antigens (LMP1 and EBNA2); considering also that this virus is endemic in humans worldwide, these observations raise some doubts on the pathogenic role of EBV in this disease [131].

9.4.3 *Follicular Lymphoma*

FL is characterized by an indolent clinical course but remains incurable and ultimately leads to death often accompanied by histologic transformation to an aggressive lymphoma with a DLBCL phenotype (20–30 % of cases) [132, 133]. The derivation of FL from a GC B cell is supported by the expression of specific GC B cell markers together with the presence of SHM-mutated *IG* genes [24].

Eighty to ninety percent of FL cases are characterized by chromosomal translocations that affect the *IG* locus and the *BCL2* gene on chromosome band 18q21.3 [78, 134–137]. These rearrangements join the 3′ untranslated region of *BCL2* to an *IG* J_H segment, leading to ectopic expression of the BCL2 protein in GC B cells [134, 135, 138–142], where its transcription is normally repressed by BCL6 [17, 143]. Approximately 70 % of the breakpoints on chromosome 18 cluster within the major breakpoint region, while the remaining 5–25 % map to the more distant minor cluster region, located ~20 kb downstream of the *BCL2* gene (Fig. 9.4)[134, 135, 138, 139]. More rarely, rearrangements involve the 5′ flanking sequences of *BCL2* (Fig. 9.4)[144]. *BCL2* encodes for a major negative regulator of programmed cell death and may thus contribute to lymphomagenesis by conferring resistance to

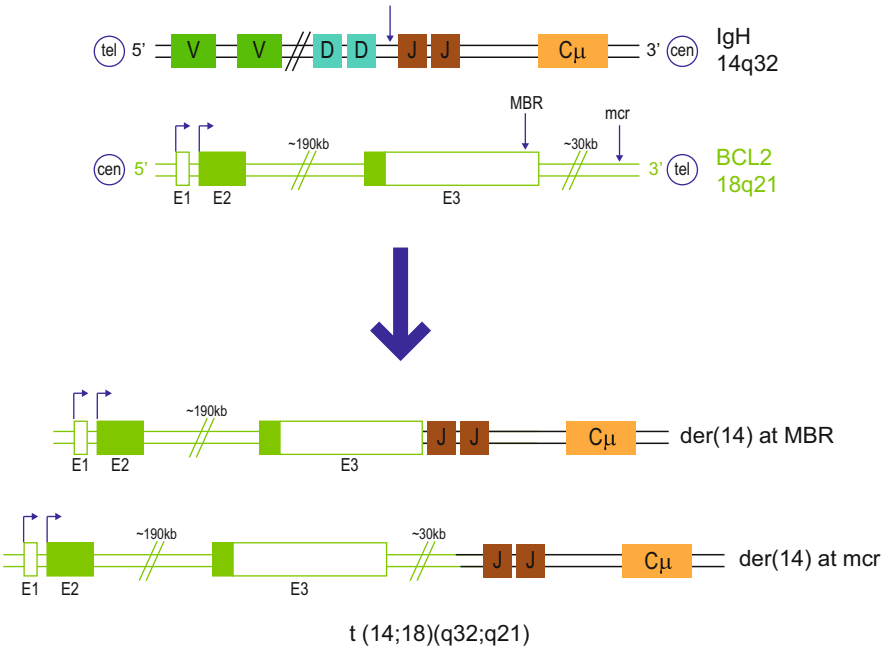

Fig. 9.4 Molecular anatomy of chromosomal translocations involving *BCL2*. *Top panel*, genomic configuration of the germline *IGH* and *BCL2* loci (not in scale). The translocation t(14;18) leads to the juxtaposition of the *IGH* enhancer sequences to the *BCL2* coding region (*bottom panel*), causing the deregulated expression of an intact protein. Only one of the derivative chromosomes is shown. *TEL* telomeric end, *CEN* centromeric end, *MBR* major breakpoint region, *mcr* minor cluster region

apoptosis independent of antigen selection. Other genes recurrently targeted by mutations in FL include those encoding for the methyltransferase KMT2D/MLL2 (up to 80 % of cases), the polycomb-group oncogene *EZH2* (7–20 % of patients), and the acetyltransferases *CREBBP* and *EP300* (40 % of cases), all of which may facilitate transformation by epigenetic remodelling of the precursor cancer cell.

