

Genetic alterations and their clinical implications in DLBCL

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Abstract | Diffuse large B cell lymphoma (DLBCL) is a highly heterogeneous lymphoid neoplasm with variations in gene expression profiles and genetic alterations, which lead to substantial variations in clinical course and response to therapy. The advent of high-throughput genome sequencing platforms, and especially whole-exome sequencing, has helped to define the genetic landscape of DLBCL. In the past 10 years, these studies have identified many genetic alterations in DLBCL, some of which are specific to B cell lymphomas, whereas others can also be observed in other types of cancer. These aberrations result in altered activation of a wide range of signalling pathways and other cellular processes, including those involved in B cell differentiation, B cell receptor signalling, activation of the NF- κ B pathway, apoptosis and epigenetic regulation. Further elaboration of the genetics of DLBCL will not only improve our understanding of disease pathogenesis but also provide further insight into disease classification, prognostication and therapeutic targets. In this Review, we describe the current understanding of the prevalence and causes of specific genetic alterations in DLBCL and their role in disease development and progression. We also summarize the available clinical data on therapies designed to target the aberrant pathways driven by these alterations.

Diffuse large B cell lymphomas (DLBCLs) are neoplasms of medium or large B lymphoid cells with a diffuse growth pattern. DLBCL encompasses many different disease entities with distinct clinical, pathological and biological features¹ (Supplementary Table 1). DLBCLs that cannot be categorized into a specific entity are diagnosed as DLBCL not otherwise specified, hereafter referred to simply as DLBCL. DLBCL is the most common form of lymphoma and accounts for 25–35% of all non-Hodgkin lymphomas¹. In the past two decades, the results of several phase III trials have established the regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) as the standard-of-care therapy for patients with DLBCL, with 50–70% of patients typically being cured using this approach^{2–4}. However, the remaining patients are either refractory to treatment with R-CHOP or have relapsed disease after a complete response (CR)⁵. Only 10% of patients with refractory or relapsed DLBCL can be cured by conventional salvage immunochemotherapy followed by autologous stem cell transplantation^{6,7}, whereas the outcome of the remaining 90% of patients remains dismal, suggesting a major unmet therapeutic need.

Understanding the biology of DLBCL is essential for identifying patients who are not, or are unlikely to be, cured by R-CHOP and for uncovering potential alternative pathways that could be targeted. The identification

of biologically distinct subtypes of DLBCL was a milestone of research in this area, with the most widely used system dividing DLBCL into either germinal centre B cell (GCB)-like or activated B cell (ABC)-like subtypes⁸. These two subtypes have distinct genomic profiles and are associated with different clinical outcomes^{8–10}. With the advent of high-throughput sequencing platforms, an increasing number of driver genes have been shown to have a role in the pathogenesis of DLBCL. Data from three studies using whole-exome sequencing in combination with other high-throughput techniques to assess over 1,800 DLBCLs have defined the genomic landscape of DLBCL, thus providing deeper insights into both the development of this disease and the identity of potential therapeutic targets^{11–13}. Herein, we review the prevalence, functional roles and clinical implications of specific genetic events, including somatic mutations, copy number alterations and chromosomal translocations, in DLBCL. This Review is focused on de novo DLBCL in general, although specific subtypes of DLBCL will be mentioned when relevant.

Mechanisms of mutagenesis in DLBCL

Elucidation of the mechanisms that induce the genetic alterations observed in DLBCL is helpful in understanding the pathogenesis of this disease. An analysis of mutational signatures indicates that ageing-related

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Key points

- Application of next-generation sequencing technologies, especially whole-exome sequencing, has helped to define the genomic landscape of diffuse large B cell lymphoma (DLBCL).
- Characterization of genetic events provides important insights into the pathogenesis of DLBCL.
- The genetic events identified in DLBCL have prognostic implications and can also enable the molecular classification of DLBCL into specific subtypes.
- Novel agents have been developed to target the dysregulated signalling pathways caused by genetic events in DLBCL, and some of these agents have achieved promising efficacies.
- Several genetic biomarkers are predictive of a response to novel targeted agents in patients with DLBCL and could be used in the future to guide patient selection for clinical trials.

spontaneous deamination is responsible for ~80% of all mutations in DLBCL^{13,14}. Processes specific to B cells are also implicated in the generation of genetic alterations in DLBCL. For example, RAG1 and/or RAG2 can induce breakpoints in the *IGH* locus, leading to the formation of gene fusions including *IGH-BCL2* (REF.¹⁵) (FIG. 1a). Single-stranded DNA-specific cytidine deaminase (AID) mediates somatic hypermutation and class-switch recombination by converting cytosine residues into uracil residues. In addition to immunoglobulin gene variable and switch recombination sequences, AID can also target transcriptionally active genes including *BCL6* and *MYC*, thus generating *MYC* and *BCL6* breaks¹⁶

(FIG. 1b). For *IGH-MYC* and *IGH-BCL6* translocations, most breaks involve the switch region of *IGH*, indicating that these translocations are generated during AID-mediated class-switch recombination^{17,18}. *BCL2* breaks are also caused by AID in pre-B cells, in which expression of AID is lower than that of germinal centre B cells; the RAG complex is not involved because the *BCL2* breakpoint region consists of a GC-rich motif that cannot be targeted by the RAG complex¹⁷. AID-mediated off-target hypermutation can also be a source of oncogenic mutations in DLBCL. Hypermutations affecting non-immunoglobulin genes have been reported in more than half of patients with DLBCL^{19,20}. The results of a study published in 2018 revealed that mutations in *BCL2*, *SGK1*, *PIM1* and *IGLL5* are predominantly mediated by AID¹³. These AID-induced mutations include a predominance of single-nucleotide substitutions, with duplications or deletions being less common, and a preference for transitions rather than transversions and specific targeting of the RGYW motif — all of which suggest a role for somatic hypermutation²¹.

Genetic alterations in DLBCL

Pathways affected by genetic events in DLBCL include those specific to B cell lymphomas, including B cell differentiation and B cell receptor (BCR) signalling, as well as those common to most forms of cancer, including the regulation of cellular proliferation, apoptosis and others (TABLE 1). The genetics of DLBCL are complex; therefore,

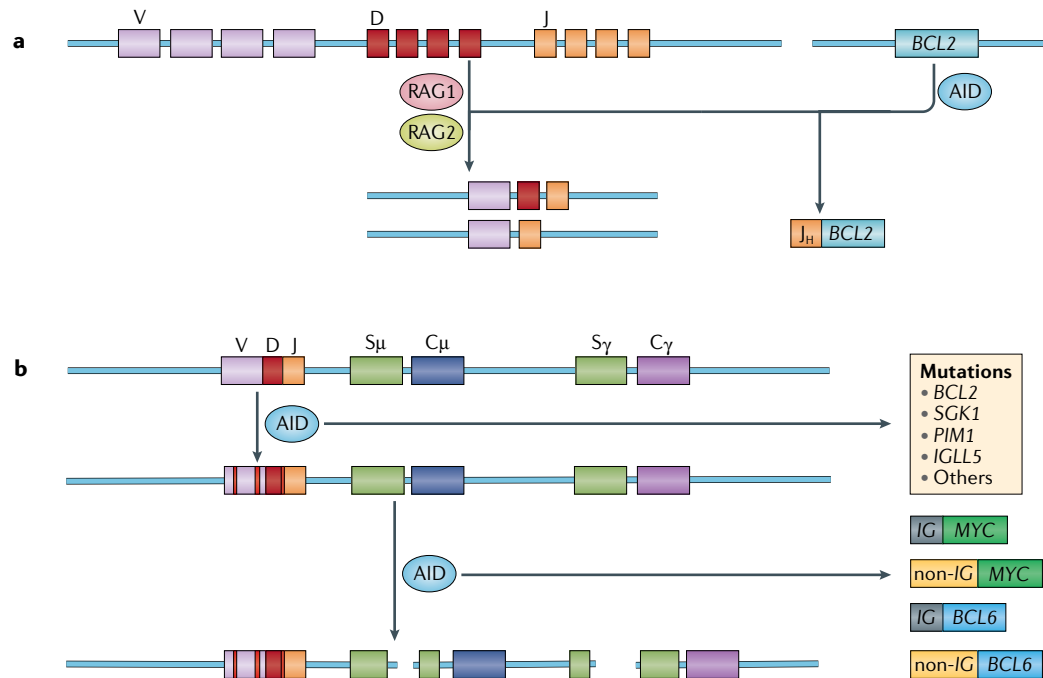


Fig. 1 | Genetic aberrations generated by RAG1 and/or RAG2 and AID in DLBCL. Immunoglobulin gene (*IG*) V(D)J recombination, somatic hypermutation and class-switch recombination all contribute to genetic aberrations in diffuse large B cell lymphoma (DLBCL). **a** | In the bone marrow, RAG1 and RAG2, which mediate V(D)J recombination, cause breaks in genes encoding immunoglobulins. For *IGH-BCL2*, the immunoglobulin breaks are caused by RAG1 and RAG2, but the *BCL2* breaks are caused by single-stranded DNA-specific cytidine deaminase (AID). **b** | In the germinal centre, AID is involved in somatic hypermutation and class-switch recombination. Aberrant somatic hypermutation can lead to base substitutions in some genes, and class-switch recombination can cause breaks in immunoglobulin or non-immunoglobulin genes, which promotes the generation of gene translocations. AID can cause mutations involving genes including *BCL2*, *SGK1*, *PIM1*, *IGLL5* and others. C, constant; J_H, joining gene segments of immunoglobulin heavy chains; S, switch.

Table 1 | Frequencies of gene mutations involved in different pathways in DLBCL^{12,13}

| Pathways | Involved genes (frequency of mutations) |
|--|---|
| B cell development and differentiation | <i>MEF2B</i> (7–12%), <i>IRF8</i> (8–11%), <i>BCL6</i> (6–11%), <i>PRDM1</i> (7–12%), <i>EBF1</i> (8–11%), <i>ZFP36L1</i> (8–9%), <i>POU2F2</i> (6–8%), <i>ETS1</i> (5–6%), <i>YY1</i> (3–4%), <i>IKZF3</i> (3–4%) and <i>BCL11A</i> (2–3%) |
| BCR and TLR signalling | <i>MYD88</i> (18–27%), <i>CD79B</i> (14–15%), <i>CARD11</i> (11–15%), <i>PRKCB</i> (4–5%), <i>PTPN6</i> (4–5%), <i>LYN</i> (3–4%), <i>GRB2</i> (2–3%) and <i>TLR2</i> (3%) |
| NF-κB pathway | <i>TNFAIP3</i> (9–18%), <i>TBL1XR1</i> (7–13%), <i>KLHL6</i> (9–10%), <i>NFKBIE</i> (3–8%), <i>ZC3H12A</i> (3–7%) and <i>NFKBIA</i> (5%) |
| MAPK–ERK pathway | <i>BRAF</i> (3–6%) and <i>KRAS</i> (3–4%) |
| PI3K–AKT–mTOR | <i>PTEN</i> (3–4%) |
| p53 and DNA damage | <i>TP53</i> (21–24%), <i>UBE2A</i> (4–8%) and <i>ZNF423</i> (0.4–2%) |
| Cell cycle | <i>PIM1</i> (22–29%), <i>BTG1</i> (14–16%) and <i>CCND3</i> (5–11%) |
| Cell apoptosis | <i>BCL2</i> (10–17%) and <i>FAS</i> (8–10%) |
| NOTCH pathway | <i>DTX1</i> (12–15%), <i>SPEN</i> (9–11%) and <i>NOTCH2</i> (7–8%) |
| Cell migration | <i>GNA13</i> (8–11%), <i>RHOA</i> (4–5%) and <i>CXCR4</i> (2–3%) |
| JAK–STAT | <i>STAT3</i> (6–10%), <i>STAT6</i> (4–5%) and <i>IL6</i> (2%) |
| Epigenetic regulators | <i>KMT2D</i> (25–33%), <i>HIST1H1E</i> (13–16%), <i>CREBBP</i> (17–18%), <i>HIST1H1C</i> (10–12%), <i>EZH2</i> (7–9%), <i>HIST1H1B</i> (9%), <i>EP300</i> (8%), <i>HIST1H2BK</i> (4–8%), <i>HIST1H1D</i> (6–7%), <i>HIST1H2BC</i> (5–6%), <i>HIST1H2AC</i> (6%), <i>HIST1H2AM</i> (6%), <i>HIST2H2BE</i> (2–5%) and <i>HIST1H3B</i> (1–3%) |
| Immune escape | <i>HLAB</i> (12–22%), <i>B2M</i> (9–17%), <i>HCAA</i> (8–16%), <i>CD70</i> (9%), <i>CD58</i> (6–11%), <i>HLAC</i> (4–7%), <i>CD83</i> (3–6%), <i>CIITA</i> (3–6%), <i>PDL1</i> (2–3%) and <i>HLADMA</i> (1–2%) |
| Others | <i>TNFRSF14</i> (14%), <i>TMSB4X</i> (12–17%), <i>SGK1</i> (10–14%), <i>ACTB</i> (9–11%), <i>ETV6</i> (7–10%), <i>PDE4DIP</i> (6–8%), <i>ZEB2</i> (4–7%), <i>LTB</i> (6–7%), <i>TMEM30A</i> (6%), <i>EEF1A1</i> (2–6%), <i>TOX</i> (4%), <i>POU2AF1</i> (3–4%), <i>SIN3A</i> (2–4%), <i>HVCN1</i> (2–3%), <i>NLRP8</i> (1–3%), <i>CRIP1</i> (1–2%), <i>XPO1</i> (1–2%), <i>SF3B1</i> (1–2%), <i>PRPS1</i> (1%), <i>CCL4</i> (1%) and <i>COQ7</i> (0.4–1%) |

BCR, B cell receptor; DLBCL, diffuse large B cell lymphoma; TLR, Toll-like receptor.

we focus on key genetic alterations and how they are likely to contribute to the pathogenesis of DLBCL.