The genomic analysis of clonally related FL and tFL biopsies has recently allowed the identification of the genetic lesions that are specifically acquired during histologic progression to DLBCL. These lesions include inactivation of *CDKN2A*/*CDKN2B* through deletion, mutation and hypermethylation (one third of patients) [61, 91], rearrangements and amplifications of *MYC* [145], *TP53* mutations/deletions (25–30 % of cases) [66, 146–148], loss of chromosome 6 (20 %) [126], and ASHM [61]. Additionally, Biallelic inactivation of the gene encoding *B2M*, leading to the loss of HLA class I expression on the cell surface of the tumour cells (see below) suggests that escape from immune surveillance may be important for FL transformation to DLBCL.

9.4.4 Diffuse Large B Cell Lymphoma

DLBCL is an aggressive disease that includes cases arising *de novo* as well as cases derived from the clinical evolution of FL and CLL [88]. Gene expression profile analysis has identified three well-characterized molecular subtypes of DLBCL, which reflect the derivation from different stages of B cell development. Germinal centre B cell-like (GCB) DLBCL is thought to derive from GC B cells with a phenotype intermediate between CB and CC; activated B cell-like (ABC) DLBCL is related to B cells committed to plasmablastic differentiation; and PMBCL arises from thymic B cells that have experienced the GC; the remaining 15–30 % of cases is still unclassified [149–153]. Of note, patients diagnosed with GCB-DLBCL have favourable prognosis compared to ABC-DLBCL [45].

Compared to other B cell malignancies, DLBCL shows a significantly higher degree of genomic complexity, carrying on average 50–100 lesions/case, with significant heterogeneity across patients [55, 56, 154]. Many of the lesions identified can be variably found in both molecular subtypes of the disease, consistent with a general role during transformation, while others appear to be preferentially or exclusively associated with individual DLBCL subtypes, indicating that GCB-DLBCL, ABC-DLBCL and PMBCL are genetically, phenotypically and clinically distinct diseases (Fig. 9.5).

9.4.4.1 Genetic Lesions Common to GCB- and ABC-DLBCL

A major contributor to DLBCL pathogenesis, in both GCB- and ABC-DLBCL, is represented by the deregulated activity of the BCL6 oncoprotein, which results from multiple genetic lesions. Chromosomal translocations involving the *BCL6* gene at band 3q27 are observed in up to 35 % of cases [155–157], with a twofold

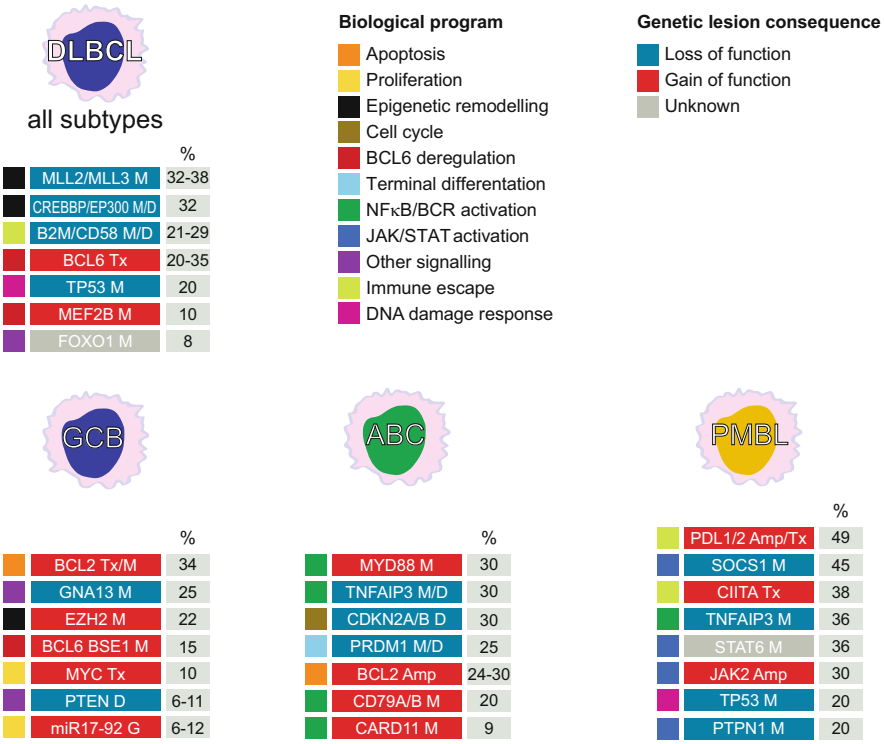

Fig. 9.5 Genetic lesions associated with DLBCL. Most common genetic alterations identified in GCB-DLBCL, ABC-DLBCL and PMBCL. The biological function/signalling pathway affected by the lesion is indicated by colour-coded squares and is explained in the *upper right panel*. *M* mutation, *D* deletion, *Tx* translocation, *Amp* amplification

higher frequency in the ABC-DLBCL subtype [158]. These translocations juxtapose the coding exons of *BCL6* downstream and in the same transcriptional orientation to heterologous sequences derived from a variety of partner chromosomes, including *IGH* (14q32.3), *IGK* (2p11.2), *IGL* (22q11.2), and at least 20 other chromosomal sites unrelated to the *IG* loci (Fig. 9.6) [32–39].

Most translocations result in a fusion transcript in which the promoter region and the first non-coding exon of *BCL6* are replaced by sequences derived from the partner gene [33, 159]. Since the common denominator of these promoters is the expression in the post-GC differentiation stage, the translocation is thought to prevent the downregulation of *BCL6* expression that is normally associated with differentiation into post-GC cells. Deregulated expression of an intact BCL6 gene product is also sustained by a variety of indirect mechanisms, including gain-of-function mutations in its positive regulator MEF2B (~11 % of cases) [160], inactivating mutations/deletions of *CREBBP*/*EP300* [54], which in normal cells impair BCL6 activity (see below) [161], and mutations/deletions of *FBXO11* (~5 %) [162], encoding a ubiquitin ligase involved in the control of BCL6 protein degradation. As documented by a mouse model in which deregulated BCL6 expression in GC B cells leads to the development

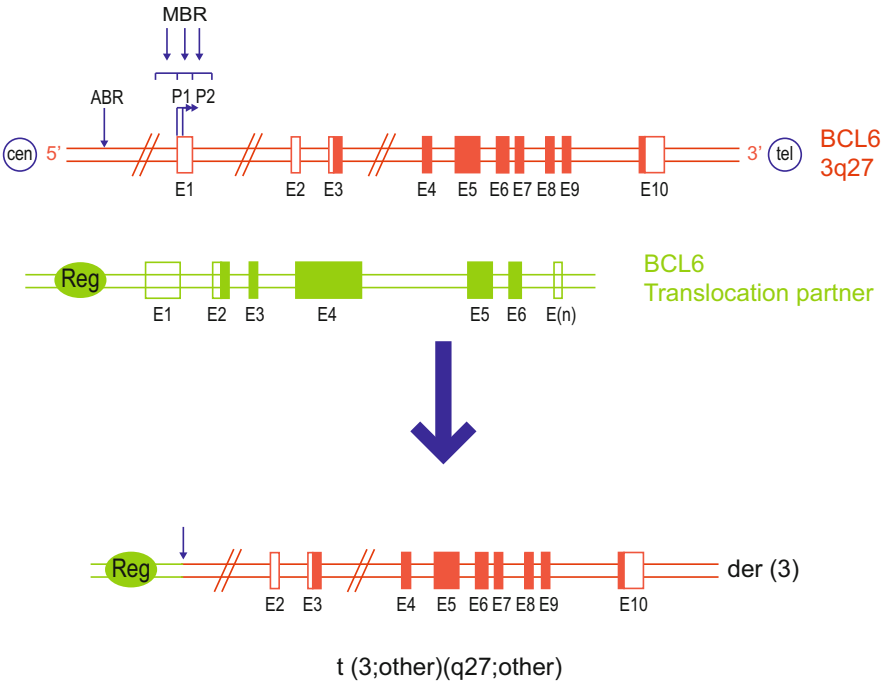

Fig. 9.6 Molecular anatomy of chromosomal translocations involving *BCL6*. *Top panel*, genomic configuration of the germline *BCL6* locus and a representative gene involved in the translocation partner chromosome (not in scale). *Bottom panel*, schematic representation of the derivative chromosome resulting from the translocation; only one of the derivative chromosomes is shown. *TEL* telomeric end, *CEN* centromeric end, *Reg* regulatory sequences

of DLBCL [163], BCL6 plays a critical role in lymphomagenesis by enforcing the proliferative phenotype typical of GC cells, suppressing proper DNA damage responses, and blocking terminal differentiation.