B cell differentiation

The processes of nonmalignant B cell differentiation have been described in detail elsewhere^{22,23}. Disruptions in B cell differentiation can contribute to lymphomagenesis²³. Several genetic alterations that disrupt B cell differentiation have been reported in patients with DLBCL²³. Of the molecules involved in B cell differentiation that are disrupted in DLBCL, *BCL-6* is recognized as the master regulator of the germinal centre reaction, and *PRDM1* (also known as *BLIMP1*) is the key regulator responsible for plasma cell differentiation²³. Therefore, we discuss genetic alterations affecting *BCL-6* and *PRDM1*.

BCL-6. Physiologically, *BCL-6* recruits the SMRT–NCOR complex, which results in recruitment of histone deacetylase 3 (*HDAC3*)²⁴. *HDAC3* deacetylates the transcriptional enhancers bound by *BCL-6*, thus resulting in reduced levels of gene expression. *BCL-6* has an important role in germinal centre biology by regulating different pathways, including those that regulate the cell cycle, DNA damage repair and several others²³ (FIG. 2). Genetic alterations involving multiple molecules can lead to *BCL-6* dysregulation in DLBCL. *BCL6* translocations causing *BCL-6* overexpression are present in 19–45% of patients with DLBCL and are more common in ABC DLBCLs (24–57%) than in GCB DLBCLs (10–31%)^{25–29}. Additionally, mutations within the first non-coding region of *BCL6* are present in ~16% of patients with DLBCL who lack a detectable *BCL6* translocation; these mutations involve two *BCL-6* binding sites, thus

preventing *BCL-6* from binding to its own gene promoter region and thereby impairing negative autoregulation³⁰. Moreover, *MEF2B* mutations, which can occur in both the GCB (11–15%) and ABC (4–10%) subtypes, lead to enhanced levels of transcriptional activity, thus increasing transcription of *BCL6* (REFS^{12,31}). *FBXO11*, which mediates the ubiquitylation and degradation of *BCL-6*, is inactivated by either point mutations or small insertions or deletions (referred to hereafter as mutations) (2–4%) or deletions (2–9%) in a subset of DLBCLs^{12,32}. *FBXO11* inactivation increases *BCL-6* expression by decreasing the rate of degradation, thus stabilizing this protein³². Furthermore, mutations affecting *CREBBP* or *EP300* prevent the acetylation of *BCL-6*, thereby increasing its activity as a transcriptional repressor³³. Aberrant *BCL-6* expression in B cells promotes GC formation and disrupts plasma cell differentiation³⁴. Mice with dysregulated *BCL-6* expression develop B cell lymphomas, most of which resemble human DLBCLs, thus underscoring the importance of *BCL6* alterations in the pathogenesis of DLBCL³⁴.

PRDM1. The physiological function of *PRDM1* is to suppress the expression of genes responsible for BCR signalling and cell proliferation and promote the differentiation of germinal centre B cells into plasma cells³⁵. Truncating *PRDM1* mutations and homozygous deletions are present only in ABC DLBCLs (in 20–24% and 3–6%, respectively)^{12,36,37}. Most DLBCLs with a truncating *PRDM1* mutation (~90%) also have loss of the other *PRDM1* allele, suggesting biallelic inactivation of *PRDM1* (REF³⁷). Additionally, missense mutations in *PRDM1* can lead to decreased stability and/or transcriptional function of *PRDM1* in some patients³⁸. In mice,

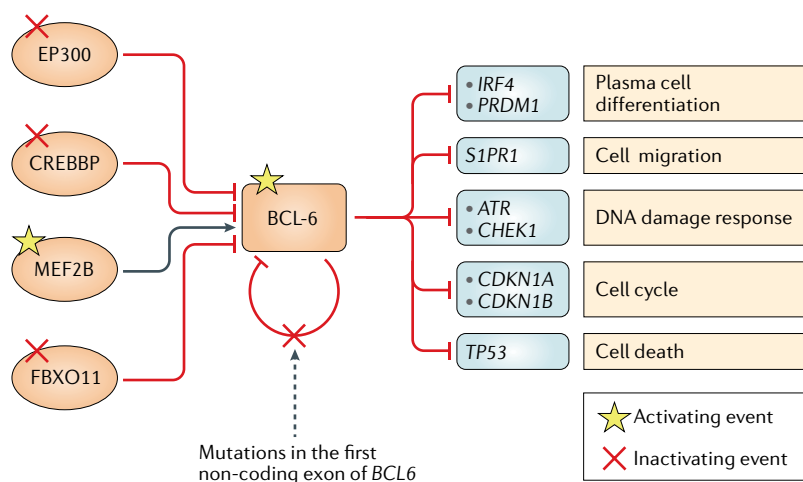


Fig. 2 | Disruption of BCL-6. BCL-6 has an important role in the germinal centre, including suppression of the transcription of genes involved in plasma cell differentiation and the DNA damage response. CREBBP, EP300 and FBXO11, which suppress the activity or stability of BCL-6, are inactivated in some diffuse large B cell lymphomas. Mutations in *MEF2B* and the first non-coding exon of *BCL6* and *BCL6* translocations promote BCL-6 expression.

conditional knockout of *Prdm1* in B cells results in constitutive NF- κ B activation and development of lymphoproliferative disorders, some of which have characteristics similar to those of human ABC DLBCLs³⁷. These data suggest that *PRDM1* alterations promote lymphomagenesis by increasing the level of NF- κ B activation and thus blocking plasma cell differentiation.

BCR signalling and related pathways

BCR signalling. Physiologically, BCR signalling is involved in the regulation of B cell survival, development and differentiation³⁹. BCR signalling in patients with DLBCL can be categorized into chronic active or tonic signalling. Chronic active BCR signalling resembles antigen-dependent active BCR signalling in nonmalignant B cells and is characterized by BCR clustering^{40–42}. Tonic BCR signalling is antigen-independent, and clustering is typically not observed in B cells that depend on tonic BCR signalling⁴⁰. ABC DLBCLs are characterized by chronic active BCR signalling, whereas GCB DLBCLs are dependent on tonic BCR signalling^{40,43}. Genetic events targeting BCR signalling regulators have been reported in DLBCL (FIG. 3).

CD79A and CD79B form a heterodimer and constitute important parts of the BCR signalling complex (FIG. 3). Following dual phosphorylation by members of the SRC family of tyrosine kinases, the intracellular immunotyrosine-based activation motifs (ITAMs) of CD79A and CD79B recruit and activate SYK kinase. SYK then activates BTK, leading to downstream activation of BCR signalling. Mutations involving the ITAMs of CD79B are detected in ~20% of ABC DLBCLs but only in 3% of GCB DLBCLs⁴⁰. Mutations in the ITAMs of CD79A are also detected in a small fraction of ABC DLBCLs (3%)⁴⁰. Most mutations in CD79B affect the first tyrosine of the ITAM, resulting in increased cell surface IgM expression and reduced LYN kinase activity, which normally inhibits BCR signalling via negative feedback⁴⁰. Thus, CD79B mutations might promote

lymphomagenesis by increasing cell surface BCR expression and reducing the negative feedback-mediated inhibition of BCR signalling⁴⁰.

Physiologically, activation of BTK by proximal BCR signalling leads to PLC γ 2 and PKC β activation (FIG. 3). Activated PKC β phosphorylates the scaffold protein CARD11, thus recruiting BCL-10 and the paracaspase MALT1 to form a complex that then activates IKK and ultimately the NF- κ B pathway⁴⁰. *CARD11* mutations, which are mostly located in the coil-coil domain, occur in both ABC (7–18%) and GCB (4–17%) DLBCLs^{12,44,45}. *CARD11* mutations impair the auto-inhibition conferred by the inhibitory domain of the wild-type protein, thus conferring a CARD11-hyperactive state that leads to constitutive activation of NF- κ B, which becomes intensified during antigen stimulation⁴⁶. The wild-type scaffold protein BCL-10 can induce apoptosis and NF- κ B activation⁴⁷. Investigators reported that *BCL10* translocations, which might contribute to BCL-10 overexpression, were present in both GCB (25%) and ABC (11%) DLBCLs²⁸. *BCL10* amplifications were also identified in 2% of both DLBCL subtypes¹². Mutations in *BCL10* have been reported in both the ABC (10%) and GCB (6%) subtypes of DLBCL¹². Potentially pathogenic mutations in *BCL10* are predominantly localized to the carboxy-terminal domain, most of which cause truncation of the BCL-10 protein⁴⁸. Truncated BCL-10 loses its pro-apoptotic activities but can still activate the NF- κ B pathway, which might explain the pathogenic role of this protein in DLBCL⁴⁸. MALT1 paracaspase activity is indispensable for the survival of ABC DLBCL cells⁴⁹. Amplifications involving *MALT1* have been detected in 7% of ABC DLBCLs, but rarely in GCB DLBCLs (1%), thus supporting a role of *MALT1* as an oncogene in ABC DLBCLs¹².

Toll-like receptor signalling. Wild-type MYD88 functions as an adaptor protein that mediates Toll-like receptor (TLR) and/or IL-1 receptor signalling (FIG. 3). Mutations in *MYD88* are more common in ABC DLBCLs (~40%) than in GCB DLBCLs (8–14%)^{12,50,51}, and the hotspot *MYD88*^{L265P} mutation is present exclusively in ABC DLBCLs (~30%)⁵¹. DLBCLs harbouring *MYD88*^{L265P} have distinctly different genomic and clinical features to those of DLBCLs harbouring other *MYD88* mutations^{51,52}. *MYD88*^{L265P} mutations are more common in DLBCLs located at specific extranodal sites, including in the central nervous system (CNS; primary DLBCL of the CNS; 36–86%)^{53–56}, breast (39–59%)^{57–59}, skin (primary cutaneous DLBCL, leg type; 59–74%)^{60–63} and testis (79–82%)^{56,64,65}. The *MYD88*^{L265P} mutation promotes the assembly of a complex composed of IRAK1 and IRAK4, resulting in enhanced IRAK4 kinase activity and IRAK1 phosphorylation⁵⁰. Hyperphosphorylated IRAK1 causes downstream activation of NF- κ B and JAK-STAT signalling, even in an absence of foreign TLR ligands. *MYD88* mutations and CD79A or CD79B mutations co-occur in ~10% of ABC DLBCLs¹². CD79A or CD79B mutations are more prevalent in ABC DLBCLs harbouring *MYD88*^{L265P} (34%) than in those without (18%)⁵⁰, suggesting that these mutations function cooperatively in the development

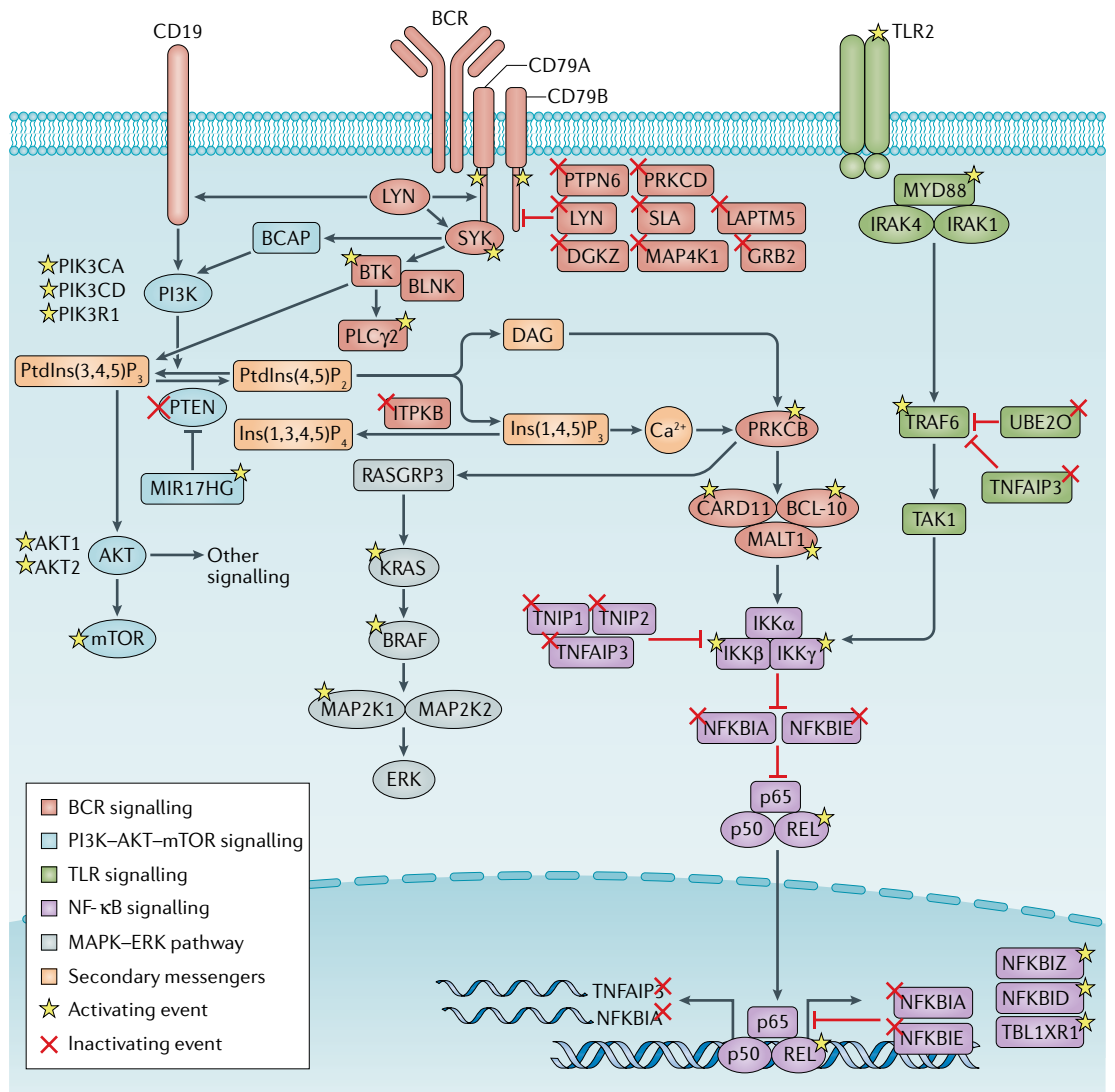


Fig. 3 | Genetic aberrations involving BCR signalling and related pathways. Antigen binding to the B cell receptor (BCR) triggers the activation of SYK, BTK and PKCβ, which promotes the formation of the CARD11–BCL-10–MALT1 complex. This complex recruits and activates IKK, leading to downstream NF-κB activation. Both activating genetic aberrations targeting positive regulators and inactivating events involving negative BCR signalling are frequent occurrences in diffuse large B cell lymphoma (DLBCL). PKCβ also activates MAPK–ERK signalling. Mutations in genes that encode components of the MAPK–ERK signalling pathway can also be identified in a subset of DLBCLs¹². Mutations in *MYD88* activate Toll-like receptor (TLR) signalling, and activating genetic events involving other positive regulators, including *TLR2* and *TRAF6*, have also been reported¹². IKK activation is essential for the activation of downstream NF-κB signalling, and many genetic aberrations targeting positive or negative regulators are able to modulate NF-κB activation. Activating events involving PI3K subunits (*PIK3CA*, *PIK3CD* and *PIK3R1*) could lead to downstream AKT activation. Loss of PTEN function and/or AKT–mTOR activating events can also contribute to the activation of this pathway. Ins(1,3,4,5)P₄, inositol-1,3,4,5-tetrakisphosphate; Ins(1,4,5)P₃, inositol-1,4,5-trisphosphate; PtdIns(3,4,5)P₃, phosphatidylinositol-3,4,5-trisphosphate; PtdIns(4,5)P₂, phosphatidylinositol-4,5-bisphosphate.

of ABC DLBCLs. Data published in 2018 demonstrate that MYD88, TLR9 and BCR form a multiprotein supercomplex (the My-T-BCR supercomplex), which colocalizes with mTOR on endolysosomes, thus promoting downstream NF-κB and mTOR signalling⁶⁶. The survival of *MYD88*^{L265P} and *CD79A*-mutant or *CD79B*-mutant ABC DLBCL cell lines is much more dependent on the My-T-BCR supercomplex than that of other ABC DLBCL and GCB DLBCL cell lines⁶⁶, thus highlighting the importance of the My-T-BCR supercomplex in this form of ABC DLBCL.

NF-κB regulators. Signalling via the NF-κB pathway is finely tuned by various positive and negative regulators (FIG. 3). For example, the proto-oncogene REL is an NF-κB family member that transactivates target genes by forming homodimers or heterodimers with other NF-κB family members including p65 and p50 (REFS^{67,68}). *REL* is amplified predominantly in a subset of GCB DLBCLs (~7%), and amplification is associated with elevated levels of *REL* mRNA⁶⁹. Increased REL expression might promote lymphomagenesis by increasing the level of NF-κB activation. The ubiquitin-modifying enzyme

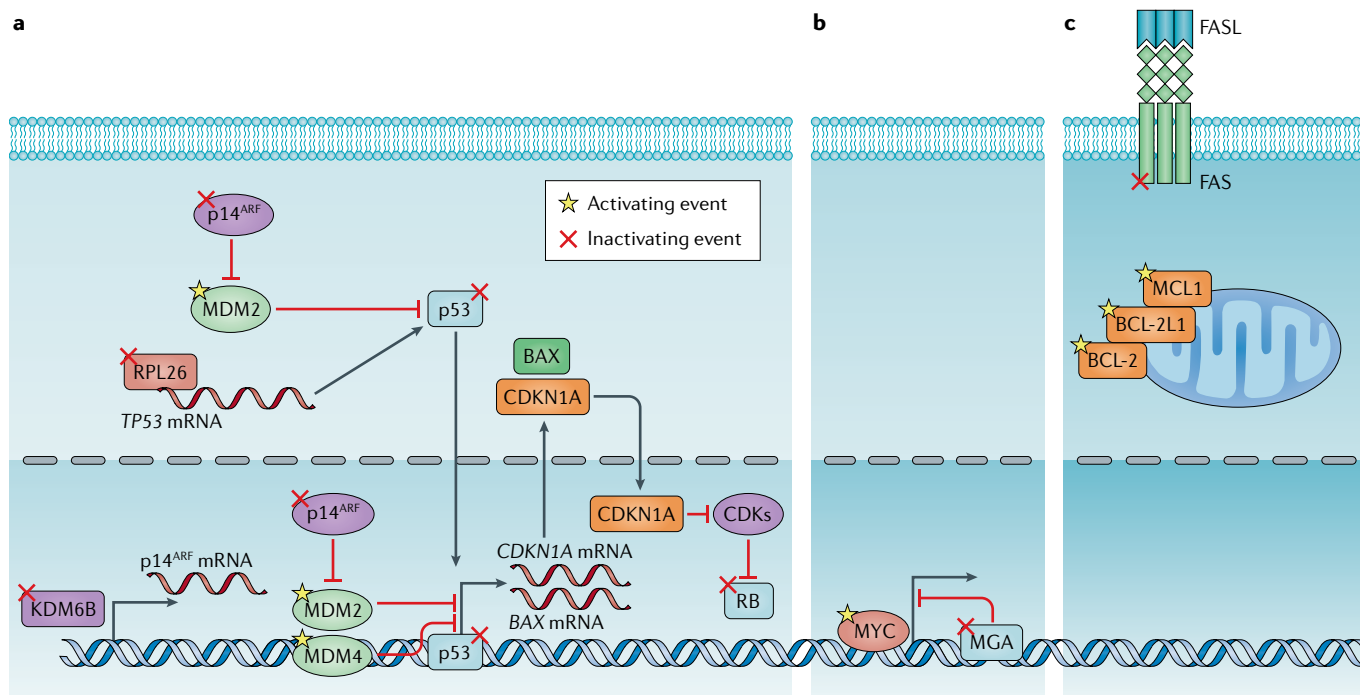


Fig. 4 | Genetic events and aberrations in p53, MYC and apoptotic pathways. **a** | p53 activates the transcription of a group of genes, including *BAX*, *CDKN1A* and others, which regulate several cellular processes including cell death and cell cycle progression. Genetic alterations can impair the activity of p53 by affecting p53 translation (*RPL26*) and protein stability (*MDM2*) as well as transcriptional activity (*MDM2* and *MDM4*). *MDM2* is inactivated by *p14^{ARF}*; the *CDKN2A* locus, which contains the gene encoding *p14^{ARF}*, is deleted in 30–40% of activated B cell diffuse large B cell lymphomas (ABC DLBCLs)^{12,80}. *KDM6B*, which transcriptionally activates *p14^{ARF}*, is also inactivated by deletions (~10% of all DLBCLs)⁸⁴. **b** | *MAX* gene-associated protein (*MGA*) negatively regulates *MYC* transcriptional activity; *MYC* translocations, amplifications and mutations leading to *MGA* inactivation can all result in *MYC* activation. **c** | Alterations in *FAS* that impair extrinsic apoptosis pathways, as well as alterations in *BCL2*, *BCL2L1* and *MCL1* that impair intrinsic apoptosis pathways, have been identified in some DLBCLs.

TNFAIP3 also inhibits the NF-κB pathway by targeting *IKK⁷⁰*. *TNFAIP3* aberrations can be identified in GCB DLBCLs, although biallelic *TNFAIP3* inactivation owing to deletions and/or mutations is more common in ABC DLBCLs (~30%) and leads to hyperactivation of the NF-κB pathway^{71,72}. *TNFAIP3* mutations accompany *MYD88^{L265P}* mutations in 7% of ABC DLBCLs, and the loss of *TNFAIP3* potentiates signalling driven by *MYD88^{L265P}*, suggesting that *TNFAIP3* inactivating mutations and *MYD88^{L265P}* are able to cooperate in the pathogenesis of ABC DLBCL^{73,74}.

PI3K–AKT–mTOR. Both the BCR co-receptor *CD19* and *SYK* kinase are able to activate *PI3K* signalling⁴¹. Activated *PI3K* triggers *AKT* activation, leading to activation of *mTOR* and other signalling pathways that promote cell survival⁷⁵ (FIG. 3). Abnormalities involving genes encoding *PI3K* subunits have been reported, and preliminary functional studies suggest that these abnormalities have a role in the pathogenesis of DLBCL^{12,76}. Amplifications or activating mutations involving the *PI3K* subunit *PIK3CA* have been identified in ~6% of ABC DLBCLs but not in GCB DLBCLs¹². *PTEN* deletions are detected in 9–11% of DLBCLs, including in both the GCB and ABC subtypes^{12,13,77–79}. These *PTEN* deletions promote *PI3K–AKT* signalling, thereby contributing to lymphomagenesis^{13,77}. *MIR17HG*, which encodes a microRNA that targets *PTEN* mRNA, is amplified

predominantly in GCB DLBCLs (~8%)¹². *MIR17HG* amplification leads to reduced *PTEN* expression and promotes *mTOR* signalling.

p53 pathway

TP53. *TP53* is deleted in 8–24% of all DLBCLs, including both the ABC and GCB subtypes⁸⁰ (FIG. 4a). Approximately 20% of both the ABC and GCB subtypes of DLBCL harbour mutations in *TP53* (REFS^{12,81,82}). In DLBCL, most *TP53* mutations are located in exons 5–8 and disrupt the DNA-binding motifs, thus impairing p53-mediated transcriptional regulation⁸². Novel single-nucleotide variations (SNVs) within the 3' untranslated region (UTR) of *TP53* have also been identified in ~30% of DLBCLs⁸³. Most of these SNVs cluster in regions that are complementary to the seeding sequence of microRNAs that could potentially target *TP53* mRNA⁸³. A possible explanation of this mechanism is that mutations in the 3' UTR, when co-occurring with mutations in the coding sequence (CDS), impede the inhibitory effects of microRNAs on *TP53* translation, thus further increasing the expression of mutant p53 (REF.⁸³).

Genes encoding proteins modifying p53 expression, stability or activity. Several genetic alterations that impede the expression or activity of p53 have been identified in DLBCL⁸⁴ (FIG. 4a). The E3 ubiquitin ligase *MDM2* promotes p53 degradation and inhibits the transcription of

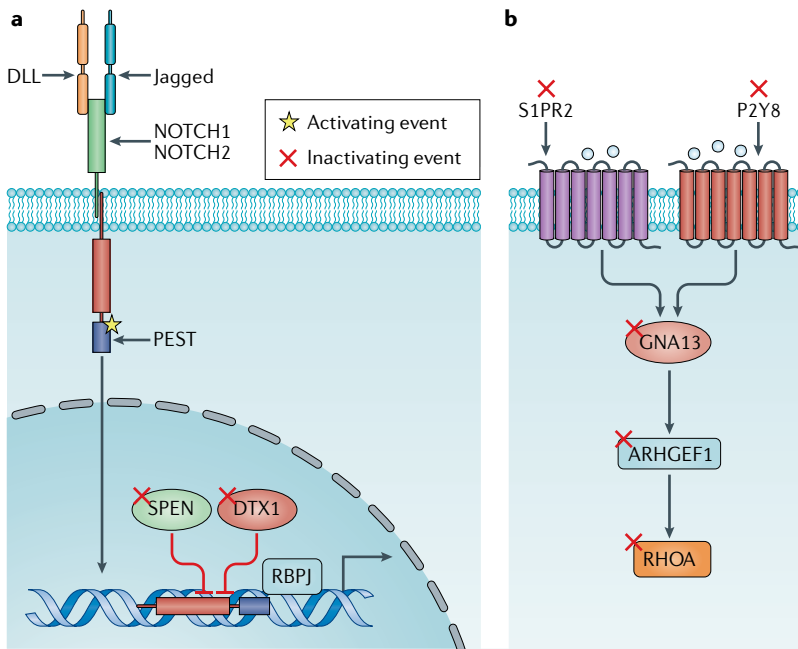


Fig. 5 | Genetic events and aberrations in NOTCH signalling and cellular migration pathways. a | Both the stability and transcriptional activity of NOTCH have implications for the regulation of NOTCH signalling. Mutations affecting the stability of NOTCH proteins (in *NOTCH1* and *NOTCH2*) and NOTCH transcriptional activity (in *DTX1* and *SPEN*) activate NOTCH signalling. **b** | G protein-coupled receptors, including sphingosine 1-phosphate receptor 2 (*S1PR2*) and *P2Y8* regulate cellular migration. Genetic alterations targeting these receptors and their associated downstream signalling proteins promote lymphomagenesis by affecting cell migration.

p53 target genes. MDM2 is usually inactivated by p14^{ARF}, thereby promoting the stability and transcriptional activity of p53. p14^{ARF} is an alternative reading frame product of *CDKN2A*, which also encodes p16^{INK4A} and can be deleted in 30–40% of ABC DLBCLs, although only in ~5% of GCB DLBCLs^{12,78,80}. Loss of *CDKN2A* might impair the p14^{ARF} pathway, thus contributing to decreased p53 expression and function⁸⁰. A variety of other genetic events that affect the expression, stability or activity of p53 have also been reported^{84,85} (FIG. 4a).