The most frequently disrupted function in DLBCL, independent of subtype, is represented by epigenetic remodelling, due to mutations in the *CREBBP/EP300* acetyltransferase genes (35 % of cases) [54] and the *KMT2D/MLL2* H3K4 methyltransferase (~30 % of all DLBCL) [54–56]. These lesions may favour malignant transformation by reprogramming the cancer epigenome, and in the case of *CREBBP/EP300*, by altering the balance between the activity of the *BCL6* oncogene, which is typically inactivated by acetylation, and the tumour suppressor TP53, which requires acetylation at specific residues for its function as a tumour suppressor [54].

Escape from both arms of immune surveillance, including CTL-mediated cytotoxicity (through genetic loss of the *B2M/HLA-I* genes) and NK cell-mediated death (through genetic loss of the CD58 molecule) also appears a major feature of the DLBCL phenotype [164]. Analogous effects may be achieved in PMBCL by

disruption of the MHC-II transactivator CIITA [165] and amplification of the genes encoding for the immunomodulatory proteins PDL1/PDL2 [46].

Finally, approximately 50 % of all DLBCL are associated with ASHM [71]. The number and identity of the genes that accumulate mutations in their coding and non-coding regions due to this mechanism varies in different cases and is still largely undefined [166]. ASHM may therefore contribute to the heterogeneity of DLBCL via the alteration of different cellular pathways in different cases.

9.4.4.2 Genetic Lesions of GCB-DLBCL

These include the t(14;18) and t(8;14) translocations, which deregulate the *BCL2* and *MYC* oncogenes in 34 % and 10 % of cases, respectively [45, 143, 167–169]. Virtually restricted to this subtype are also mutations of EZH2 [170], a histone methyltransferase that trimethylates Lys27 of histone H3 (H3K27); mutations of several genes in the Galpha13 pathway, including the *GNA13* gene, which are involved in the ability of DLBCL cells to spread from their lymphoid sites to the peripheral blood and bone marrow; and deletions of the tumour suppressor *PTEN* [62, 171]. Mutations affecting an autoregulatory domain within the *BCL6* 5′ untranslated exon 1 [158, 172, 173] are detected in up to 75 % of DLBCL cases [69, 174, 175], and reflect the activity of the physiologic SHM mechanism that operates in normal GC B cells [69, 176]. Functional analysis of numerous mutated *BCL6* alleles uncovered a subset of mutations that are specifically associated with GCB-DLBCL [172], and deregulate *BCL6* transcription by disrupting an autoregulatory circuit through which the BCL6 protein controls its own expression levels via binding to the promoter region of the gene [172, 173] or by preventing CD40-induced BCL6 downregulation in post-GC B cells [177]. However, the full extent of mutations deregulating BCL6 expression has not been characterized, and therefore the fraction of DLBCL cases carrying abnormalities in the *BCL6* gene remains undefined.

9.4.4.3 Genetic Lesions of ABC-DLBCL

ABC-DLBCL depends on the constitutive activation of the NF-κB signalling pathway caused by a variety of alterations in positive and negative regulators of NF-κB. In ~30 % of cases, the *TNFAIP3* gene, encoding for the negative regulator A20, is biallelically inactivated by mutations and/or deletions, thus preventing termination of NF-κB-responses [50, 51]. In an additional ~10 % of ABC-DLBCL, the *CARD11* gene is targeted by oncogenic mutations clustering in the protein coiled-coil domain and enhancing its ability to transactivate NF-κB-target genes [178]. Finally, nearly 30 % of ABC-DLBCL cases recurrently show a hotspot mutation (L265P) in the intracellular Toll/interleukin-1 receptor domain of the MYD88 adaptor molecule, which has the potential to activate NF-κB as well as JAK/STAT3 transcriptional responses [179]. At lower frequencies, mutations were found in a number of additional genes encoding for NF-κB pathway components.