MYC

MYC dysregulation contributes to lymphomagenesis by modulating many cellular functions, including metabolism and energy regulation, DNA replication, nucleotide and protein biosynthesis and cell proliferation⁸⁶ (FIG. 4b). *MYC* translocations with immunoglobulin gene partners (including *IGH*, *IGK* and *IGL*) or non-immunoglobulin partners can occur in 4–14% of DLBCLs and can affect both the GCB and ABC subtypes⁸⁶. *IG-MYC* translocations juxtapose *MYC* to the immunoglobulin enhancers, thereby resulting in constitutive *MYC* expression; such fusions account for approximately half of all *MYC* translocations in DLBCL^{86,87}. DLBCLs harbouring *MYC* rearrangements that do not involve immunoglobulin genes have higher levels of *MYC* expression than those that lack *MYC* translocations but lower levels than those of DLBCLs harbouring *IG-MYC* rearrangements. The mechanisms of *MYC* dysregulation in non-*IG-MYC*-rearranged DLBCLs remain unclear. *MYC* gains or amplifications can also be identified in 11–30% of DLBCLs,

including both the GCB and ABC subtypes, and are associated with elevated *MYC* mRNA expression^{88–90}. *MYC* mutations are found in the CDS or UTRs of ~30% of patients with DLBCL and are equally distributed across the GCB and ABC subtypes⁹¹. The *MYC*^{T58} mutation impairs the phosphorylation of T58 and subsequent ubiquitylation of the *MYC* protein, thereby stabilizing the *MYC* protein. Interestingly, data from in vivo and in vitro studies have shown that a large proportion of exonic *MYC* mutations result in loss of function⁹¹. Less is known about the biological implications of mutations in the *MYC* UTRs. Mutations in the 3' UTR are postulated to affect *MYC* expression by impeding inhibition by microRNAs⁹¹.

Apoptosis

BCL-2. A lack of *BCL-2* activity is essential for inducing apoptosis in germinal centre B cells that lack affinity for a specific antigen. Constitutive *BCL-2* activation enables B cells to avoid the germinal centre apoptotic programme, thereby contributing to lymphomagenesis. Aberrant *BCL-2* activation is often driven by genetic aberrations in *BCL2* itself (FIG. 4c). The t(14;18)(q32;q21) translocation occurs almost exclusively in the GCB subtype of DLBCL and has been identified in 34–44% of GCB DLBCLs^{90,92,93}. This translocation juxtaposes *BCL2* adjacent to *IGH*, thus leading to constitutive *BCL-2* expression⁹⁴. *BCL2* gains or amplifications, which are also associated with *BCL-2* overexpression, occur almost exclusively in DLBCLs of the ABC subtype (~14%)^{95–97}. Somatic mutations involving the promoter and coding regions of *BCL2* are caused by somatic hypermutation, can be detected in ~35% of DLBCLs and are significantly enriched in the GCB subtype⁹⁸. Not all *BCL2* mutations have functional consequences because somatic hypermutation often generates functionally irrelevant mutations. Mutations affecting the *BCL2* promoter region disrupt *BCL-6* binding and thereby impair *BCL-6*-mediated repression of *BCL2* transcription, resulting in increased *BCL-2* expression⁹⁹. Mutations located in the exons of *BCL2* are distributed mostly in the BH4 domain and flexible loop domain (FLD). Mutations in the BH4 domain of *BCL2* might prevent interactions with the endoplasmic reticulum-bound inositol-1,4,5-triphosphate (Ins(1,4,5)P₃) receptor, thereby impeding both Ins(1,4,5)P₃-mediated Ca²⁺ release and apoptosis¹⁰⁰. Mutations located in a negative regulatory region of the FLD of *BCL2* might disrupt p53–*BCL-2* interactions, thereby enhancing the anti-apoptotic activity of *BCL-2* (REF.¹⁰¹). D34H/G mutations in the FLD of *BCL2* result in alterations at the caspase 3 cleavage site, thus preventing proteolysis of *BCL-2* and subsequent apoptosis^{98,102}. Notably, almost all mutations in *BCL2* spare the BH3 domain, which is the target of the *BCL-2* inhibitor venetoclax^{98,103}.

NOTCH signalling

Genetic aberrations that disrupt NOTCH signalling have been reported in DLBCL (FIG. 5a). *NOTCH1* is exclusively mutated in ABC DLBCL (~6%), and *NOTCH2* mutations are enriched in unclassified DLBCL (~21% of this subtype)¹². *NOTCH1* and *NOTCH2* mutations result in truncation of the PEST domain, resulting in an increase in the stability of this protein^{104,105}. *SPEN*,

which encodes a NOTCH pathway inhibitor, is mutated in ~11% of DLBCLs, and mutations in this protein occur more frequently in unclassified DLBCLs (~18%)¹². Loss of SPEN inhibitory function leads to activation of the NOTCH pathway and is likely to contribute to the pathogenesis of DLBCL.

Cell migration and adhesion

Under nonmalignant conditions, germinal centre B cells do not enter the circulation and cannot survive outside of the germinal centre. Sphingosine 1-phosphate (S1P) receptor 2 (S1PR2) and the downstream mediators Ga13 (encoded by *GNA13*) and ARHGEF1 are involved in Ga13 signalling, which controls the growth of germinal centre B cells and confines these cells to the germinal centre¹⁰⁶ (FIG. 5b). Ligation of S1PR2 by S1P activates Ga13 signalling, thereby inhibiting CXCL12-induced AKT phosphorylation and cell migration and maintaining germinal centre homeostasis. Additionally, the P2Y8 receptor also inhibits germinal centre B cell growth and promotes

the confinement of germinal centre B cells via Ga13 signalling¹⁰⁷. Mutations affecting *S1PR2*, *GNA13*, *ARHGEF1* or *P2RY8* have been identified in ~30% of GCB DLBCLs but are rarely detected in ABC DLBCLs¹⁰⁸. These mutations disrupt Ga13 signalling, leading to dissemination of germinal centre B cells. Furthermore, *GNA13* mutations and *BCL2* translocations, and possibly activating mutations, frequently co-occur in GCB DLBCL^{108,109}, suggesting that these abnormalities are able to synergize in promoting the development of GCB DLBCL. Ga13 deficiencies promote the dissemination of germinal centre B cells, and BCL-2 overexpression confers a further survival advantage to these cells outside of the germinal centre niche, thus contributing to lymphomagenesis¹⁰⁸.

Epigenetic regulators

Dysregulation of the epigenome is a driving force in the pathogenesis of DLBCL. Genes encoding histone methyltransferases or acetyltransferases are frequently disrupted in DLBCL (FIG. 6).

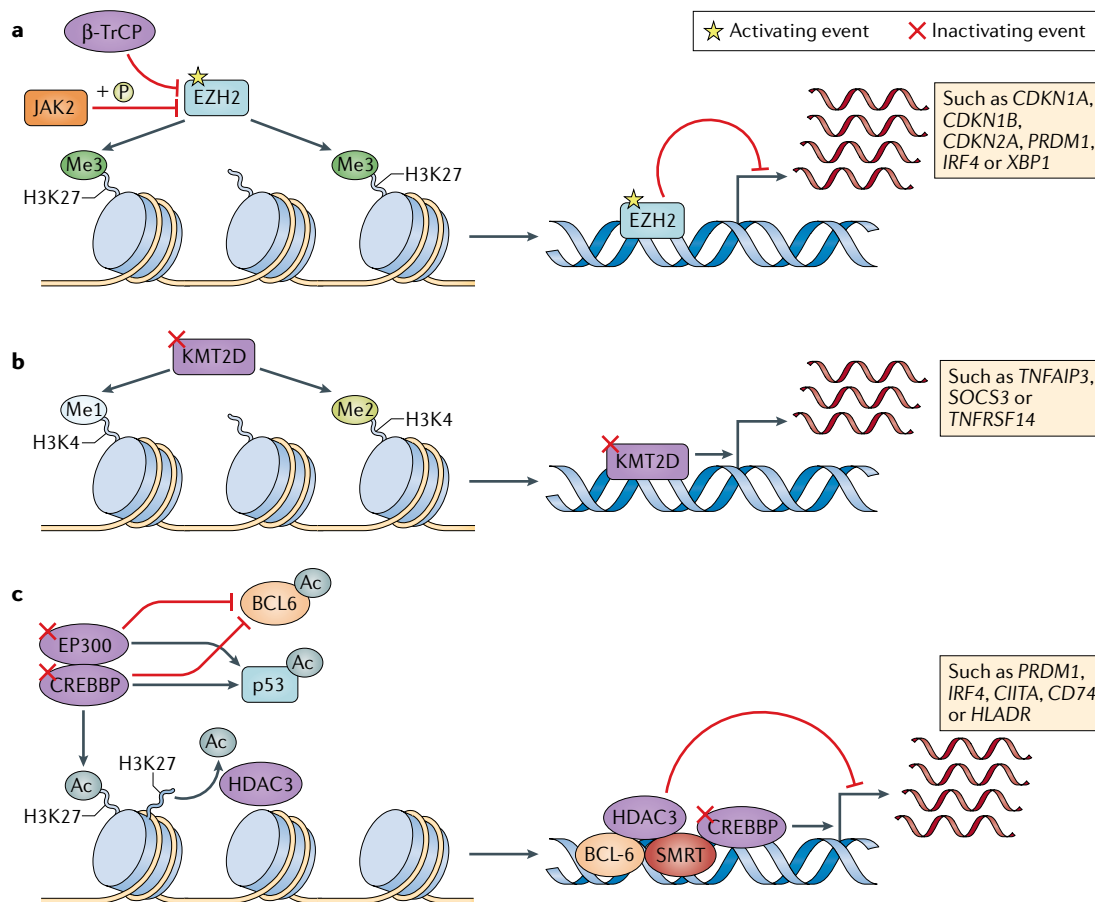


Fig. 6 | **Alterations in epigenetic regulation that contribute to the development of lymphoma.** a | EZH2 mediates trimethylation of Lys27 of the histone H3 subunit (H3K27), which suppresses transcriptional activity. Activating mutations in *EZH2* lead to increased trimethylation of H3K27, thus inhibiting the expression of genes involved in cell cycle regulation and plasma cell differentiation. b | KMT2D facilitates transcription by inducing H3K4 monomethylation and dimethylation. Alterations in *KMT2D* inactivate KMT2D, thus downregulating the expression of several tumour suppressor genes. c | CREBBP and EP300 mediate H3K27 acetylation, thus promoting transcription. CREBBP also acetylates BCL-6 and p53, resulting in decreased levels of BCL-6 activity and increased p53 activity, respectively. CREBBP inactivation results in decreased expression of genes involved in plasma cell differentiation and immune responses, thus contributing to tumorigenesis. Ac, acetylated; HDAC3, histone deacetylase 3; Me1, monomethylated; Me2, dimethylated; Me3, trimethylated.

EZH2. *EZH2* encodes the catalytic subunit of Polycomb repressive complex 2 (PRC2) and is responsible for methylating the Lys27 residue of histone H3 (REF.¹¹⁰). (FIG. 6a). *EZH2* inactivation in germinal centre B cells results in defective germinal centre formation. In germinal centre B cells, *EZH2* binds to bivalent promoters, which are characterized by the presence of both activating (trimethylation of Lys4 of histone H3) and repressing (trimethylation of Lys27 of histone H3) chromatin markers; by mediating trimethylation of Lys27 of histone H3, *EZH2* represses the expression of genes involved in cell cycle regulation and plasma cell differentiation, thereby improving B cell proliferation, protecting germinal centre B cells from AID-dependent genotoxic damage-induced apoptosis and restricting plasma cell differentiation^{111–113}.

Tyr641 mutations in a single allele of *EZH2* have been detected in ~20% of GCB DLBCLs but are generally absent from ABC DLBCLs^{12,114}. Mutant and wild-type forms of *EZH2* have been reported to cooperate in the development of B cell lymphomas¹¹⁵. *EZH2*^{Y641F/N} mutations confer altered substrate specificity, favouring the methylation of dimethylated peptides, which consequently improves the transition from dimethylation to trimethylation¹¹⁶. Additionally, *EZH2*^{Y641} mutations abrogate phosphorylation of this protein by JAK2, thus impairing the interaction of *EZH2* with the E3 ligase β -TrCP and leading to diminished protein degradation and increased *EZH2* stability¹¹⁷. DLBCLs harbouring *EZH2*^{Y641} mutations have remarkably higher levels of trimethylated histones (H3K27me3) than *EZH2* wild-type DLBCLs, suggesting enhanced activity of PRC2¹¹⁶. *EZH2*^{Y641} mutations confer suppression of *CDKN1A* and *PRDM1* expression, which contributes to hyperproliferation of germinal centre B cells and blockade of plasma cell differentiation, respectively¹¹³. Although *EZH2*^{Y641} mutations induce substantial levels of germ cell hyperplasia, *EZH2*^{Y641N} knock-in alone does not generate B cell lymphomas, whereas overexpression of BCL-2 combined with *EZH2*^{Y641} mutation induces aggressive B cell lymphomas in mice¹¹³, suggesting that BCL-2 aberrations and the mutated *EZH2*^{Y641} allele are able to synergize in the development of DLBCL.

KMT2D. The histone monomethyltransferase KMT2D induces both monomethylated and dimethylated H3K4 (H3K4me1 and H3K4me2, respectively), thereby promoting transcription (FIG. 6b). Approximately 30% of all DLBCLs, including those of both the GCB and ABC subtypes, harbour *KMT2D* mutations, most of which are nonsense or frameshift mutations that are likely to confer loss of KMT2D function^{12,109,118}. *KMT2D* missense mutations located in the carboxy-terminal enzymatic domains are also able to impair the methyltransferase activity of KMT2D¹¹⁹. Reduced KMT2D expression can also be observed in a subset of DLBCLs that lack *KMT2D* alterations, suggesting that other mechanisms, including epigenetic regulation, might have a role in regulating KMT2D function¹¹⁹.

A lack of functional KMT2D delays the involution of the germinal centre, inhibits B cell differentiation and class-switch recombination and promotes

lymphomagenesis in mouse models^{118,119}. Loss of KMT2D function in lymphoma cells results in a global reduction in H3K4 methylation, which is related to dysregulated expression of genes involved in BCR, CD40 and JAK–STAT signalling¹¹⁸. Notably, a combination of data from chromatin immunoprecipitation and RNA sequencing studies demonstrates that KMT2D targets tumour suppressor genes in DLBCL, such as *TNFAIP3*, *SOCS3* and *TNFRSF14* (REF.¹¹⁸). KMT2D inactivation might also disrupt the expression of genes involved in the cell cycle and apoptosis, such as *CDK6* and *BCL2* (REF.¹¹⁹). Thus, *KMT2D* aberrations promote the development of DLBCL by perturbing genes involved in B cell activation, the cell cycle and apoptosis.

CREBBP and EP300. The histone acetyltransferase CREBBP mediates H3K27 acetylation, which is important for gene enhancer activation (FIG. 6c). *CREBBP* mutations, including truncating and missense mutations in the histone acetyltransferase domain, have been reported in ~20% of patients with DLBCL^{120,121} and are more commonly associated with the GCB subtype than the ABC subtype. *CREBBP* mutations can be detected in haematopoietic stem cells from patients with *CREBBP*-mutated lymphomas, suggesting that *CREBBP* mutations are an early event in lymphomagenesis¹²². *CREBBP* deletions can also occur in DLBCL. Such aberrations generally involve only one *CREBBP* allele, suggesting that, in DLBCL, *CREBBP* is a haploinsufficient tumour suppressor¹²³.

CREBBP has an important role in regulating germinal centre physiology in the absence of malignancy. Conditional knockout of *Crebbp* in germinal centre B cells in mouse models leads to a remarkable increase in the number of germinal centre B cells, resulting in enlargement of the germinal centre and promoting the development of MYC-driven lymphoma¹²⁴. *CREBBP* deficiency promotes lymphomagenesis by remodelling the epigenetic landscape. In both lymphoma cells and nonmalignant germinal centre B cells, *CREBBP* deficiency leads to the loss of enhancer H3K27 acetylation and decreased expression of genes located near those enhancers, including those involved in germinal centre exit and the immune response^{123,125}. Accordingly, *CREBBP*-mutant lymphomas have decreased expression of genes involved in germinal centre exit, those responsible for plasma cell differentiation and those associated with antigen presentation by MHC class II, suggesting that *CREBBP* deficiencies contribute to lymphomagenesis by blocking B cell differentiation and facilitating immune escape¹²⁵. Most *CREBBP*-bound regions are also direct targets of BCL-6, suggesting that BCL-6 and *CREBBP* have opposing roles in transcriptional regulation¹²⁵. Moreover, *CREBBP* mediates acetylation of BCL-6; therefore, loss of *CREBBP* function impairs the acetylation-mediated inactivation of BCL-6 (REF.³³). *CREBBP* inactivation also abrogates the acetylation of p53, thus rendering it unable to undergo post-transcriptional activation¹²⁶. Defects in p53 activation by *CREBBP* attenuate the DNA damage response in lymphoid progenitors, allowing more mutations to be acquired and favouring the subsequent transformation to cells of a malignant phenotype¹²².

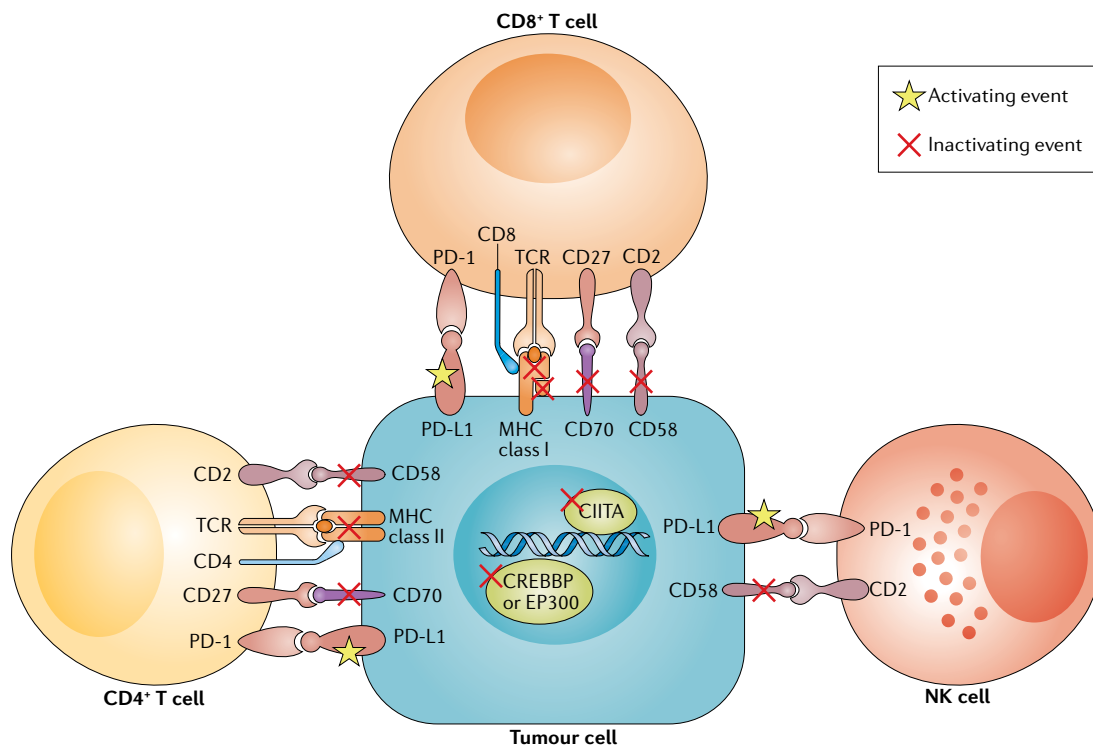


Fig. 7 | **Genetic alterations related to immune escape.** Mutations leading to the loss of MHC class I and class II molecules abrogate the presentation of antigens to T cells. Other abnormalities result in the failure to activate T cells (*CD70* aberrations) or natural killer (NK) cells (*CD58* aberrations) or lead to increased suppression of T cells and NK cells by tumour cells (*PDL1* aberrations). PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; TCR, T cell receptor.

EP300 is another histone acetyltransferase that maintains H3K27 acetylation. *EP300* is mutated in ~10% of DLBCLs, including both the GCB and ABC subtypes³³. *EP300* and *CREBBP* mutations are mutually exclusive in DLBCL, suggesting that the encoded proteins have overlapping functions. Inactivation of *EP300* leads to decreased H3K27 acetylation, thus resulting in alterations in gene expression that are similar to *CREBBP* mutations¹²⁴. *VavP-Bcl2* transgenic mice deficient in *EP300* have similar phenotypes to those lacking *CREBBP*, thus providing further support for common roles of *EP300* and *CREBBP* in DLBCL¹²³.

Immune evasion

Alterations in genes involved in antigen presentation and T cell activation or inhibition have been identified, thus improving our understanding of the mechanisms of immune escape involved in DLBCL development (FIG. 7).

MHC molecules. The MHC class I complex consists of a chain encoded by the HLA genes (*HLAA*, *HLAB* and *HLAC*) and β_2 -microglobulin. Deletions or inactivating mutations in *HLAA*, *HLAB* and *HLAC* occur frequently in DLBCL, especially in the ABC subtype¹². Deletions or mutations resulting in inactivation of β_2 -microglobulin have been detected in 29% of DLBCLs, including both the GCB and ABC subtypes¹²⁷. Loss of functional β_2 -microglobulin results in loss of MHC class I expression on the cell surface, thus contributing to evasion of CD8⁺ T cell-mediated cytotoxicity¹²⁷. *HLA-DMA* and *HLA-DMB* mutations, which disrupt the MHC class II

complex, have also been reported in DLBCL, predominantly in the GCB subtype (~10%)¹². Physiologically, MHC class II expression, which is essential for an effective CD4⁺ T cell-mediated antitumour response, occurs via transactivation by the MHC class II transactivator protein *CIITA*¹²⁸. *CIITA* aberrations, including mutations, deletions and rearrangements, are more common in the GCB (~20%) than in the ABC (~10%) subtype and typically result in reduced MHC class II expression¹². As mentioned above, *CREBBP* and *EP300* alterations can also contribute to decreased MHC II expression^{124,125}. These observations, taken together, suggest that genetic aberrations in MHCs and related genes are able to facilitate the development of lymphoma, at least in part by impairing CD8⁺ or CD4⁺ T cell-mediated antitumour immunity.

CD58. As a ligand of the CD2 receptor expressed on T cells and natural killer (NK) cells, CD58 regulates the adhesion and activation of these cells. *CD58* mutations and deletions occur in ~21% of DLBCLs and are more common in the ABC subtype (in 68%) than in the GCB subtype (32%)¹²⁷. Both mutations and deletions of *CD58* cause loss of surface CD58 protein, thus impairing cytolysis of DLBCL cells mediated by NK cells.

PD-L1 and PD-L2. *PDL1* and/or *PDL2* copy number gains, amplifications and translocations, have been identified in DLBCL and are more frequent in the non-GCB (27%) than in the GCB (6%) subtype¹²⁹. These *PDL1* aberrations correlate with programmed cell death 1

ligand 1 (PD-L1) overexpression, thus facilitating T cell exhaustion in the microenvironment. Structural variations including tandem duplications, inversions, translocations and deletions that disrupt the 3' UTR of *PDL1* mRNA have been identified in ~8% of DLBCLs¹³⁰. These structural variations potentially prevent the binding of certain inhibitory microRNAs, thus leading to increased PD-L1 expression^{131,132}. Furthermore, disruption of the 3' UTR of *PDL1* mRNA promotes immune escape and tumour growth in mouse models, suggesting a role of aberrations in the 3' UTR of *PDL1* mRNA in the pathogenesis of DLBCL¹³⁰.

Other molecules

Genetic events involving other pathways have also been identified in DLBCL. For example, mutations in *TNFRSF14* have been identified exclusively in GCB DLBCLs (~30%)¹². The loss of *TNFRSF14* drives the cell-autonomous activation of B cell proliferation and promotes the development of germinal centre lymphomas in vivo, suggesting that *TNFRSF14* is an important tumour suppressor in GCB DLBCLs¹³³.

Genetics facilitates prognostication

Prognostic implications of genetic events

Clinical outcomes of patients with DLBCL treated with R-CHOP are heterogeneous; therefore, further research with an aim of identifying more efficient prognostic tools is warranted. The identification of multiple genetic aberrations will enable the risk stratification of patients with DLBCL to be refined. Many studies have incorporated information on genetic aberrations into prognostic models of DLBCL, and some of this information will provide advantages over risk stratification systems that are based solely on traditional clinical parameters.

TP53. The presence of *TP53* mutations has long been recognized as a negative prognostic factor in patients with DLBCL, both in those receiving CHOP and in those receiving R-CHOP. Mutations in the DNA-binding domains of *TP53* in particular are associated with unfavourable clinical parameters and a lower CR rate and predict worse overall survival (OS) in patients with DLBCL^{134–136}. The prognostic value of *TP53* mutations applies to both the GCB and ABC subtypes of DLBCL⁸². Furthermore, in patients with *TP53* mutations in the CDS, the presence of 3' UTR variants is linked with unfavourable OS⁸³. Mutated p53, which lacks tumour suppressor function, also has impaired protein degradation that, remarkably, correlates with increased p53 expression in DLBCL¹³⁷. Thus, immunohistochemistry with anti-p53 antibodies can be used as a surrogate to facilitate risk stratification in patients with DLBCL if investigations for *TP53* mutations are not possible⁸². The prognostic value of *TP53* deletions seems to be more controversial: some studies indicate negative prognostic implications^{138,139}, and others do not⁸².

MYC aberrations. The presence of *MYC* rearrangements is a robust predictor of a poor prognosis in patients with DLBCL receiving R-CHOP, especially when concurrent with *BCL2* and/or *BCL6* translocations^{140–144}.