Overall, lesions affecting NF-κB activation account for over 50 % of all ABC-DLBCL [50, 51], suggesting that additional mechanisms and/or yet unidentified lesions are responsible for the constitutive NF-κB activity in the remaining cases.

ABC-DLBCLs also depend upon chronic active BCR signalling (which also lead to NF-κB activation). This is associated in ~10 % of cases with somatic mutations of *CD79B* and *CD79A* [180], typically located within the immunoreceptor tyrosine-based activation motif (ITAM). Since silencing of several BCR proximal and distal subunits is toxic to ABC-DLBCL [180], there is conceptual support for the development of therapies that target BCR signalling components. In fact, preliminary data suggest that the Bruton Tyrosine Kinase (BTK) inhibitor Ibrutinib, may be effective against a subset of ABC-DLBCL cases.

Biallelic truncating or missense mutations and/or genomic deletions of the *PRDM1*/*BLIMP1* gene, which encodes for a zinc finger transcriptional repressor required for terminal B cell differentiation [181], block DLBCL cells in the plasmablastic stage in ~25 % of ABC-DLBCL [47–49]. In an additional 25 % of cases, the same consequence is caused by transcriptional repression of PRDM1/BLIMP1 by constitutively active BCL6 alleles [47–49]. Accordingly, translocations deregulating the *BCL6* gene and *BLIMP1* inactivation are mutually exclusive in DLBCL, consistent with these alterations representing alternative oncogenic mechanisms contributing to blocking differentiation during lymphomagenesis (Fig. 9.7).

9.4.4.4 Genetic Lesions of DLBCL Derived from CLL and FL Transformation

The genomic analysis of sequential biopsies of CLL and FL pre- and post-transformation to DLBCL have provided insights onto the mechanisms underlying these transformation processes. These studies have revealed that the transformation of CLL into DLBCL (called Richter Syndrome) derives from the dominant CLL clone through a linear pattern, involving the maintenance of the CLL-associated lesions and the acquisition of new ones, namely *NOTCH1* mutations, *CDKN2A*/*CDKN2B* loss, *TP53* loss, and *MYC* translocations [60]. Conversely, FL and tFL derive from a common mutated precursor clone by divergent evolution involving the disruption of distinct genes and pathways; lesions specifically acquired at transformation include *CDKN2A*/*B* loss, *TP53* loss, *MYC* translocations, ASHM and *B2M* inactivation [61, 182]. Comparison with *de novo* DLBCL showed that, despite their morphologic resemblance, the genomic landscapes of RS and tFL are largely unique since they are characterized in part by distinct combinations of alterations otherwise not commonly observed in *de novo* DLBCL [60, 61]. Thus, the histologic diagnosis of DLBCL may include at least five genetically distinct diseases: GCB-DLBCL, ABC-DLBCL, PMBCL, tFL, and RS DLBCL. This distinction has implications for the development of targeted therapies.