Patients with these translocations also do not respond well to second-line chemotherapy followed by high-dose chemotherapy plus autologous haematopoietic stem cell transplantation (HSCT)¹⁴⁵. Lai et al.¹⁴⁶ found that *MYC* rearrangements are not predictive of a poorer prognosis in patients receiving the DA-EPOCH-R regimen (comprising etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab), suggesting that this intensive regimen might mitigate the poorer prognosis typically associated with *MYC*-rearranged DLBCL. In another study, in which patients from the Groupe d'Etude des Lymphomes de l'Adult-Lymphoma Study Association (GELA-LYSA) study were included, the prognostic significance of a *MYC* rearrangement was found to be affected by the *MYC* partner, with patients with *MYC-IG* translocations having a substantially worse prognosis than those with other *MYC* translocations⁸⁷. In this study, patients with non-immunoglobulin-containing *MYC* rearrangements had outcomes similar to those of patients with DLBCLs without *MYC* rearrangements⁸⁷.

The prognostic value of *MYC* gains or amplifications is less well defined, with different studies having conflicting results^{90,147–149}. A few attempts have been made to investigate the prognostic value of *MYC* mutations. Xu-Monette et al.⁹¹ found that *MYC* mutations in specific locations including T58, F138 or the 3' UTR had a negative effect on prognosis, whereas other *MYC* mutations did not confer worse outcomes.

Other aberrations. In another GELA study⁸⁰, *CDKN2A* deletions were associated with ABC DLBCL and were found to independently predict unfavourable outcomes. Similarly, an analysis of data from the SAKK 38/07 clinical trial cohort demonstrated that the presence of *CREBBP* and *EP300* mutations is independently predictive of unfavourable outcomes in patients with DLBCL receiving treatment with R-CHOP, whereas *SOCS1* mutations are associated with improved progression-free survival (PFS)¹⁵⁰. An analysis of data from an LYSA cohort suggests that the presence of mutations in *TNFAIP3* and *GNAI3* is associated with an unfavourable prognosis in patients with DLBCL receiving R-CHOP¹⁵¹. A study that included 1,001 patients with DLBCL identified numerous genetic aberrations that have prognostic value in patients with DLBCL¹¹. For DLBCL overall, these alterations include those involving *NFI*, *SGK1*, *CD79B*, *MYC* and *ZFAT*. For ABC DLBCL specifically, these alterations include *CREBBP*, *CDKN2A*, *PAX5*, *BTG1* and *KLHL14*; for GCB DLBCL, they involve *ARID5B*, *MYD88*, *EZH2*, *NCOR1* and *NFKBIA*¹¹. More data from studies incorporating prospective cohorts are needed in order to validate the reported prognostic values of these various genetic aberrations.

Molecular classification of DLBCL

The current classification system, which is based on gene expression profiling results, has, according to most study results, improved the risk stratification of patients with DLBCL and provided insights into both molecular mechanisms and therapeutic targets (FIG. 8). Both the ABC and GCB subtypes of DLBCL

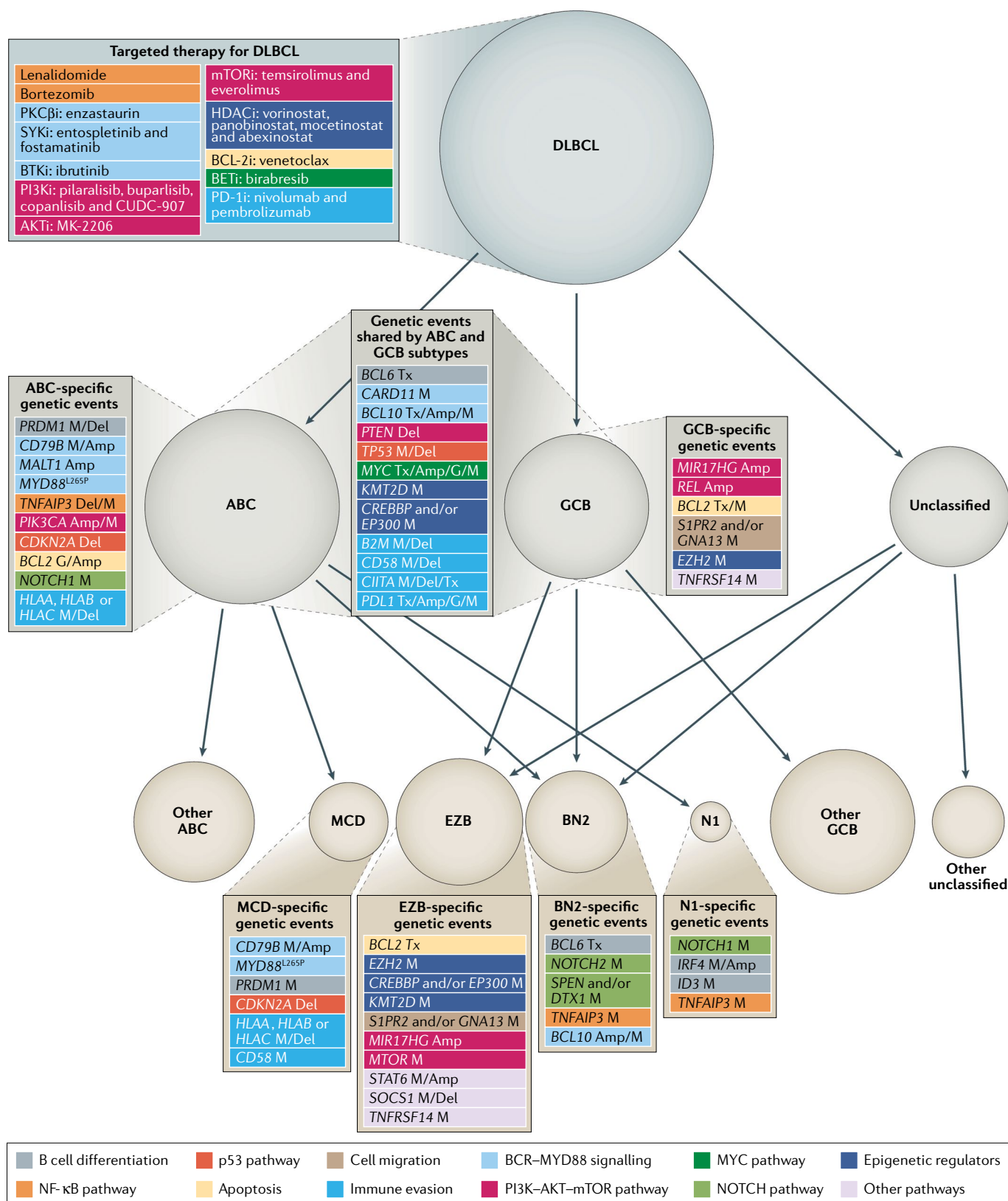


Fig. 8 | Gene expression profiles and genetic subgroups of DLBCL. Approximately 80% of diffuse large B cell lymphomas (DLBCLs) can be classified as the activated B cell (ABC) or germinal centre B cell (GCB) subtype on the basis of gene expression profiling, leaving the others unclassified (referred to as unclassified DLBCL). On the basis of genetic aberrations, half of all DLBCLs can be further classified into one of four genetic subtypes, referred to as MCD, BN2, N1 and EZB. The MCD and N1

subtypes almost exclusively comprise ABC DLBCLs, excluding a very small fraction (not shown in the figure). The EZB subgroup consists mostly of GCB DLBCLs but also contains some unclassified DLBCLs and a small fraction of ABC DLBCLs (not shown in the figure). DLBCLs of the BN2 subtype include GCB, ABC and unclassified DLBCLs. i indicates inhibitor. Amp, amplification; BCR, B cell receptor; Del, deletion; G, gain; HDAC, histone deacetylase; M, mutation; PD-1, programmed cell death 1; Tx, translocation.

each have distinct characteristic genetic events (FIG. 8). Nevertheless, according to the current classification system, 10–20% of DLBCLs remain unclassified^{12,152}. Additionally, the ABC or GCB subtypes remain heterogeneous in clinical outcome^{9,153}. In 2018, Schmitz et al.¹² studied tumour specimens from 574 patients with DLBCL using whole-exome and transcriptome sequencing, DNA copy number analysis and deep targeted amplicon sequencing. Using this multiplatform approach, the authors showed that unclassified DLBCLs were enriched for the co-occurrence of *NOTCH2* mutations and *BCL6* translocations, thus distinguishing these tumours from both the ABC and GCB subtypes¹². By implementing an algorithm based on the co-occurrence of genetic aberrations, these investigators identified four distinct genetic subtypes of DLBCL¹², which included MCD (based on the presence of *MYD88*^{L265P} and *CD79B* mutations), BN2 (based on the presence of *BCL6* fusions and *NOTCH2* mutations), N1 (based on the presence of *NOTCH1* mutations) and EZB (based on the presence of *EZH2* mutations and *BCL2* translocations) (FIG. 8). Each subtype had unique clinical, molecular and transcriptional characteristics¹². In the ABC subgroup, patients with the MCD and N1 subtypes had a poorer prognosis, whereas patients with the BN2 subtype of ABC DLBCL had better outcomes than those of patients with other ABC DLBCLs. A trend was observed among patients with GCB DLBCLs, suggesting that patients with tumours of the EZB subtype had poorer outcomes than those of patients with non-EZB GCB DLBCLs.

Chapuy et al.¹³ conducted a comprehensive investigation of the genomic features of samples from 304 patients with DLBCLs, of whom 129 were enrolled in the prospective RICOVER60 trial. By applying a different classification algorithm to that used by Schmitz et al.¹², the authors identified five subgroups of DLBCLs with prominent genetic features (C1–C5). The C1 subtype was reported to frequently harbour *BCL6* translocations and was enriched for *NOTCH2* or *SPEN* mutations, suggesting that the C1 and BN2 subtypes are identical. The C3 subtype mainly comprised GCB DLBCLs and was characterized by *BCL2* translocations and genetic alterations disrupting the epigenetic regulators *EZH2*, *CREBBP* or *KMT2D* (in most patients), suggesting that the C3 and EZB subtypes are similar entities. The C5 subtype featured the frequent co-occurrence of *MYD88*^{L265P} and *CD79B* mutations, which is a characteristic feature of the MCD subtype described by Schmitz et al.¹² Regarding clinical outcomes, patients with the C3 subtype of GCB DLBCL (compared with other tumours of the GCB type) and the C5 subtype of ABC DLBCL (compared with other tumours of the ABC type) had a similar prognosis to that of patients with the EZB or MCD subtypes, respectively. Therefore, the studies by Schmitz et al.¹² and Chapuy et al.¹³ demonstrate that the classification of DLBCLs on the basis of the co-occurrence of genetic aberrations is of clinical importance. These molecular classifications not only provide insights into the pathogenesis of DLBCL but also can help clinicians to identify patients in whom standard immunochemotherapy

is most likely to fail and/or will likely benefit more from other therapies.

Targeting dysregulated signalling

Many efforts have been devoted to develop novel agents that target oncogenic signalling pathways driven by specific genetic events (FIG. 8). Some of these drugs have been tested in clinical trials, with some promising results (Supplementary Tables 2 and 3).

NF- κ B signalling

Lenalidomide has direct antineoplastic and immunomodulatory effects. By targeting the E3 ubiquitin ligase component cereblon, lenalidomide blocks the BCR–NF- κ B pathway and thus exerts its antitumour effects¹⁵⁴. Lenalidomide has shown substantial levels of activity in patients with relapsed and/or refractory (R/R) DLBCL, either alone or in combination with other regimens, and patients with non-GCB or ABC DLBCLs typically have better responses^{155–165} (Supplementary Table 2). Lenalidomide has also been incorporated into first-line chemoimmunotherapy regimens for patients with DLBCL and has an acceptable toxicity profile with promising levels of efficacy^{166–169}. In patients with newly diagnosed DLBCL, the addition of lenalidomide seems to partly overcome the negative prognostic implications of the non-GCB phenotype, thus suggesting that lenalidomide plus cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) is particularly effective in patients with non-GCB DLBCLs¹⁶⁹. The phase III ROBUST study is currently evaluating the efficacy of R-CHOP plus lenalidomide versus that of R-CHOP in patients with previously untreated ABC DLBCLs¹⁷⁰. Additionally, lenalidomide maintenance therapy has been shown to be effective and can prolong PFS in elderly patients (defined as those of 60–80 years of age) who respond to R-CHOP^{171,172}. However, the benefit of lenalidomide maintenance therapy has been shown only in patients with GCB DLBCL and not in those with ABC DLBCL. It should be noted that the efficacy of lenalidomide maintenance therapy might reflect an immunomodulatory rather than a direct tumoricidal effect¹⁷¹.

Bortezomib is a proteasome inhibitor approved for the treatment of several haematological malignancies. Downregulation of NF- κ B activation through inhibition of I κ B degradation is one mechanism underlying the antineoplastic activity of bortezomib¹⁷³. The effectiveness of bortezomib has been evaluated in patients with R/R or untreated DLBCL, both as a monotherapy and in combinations^{174–178}. Bortezomib is generally less effective when used as a single agent, with only 1 of 12 patients responding in one trial¹⁷⁴. When combined with the EPOCH regimen (consisting of etoposide, prednisone, vincristine, doxorubicin and cyclophosphamide), bortezomib resulted in a higher response rate in patients with R/R ABC DLBCL (partial response (PR) or better in 10 of 12 patients) than in those with R/R GCB DLBCL (PR or better in 2 of 15 patients)¹⁷⁶. However, further studies have failed to show that the addition of bortezomib improves the outcomes of patients with ABC DLBCL compared with standard R-CHOP in the first-line setting^{179,180}.

BCR signalling

The observation of the chronically active status of BCR signalling in some DLBCLs has established this process as an excellent treatment target. The BTK inhibitor ibrutinib has been shown to disrupt the interaction of the My-T-BCR complex with the CARD11–BCL-10–MALT1 complex and mTOR, thus inhibiting BCR-dependent NF- κ B activation⁶⁶. Ibrutinib has been tested as a single agent or in combination with chemoimmunotherapy in both the first-line and salvage settings^{181–185} (Supplementary Table 3). The response rate is remarkably better among patients with R/R ABC DLBCL (37%) receiving ibrutinib monotherapy than among those with R/R GCB DLBCL (5%) and especially in those with concomitant *MYD88*^{L265P} and *CD79B* mutations (80%)¹⁸¹. Additionally, mutations within the coiled-coil domain of *CARD11* and TNFAIP3 inactivation are associated with inferior responses to ibrutinib in patients with ABC DLBCL¹⁸¹. The responses of DLBCLs harbouring *MYD88*^{L265P} and *CD79B* or *CD79A* mutations are a result of the presence of the My-T-BCR complex in these conditions⁶⁶. The dependence of DLBCLs with these characteristics on the My-T-BCR complex renders them vulnerable to BTK inhibition⁶⁶. However, the response of DLBCL to ibrutinib is not dependent on concurrent *MYD88*^{L265P} and *CD79B* or *CD79A* mutations, as patients with DLBCLs expressing the wild-type forms of these genes or with only *CD79A* or *CD79B* mutations also have My-T-BCR complexes and respond to ibrutinib⁶⁶. In patients with R/R DLBCL, rituximab, ifosfamide, carboplatin and etoposide (R-ICE) plus ibrutinib produces an even higher response rate, with 55% of patients having a CR¹⁸³. Of note, in this phase I study¹⁸³, all patients with DLBCL of a non-GCB phenotype had a CR to R-ICE plus ibrutinib. According to an abstract presented at the 2018 annual meeting of the American Society for Hematology (ASH), a regimen consisting of ibrutinib, lenalidomide and rituximab has also shown promising levels of activity (overall response rate (ORR) 55%; CR rate 30%) and manageable toxicities in patients with R/R non-GCB DLBCL who were not eligible for HSCT¹⁸⁴. In one study, the addition of ibrutinib to R-CHOP improved the event-free survival (EFS) and OS of patients <60 years of age with non-GCB DLBCL but not of those \geq 60 years of age¹⁸⁵; these results are encouraging, as this is the first time that the addition of a novel agent to R-CHOP has improved both the EFS and OS outcomes of patients with DLBCL in the first-line setting. For patients with primary DLBCL of the CNS, in whom concurrent *MYD88*^{L265P} and *CD79B* mutations are much more prevalent, ibrutinib monotherapy has been shown to produce high response rates (77–83%). Furthermore, combining ibrutinib and immunochemotherapy produced CRs in 63–86% of such patients^{186–188}.

PKC β is a key component of BCR signalling that could also be targeted in order to inhibit BCR signalling. However, several clinical trials have failed to show any notable level of clinical benefit among patients with R/R or newly diagnosed DLBCL receiving the PKC β inhibitor enzastaurin^{189–191}. The efficacy of the SYK inhibitors fostamatinib and entospletinib has also been evaluated in clinical trials, with limited clinical benefit observed^{192–195}.

PI3K–AKT–mTOR

The roles of PI3K–AKT and downstream mTOR signalling in the pathogenesis of DLBCL make these pathways attractive treatment targets; small molecules that target several components of these pathways have been developed. The safety and efficacy of PI3K inhibitors, as monotherapies or in combination regimens, have been tested in patients with R/R DLBCL, and some agents have shown promise^{196–199}. CUDC-907 is a small molecule that inhibits both PI3K (class Ia, β and δ) and HDAC (class I and II) enzymes. In one study¹⁹⁹, patients with *MYC*-altered DLBCL (owing to *MYC* translocation or amplification and/or *MYC* overexpression) had a higher response rate (7 out of 11; 64%) to CUDC-907 than patients with DLBCL without *MYC* alterations (2 out of 7; 29%). The AKT inhibitor MK-2206 has been shown to be effective in preclinical models of DLBCL²⁰⁰; however, none of 11 patients with DLBCL treated with MK-2206 in a phase II trial had a response, suggesting a lack of efficacy²⁰¹. The safety and efficacy of the mTOR inhibitors temsirolimus and everolimus, as monotherapy or as part of combination therapy, have also been evaluated in patients with R/R or treatment-naive DLBCL. Both inhibitors showed activity in patients with R/R DLBCL when used as single agents or in combination with other drugs^{202–205}. In the PILLAR-2 phase III trial²⁰⁶, investigators examined the efficacy of adjuvant everolimus in patients with high-risk DLBCL, with results suggesting no benefit of everolimus maintenance therapy among patients who were in complete remission but with a high risk of relapse. In a cohort of 24 patients with previously untreated DLBCL receiving everolimus in combination with R-CHOP-21 (the R-CHOP regimen delivered over a 21-day cycle) as induction therapy, no patients had disease progression or relapse at 24 months^{207,208}. This result is encouraging, although a prospective, randomized controlled trial is needed in order to demonstrate the superiority of R-CHOP-21 plus everolimus compared with the standard R-CHOP-21 regimen^{207,208}.

Epigenetic pathways

Targeting the dysregulated epigenome might improve the outcomes of patients with DLBCL. The highly selective EZH2 inhibitor tazemetostat has shown promising levels of efficacy in both *EZH2*-wild-type and *EZH2*-mutant R/R DLBCL, with a favourable safety profile^{209,210}. According to an abstract presented at the 2018 ASH annual meeting, the combination of tazemetostat with R-CHOP in patients with newly diagnosed high-risk DLBCL was well tolerated, and all patients who completed eight cycles of treatment had a CR²¹¹. Frequent disruptions involving histone-modifying enzymes provide a rationale for the use of HDAC inhibitors in the treatment of DLBCL. Inhibition of HDACs restores the acetylation of histones located at transcriptional enhancer regions and of corresponding genes in *CREBBP*-mutant DLBCLs and is a potential therapeutic strategy¹²⁵. Several clinical trials have evaluated the safety and efficacy of HDAC inhibitors, including panobinostat, vorinostat, mocetinostat and abexinostat, in patients with R/R DLBCL as both single agents and in combination and have demonstrated some clinical activity^{212–220}. Among

patients with R/R DLBCL who received panobinostat, the six patients with *MEF2B*-mutant disease had a higher response rate than those without *MEF2B* mutations (67% versus 18%)²¹⁷. Other attempts to target the epigenome include the incorporation of vorinostat or the hypomethylating agent azacitidine into high-dose regimens for patients with R/R DLBCL^{212,221–223}.

BCL-2 signalling

The central role of BCL-2 in the biology of DLBCL suggests that these neoplasms are vulnerable to BCL-2 inhibition. Among 34 patients with R/R DLBCL treated with the BCL-2 inhibitor venetoclax as a single agent, 6 had a response (18%), with 4 (12%) having a CR²²⁴. As presented at the 2018 ASH annual meeting, the combination of venetoclax with bendamustine plus rituximab resulted in an ORR of 41% in the same disease setting²²⁵. In another ASH 2018 abstract describing data from the phase II CAVALLI study²²⁶, the safety and efficacy of venetoclax plus R-CHOP were evaluated in patients with newly diagnosed DLBCL. Compared with the matched population of patients receiving R-CHOP in the GOYA phase III trial cohort, venetoclax improved the CR rate in patients with immunohistochemically confirmed BCL-2-positive disease, especially in those with *BCL2* translocations (confirmed by fluorescence in situ hybridization) and in patients with *MYC* and *BCL2* double-hit lymphomas²²⁶, suggesting that addition of venetoclax to R-CHOP improves the outcomes of selected patients with DLBCL. The response rates of patients with DLBCL receiving venetoclax monotherapy are typically low; therefore, identifying reliable biomarkers that are predictive of a response is an important goal for future studies. In vitro studies have shown that DLBCL cell lines harbouring amplifications of genes encoding the caspase-activating protein PMAIP1 are highly sensitive to BCL-2 inhibitors, while those lacking such amplifications are less sensitive; these findings need to be confirmed in a clinical trial²²⁷.

Bromodomains

Bromodomain inhibitors block the transcription of *MYC* and are therefore potentially a useful method of targeting tumours that are dependent on *MYC* expression. Birabresib specifically binds to the BRD2 and BRD3 domains of BET proteins, thereby decreasing the expression of several oncogenes including *MYC*²²⁸. In a phase I trial evaluating the safety and efficacy of birabresib²²⁸, 3 (18%) of 17 evaluable patients with DLBCL had a response, with 2 patients (12%) having a CR. *MYC* expression does not correlate with the efficacy of birabresib in patients with DLBCL, indicating that this agent kills tumour cells via mechanisms other than *MYC* downregulation. Further studies are needed to determine the efficacy of combination therapies that incorporate birabresib in patients with DLBCL.

PD-1 and PD-L1

The involvement of PD-L1—programmed cell death 1 (PD-1) signalling in immune escape in the development of a subset of DLBCLs provides a basis for the use of anti-PD-1 antibodies to restore antitumour immunity.

The anti-PD-1 antibody nivolumab has shown promising levels of activity in patients with R/R DLBCL in a phase Ib study, with an ORR of 36%²²⁹. However, in a phase II trial in patients with R/R DLBCL who either failed to respond to or were ineligible for autologous HSCT²³⁰, the ORRs to nivolumab were only 10% and 3%, respectively. In this study, among patients who were evaluable for 9p24.1 (*PDL1* and/or *PDL2*) aberrations, 16% had low-level copy number gains, and 3% had amplifications²³⁰; thus, the low frequency and magnitude of 9p24.1 aberrations might account for the low ORRs in this study. An analysis of data (presented at the 2018 ASH annual meeting) from 29 patients with R/R DLBCL enrolled in the KEYNOTE-013 trial demonstrated that alterations in *PDL1* (including copy number gains, amplifications and translocations) are associated with a remarkably higher ORR to another anti-PD-1 antibody, pembrolizumab (50% versus 9% in those without *PDL1* alterations)²³¹. This observation suggests that *PDL1* aberrations are a useful biomarker that is predictive of a response to anti-PD-1 antibodies in patients with DLBCL²³¹. In a study involving four patients with R/R primary CNS lymphoma and one patient with CNS relapse of primary testicular lymphoma, all patients responded to nivolumab, and three patients remained in continuous remission²³². The efficacy of nivolumab in these patients might be attributable to the frequent *PDL1* and/or *PDL2* gains, amplifications and translocations observed in patients with primary CNS lymphoma (~60%) and in those with primary testicular lymphoma (~60%)^{56,232}. Several clinical trials are now evaluating the safety and efficacy of the combination of an anti-PD-1 antibody with other agents in patients with R/R DLBCL.

Genetically guided patient selection

Novel agents targeting aberrant signalling pathways have shown some promise in the treatment of DLBCL; however, only a small proportion of patients with R/R DLBCL respond when treated with single agents. Furthermore, patients who do respond often do not have durable responses. Therefore, identifying patients who are most likely to benefit from certain therapies and sustaining these responses using other strategies will be crucial. Understanding the cell of origin can help predict a response to novel agents, and patients with R/R ABC DLBCL have been shown to have a better response to ibrutinib, lenalidomide and bortezomib than those with R/R GCB DLBCL^{155,165,176,181}. Several genetic biomarkers have been identified that enable the prediction of a response to novel agents (Supplementary Table 4). Several ongoing studies are using genetics to guide patient selection. For example, in a phase II study, researchers are investigating the efficacy of mocetinostat in patients with R/R DLBCL and follicular lymphoma harbouring *CREBBP* and/or *EP300* mutations (NCT02282358). The co-occurrence of genetic aberrations has been shown to be predictive of prognosis in patients receiving R-CHOP or R-CHOP-like regimens^{12,13}; therefore, the co-occurrence of genetic aberrations rather than individual alterations could be used to predict the outcomes of patients who received novel therapies or to guide the selection of patients for enrolment in clinical trials.

Future directions

The application of genetic analysis in the management of DLBCL has facilitated a better understanding of the biology of lymphoma. Although several elegant studies have elucidated the functional roles of many genetic aberrations, including those involving *BCL6*, *CREBBP*, *KMT2D* and others, the exact functional relevance of many genetic aberrations remains less well defined. Limited information is currently available on the stages of B cell maturation at which these aberrations occur. Data from mouse models might be helpful in addressing these issues. Moreover, most sequencing data currently available are from patients with untreated DLBCL, and the genetic aberrations occurring in patients with R/R disease are generally less well delineated^{233–237}. Sequencing of tumour material from patients with R/R DLBCL, especially sequential samples, will be important for elucidating the mechanisms underlying therapeutic resistance and delineating the role of clonal evolution in tumour refractoriness and disease relapse.

Understanding the biology of patients with R/R disease will also likely provide insights regarding the effects of specific aberrations that could potentially be targeted by novel therapies. The advent of single-cell sequencing will also help to define intratumoural genetic heterogeneity in DLBCL and provide insights into clonal evolution during treatment.

Conclusions

In this Review, we have summarized the genetic events that occur in DLBCL and how they contribute to the development of this type of lymphoma. We have also discussed the clinical significance of these aberrations and the available data on the efficacy of novel therapies designed to target these aberrant signalling pathways. Further delineation of the genetics and biology of DLBCL will enable the development of novel and, more importantly, precise therapies for patients with DLBCL.