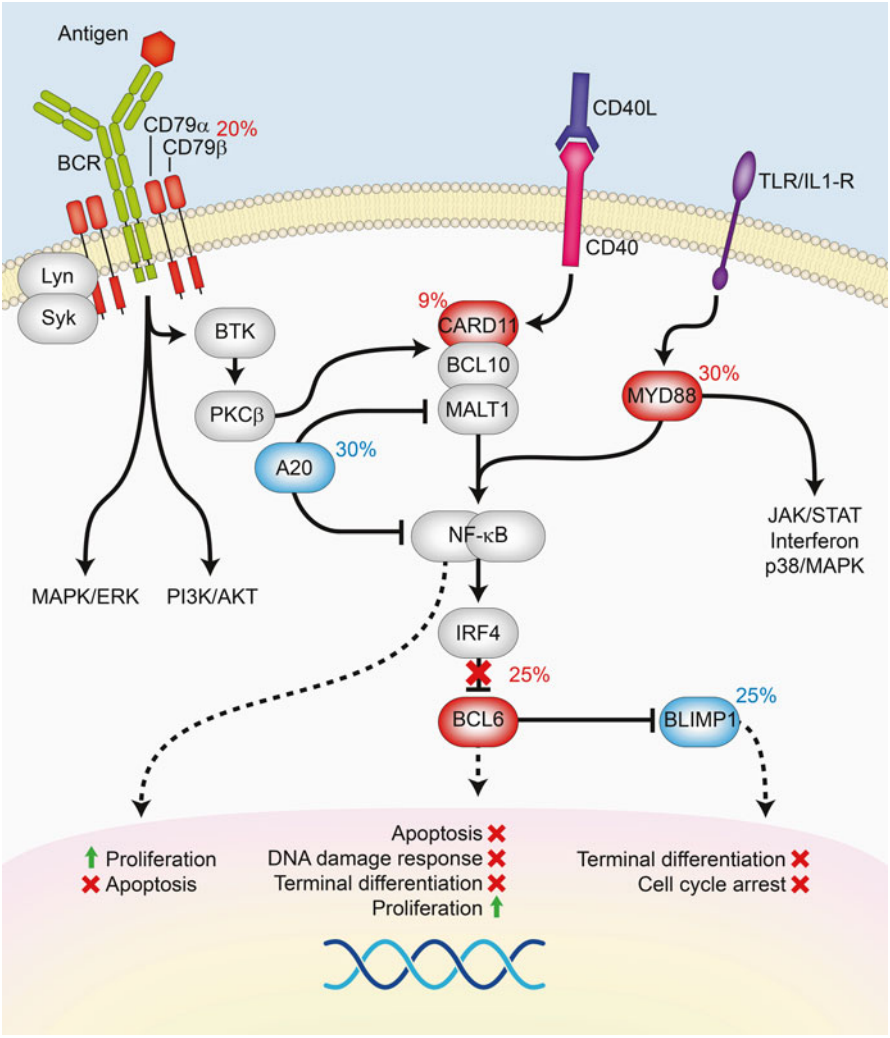

Fig. 9.7 Pathway lesions in ABC-DLBCL. Schematic representation of the signalling pathways induced following engagement of the BCR by the antigen, CD40-CD40L interaction, and activation of the TLR. These signals share the ability to activate the NF-κB pathway, leading to upregulated expression of hundreds of genes, including *IRF4* and *TNFAIP3*/*A20*. IRF4, in turn, represses BCL6, thus releasing the expression of its target PRDM1/BLIMP1. In ABC-DLBCL, multiple genetic lesions converge on this pathway, causing the constitutive activation of NF-κB, as well as chronic active BCR and JAK/STAT3 signalling, while blocking terminal B cell differentiation through mutually exclusive BCL6 deregulation and PRDM1/BLIMP1 inactivation. Genes targeted by gain-of-function mutations or translocations are in red, and genes targeted by loss-of-function genetic lesions are in blue

9.4.4.5 Genetic Lesions of PMBCL

This lymphoma displays a unique transcriptional profile that is similar to HL and suggests the derivation from post-GC thymic B cells [149–153]. One of the most common alterations in both PMBCL and HL is represented by amplification of chromosomal region 9p24, found in up to 50 % of patients [46, 183]. The amplified region encompasses multiple candidate genes, including the gene encoding for the JAK2 tyrosine kinase and the *PDL1*/*PDL2* genes, which encode for inhibitors of T-cell responses and may thus favour immune evasion of the tumour cells. Genomic breakpoints and mutations have also been described in the *CIITA* gene, encoding for the MHC class II transactivator; these lesions may reduce tumour cell immunogenicity by downregulating the expression of surface HLA class II molecules [46, 165, 184]. Analogous to HL, PMBCL patients harbour multiple genetic lesions affecting the NF-κB pathway and the JAK-STAT signalling pathway [185], including mutations of the transcription factor *STAT6*, amplifications/overexpression of *JAK2* (which promote STAT6 activation via IL3/IL4), and inactivating mutations of the STAT6 negative regulator *SOCS1*. More recently, recurrent inactivating somatic mutations of PTPN1 were reported in 22 % of PMBCL cases, where they lead to reduced phosphatase activity and increased phosphorylation of JAK-STAT pathway members [186]. Deregulation of these two signalling pathways is thus a central contributor to PMBCL pathogenesis.

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