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1. Swerdlow, S. H. et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* (IARC Press, 2017).
2. Feugier, P. et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J. Clin. Oncol.* **23**, 4117–4126 (2005).
3. Pfreundschuh, M. et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* **9**, 105–116 (2008).
4. Pfreundschuh, M. et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* **7**, 379–391 (2006).
5. Coiffier, B. & Sarkozy, C. Diffuse large B cell lymphoma: R-CHOP failure-what to do? *Hematol. Am. Soc. Hematol. Educ. Program* **2016**, 366–378 (2016).
6. Gisselbrecht, C. et al. Salvage regimens with autologous transplantation for relapsed large B cell lymphoma in the rituximab era. *J. Clin. Oncol.* **28**, 4184–4190 (2010).
7. Friedberg, J. W. Relapsed/refractory diffuse large B cell lymphoma. *Hematol. Am. Soc. Hematol. Educ. Program* **2011**, 498–505 (2011).
8. Alizadeh, A. A. et al. Distinct types of diffuse large B cell lymphoma identified by gene expression profiling. *Nature* **403**, 503–511 (2000).
9. Xu-Monette, Z. Y. et al. Assessment of CD37 B cell antigen and cell of origin significantly improves risk prediction in diffuse large B cell lymphoma. *Blood* **128**, 3083–3100 (2016).
10. Gutierrez-Garcia, G. et al. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B cell lymphoma treated with immunochemotherapy. *Blood* **117**, 4836–4843 (2011).
11. Reddy, A. et al. Genetic and functional drivers of diffuse large B cell lymphoma. *Cell* **171**, 481–494 (2017).
12. Schmitz, R. et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N. Engl. J. Med.* **378**, 1396–1407 (2018).
13. Chapuy, B. et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat. Med.* **24**, 679–690 (2018).
14. Alexandrov, L. B. et al. Signatures of mutational processes in human cancer. *Nature* **500**, 415–421 (2013).
15. Jager, U. et al. Follicular lymphomas' BCL-2/IgH junctions contain templated nucleotide insertions: novel insights into the mechanism of t(14;18) translocation. *Blood* **95**, 3520–3529 (2000).
16. Shen, H. M., Peters, A., Baron, B., Zhu, X. & Storb, U. Mutation of BCL-6 gene in normal B cells by the process of somatic hypermutation of Ig genes. *Science* **280**, 1750–1752 (1998).
17. Lieber, M. R. Mechanisms of human lymphoid chromosomal translocations. *Nat. Rev. Cancer* **16**, 387–398 (2016).
18. Lenz, G. et al. Aberrant immunoglobulin class switch recombination and switch translocations in activated B cell-like diffuse large B cell lymphoma. *J. Exp. Med.* **204**, 633–643 (2007).
19. Deutsch, A. J. et al. MALT lymphoma and extranodal diffuse large B cell lymphoma are targeted by aberrant somatic hypermutation. *Blood* **109**, 3500–3504 (2007).
20. Gordon, M. S., Kanegai, C. M., Doerr, J. R. & Wall, R. Somatic hypermutation of the B cell receptor genes B29 (Igbeta, CD79b) and mb1 (Igalpha, CD79a). *Proc. Natl Acad. Sci. USA* **100**, 4126–4131 (2003).
21. Pasqualucci, L. et al. Hypermutation of multiple proto-oncogenes in B cell diffuse large-cell lymphomas. *Nature* **412**, 341–346 (2001).
22. De Silva, N. S. & Klein, U. Dynamics of B cells in germinal centres. *Nat. Rev. Immunol.* **15**, 137–148 (2015).
23. Basso, K. & Dalla-Favera, R. Germinal centres and B cell lymphomagenesis. *Nat. Rev. Immunol.* **15**, 172–184 (2015).
24. Hatzi, K. et al. A hybrid mechanism of action for BCL6 in B cells defined by formation of functionally distinct complexes at enhancers and promoters. *Cell Rep.* **4**, 578–588 (2013).
25. Ye, B. H. et al. Alterations of a zinc finger-encoding gene, BCL-6, in diffuse large-cell lymphoma. *Science* **262**, 747–750 (1993).
26. Ye, B. H. et al. Chromosomal translocations cause deregulated BCL6 expression by promoter substitution in B cell lymphoma. *EMBO J.* **14**, 6209–6217 (1995).
27. Ye, Q. et al. Prognostic impact of concurrent MYC and BCL6 rearrangements and expression in de novo diffuse large B cell lymphoma. *Oncotarget* **7**, 2401–2416 (2016).
28. Tibiletti, M. G. et al. BCL2, BCL6, MYC, MALT 1, and BCL10 rearrangements in nodal diffuse large B cell lymphomas: a multicenter evaluation of a new set of fluorescent in situ hybridization probes and correlation with clinical outcome. *Hum. Pathol.* **40**, 645–652 (2009).
29. Iqbal, J. et al. Distinctive patterns of BCL6 molecular alterations and their functional consequences in different subgroups of diffuse large B cell lymphoma. *Leukemia* **21**, 2332–2343 (2007).
30. Pasqualucci, L. et al. Mutations of the BCL6 proto-oncogene disrupt its negative autoregulation in diffuse large B cell lymphoma. *Blood* **101**, 2914–2923 (2003).
31. Ying, C. Y. et al. MEF2B mutations lead to deregulated expression of the oncogene BCL6 in diffuse large B cell lymphoma. *Nat. Immunol.* **14**, 1084–1092 (2013).
32. Duan, S. et al. FBXO11 targets BCL6 for degradation and is inactivated in diffuse large B cell lymphomas. *Nature* **481**, 90–93 (2012).
33. Pasqualucci, L. et al. Inactivating mutations of acetyltransferase genes in B cell lymphoma. *Nature* **471**, 189–195 (2011).
34. Cattoretti, G. et al. Deregulated BCL6 expression recapitulates the pathogenesis of human diffuse large B cell lymphomas in mice. *Cancer Cell* **7**, 445–455 (2005).
35. Shaffer, A. L. et al. Blimp-1 orchestrates plasma cell differentiation by extinguishing the mature B cell gene expression program. *Immunity* **17**, 51–62 (2002).
36. Pasqualucci, L. et al. Inactivation of the PRDM1/BLIMP1 gene in diffuse large B cell lymphoma. *J. Exp. Med.* **203**, 311–317 (2006).
37. Mandelbaum, J. et al. BLIMP1 is a tumor suppressor gene frequently disrupted in activated B cell-like diffuse large B cell lymphoma. *Cancer Cell* **18**, 568–579 (2010).
38. Calado, D. P. et al. Constitutive canonical NF-kappaB activation cooperates with disruption of BLIMP1 in the pathogenesis of activated B cell-like diffuse large cell lymphoma. *Cancer Cell* **18**, 580–589 (2010).
39. Rawlings, D. J., Metzler, G., Wray-Dutra, M. & Jackson, S. W. Altered B cell signalling in autoimmunity. *Nat. Rev. Immunol.* **17**, 421–436 (2017).
40. Davis, R. E. et al. Chronic active B cell-receptor signalling in diffuse large B cell lymphoma. *Nature* **463**, 88–92 (2010).
41. Young, R. M. & Staudt, L. M. Targeting pathological B cell receptor signalling in lymphoid malignancies. *Nat. Rev. Drug Discov.* **12**, 229–243 (2013).
42. Young, R. M., Shaffer, A. L. 3rd, Phelan, J. D. & Staudt, L. M. B cell receptor signaling in diffuse large B cell lymphoma. *Semin. Hematol.* **52**, 77–85 (2015).
43. Havranek, O. et al. Tonic B cell receptor signaling in diffuse large B cell lymphoma. *Blood* **130**, 995–1006 (2017).
44. Lenz, G. et al. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. *Science* **319**, 1676–1679 (2008).
45. Bohers, E. et al. Targetable activating mutations are very frequent in GCB and ABC diffuse large B cell lymphoma. *Genes Chromosomes Cancer* **53**, 144–153 (2014).
46. Lamason, R. L., McCully, R. R., Lew, S. M. & Pomerantz, J. L. Oncogenic CARD11 mutations induce hyperactive signaling by disrupting autoinhibition by the PKC-responsive inhibitory domain. *Biochemistry* **49**, 8240–8250 (2010).
47. Liu, H. et al. T[11;18](q21;q21) is associated with advanced mucosa-associated lymphoid tissue lymphoma that expresses nuclear BCL10. *Blood* **98**, 1182–1187 (2001).
48. Willis, T. G. et al. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* **96**, 35–45 (1999).

49. Nagel, D. et al. Pharmacologic inhibition of MALT1 protease by phenothiazines as a therapeutic approach for the treatment of aggressive ABC-DLBCL. *Cancer Cell* **22**, 825–837 (2012).
50. Ngo, V. N. et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature* **470**, 115–119 (2011).
51. Dubois, S. et al. Biological and clinical relevance of associated genomic alterations in MYD88 L265P and non-L265P-mutated diffuse large B-cell lymphoma: analysis of 361 cases. *Clin. Cancer Res.* **23**, 2232–2244 (2017).
52. Rovira, J. et al. MYD88 L265P mutations, but no other variants, identify a subpopulation of DLBCL patients of activated B cell origin, extranodal involvement, and poor outcome. *Clin. Cancer Res.* **22**, 2755–2764 (2016).
53. Montesinos-Rongen, M. et al. Activating L265P mutations of the MYD88 gene are common in primary central nervous system lymphoma. *Acta Neuropathol.* **122**, 791–792 (2011).
54. Zheng, M. et al. Frequency of MYD88 and CD79B mutations, and MGMT methylation in primary central nervous system diffuse large B cell lymphoma. *Neuropathology* **37**, 509–516 (2017).
55. Fukumura, K. et al. Genomic characterization of primary central nervous system lymphoma. *Acta Neuropathol.* **131**, 865–875 (2016).
56. Chapuy, B. et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood* **127**, 869–881 (2016).
57. Taniguchi, K. et al. Frequent MYD88 L265P and CD79B mutations in primary breast diffuse large B-cell lymphoma. *Am. J. Surg. Pathol.* **40**, 324–334 (2016).
58. Cao, X. X. et al. Patients with primary breast and primary female genital tract diffuse large B cell lymphoma have a high frequency of MYD88 and CD79B mutations. *Ann. Hematol.* **96**, 1867–1871 (2017).
59. Franco, F. et al. Mutational profile of primary breast diffuse large B cell lymphoma. *Oncotarget* **8**, 102888–102897 (2017).
60. Pham-Ledard, A. et al. MYD88 somatic mutation is a genetic feature of primary cutaneous diffuse large B cell lymphoma, leg type. *J. Invest. Dermatol.* **132**, 2118–2120 (2012).
61. Pham-Ledard, A. et al. Multiple genetic alterations in primary cutaneous large B cell lymphoma, leg type support a common lymphomagenesis with activated B cell-like diffuse large B cell lymphoma. *Mod. Pathol.* **27**, 402–411 (2014).
62. Pham-Ledard, A. et al. High frequency and clinical prognostic value of MYD88 L265P mutation in primary cutaneous diffuse large B cell lymphoma, leg-type. *JAMA Dermatol.* **150**, 1173–1179 (2014).
63. Zhou, X. A. et al. Genomic analyses identify recurrent alterations in immune evasion genes in diffuse large B-cell lymphoma, leg type. *J. Invest. Dermatol.* **138**, 2365–2376 (2018).
64. Kraan, W. et al. High prevalence of oncogenic MYD88 and CD79B mutations in primary testicular diffuse large B cell lymphoma. *Leukemia* **28**, 719–720 (2014).
65. Oishi, N. et al. High prevalence of the MYD88 mutation in testicular lymphoma: Immunohistochemical and genetic analyses. *Pathol. Int.* **65**, 528–535 (2015).
66. Phelan, J. D. et al. A multiprotein supercomplex controlling oncogenic signalling in lymphoma. *Nature* **560**, 387–391 (2018).
67. Gilmore, T. D., Kalaitzidis, D., Liang, M. C. & Staszynowski, D. T. The c-Rel transcription factor and B cell proliferation: a deal with the devil. *Oncogene* **23**, 2275–2286 (2004).
68. Kaltschmidt, B., Greiner, J. F. W., Kadhim, H. M. & Kaltschmidt, C. Subunit-specific role of NF-kappaB in cancer. *Biomedicines* **6**, E44 (2018).
69. Li, L. et al. Prognostic impact of c-Rel nuclear expression and REL amplification and crosstalk between c-Rel and the p53 pathway in diffuse large B cell lymphoma. *Oncotarget* **6**, 23157–23180 (2015).
70. Ma, A. & Malynn, B. A. A20: linking a complex regulator of ubiquitylation to immunity and human disease. *Nat. Rev. Immunol.* **12**, 774–785 (2012).
71. Wertz, I. E. et al. De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling. *Nature* **430**, 694–699 (2004).
72. Compagno, M. et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B cell lymphoma. *Nature* **459**, 717–721 (2009).
73. Wang, J. Q., Jeelall, Y. S., Beutler, B., Horikawa, K. & Goodnow, C. C. Consequences of the recurrent MYD88(L265P) somatic mutation for B cell tolerance. *J. Exp. Med.* **211**, 413–426 (2014).
74. Wenzl, K. et al. Loss of TNFAIP3 enhances MYD88L265P-driven signaling in non-Hodgkin lymphoma. *Blood Cancer J.* **8**, 97 (2018).
75. Uddin, S. et al. Role of phosphatidylinositol 3'-kinase/AKT pathway in diffuse large B cell lymphoma survival. *Blood* **108**, 4178–4186 (2006).
76. Zhang, J. et al. Genetic heterogeneity of diffuse large B cell lymphoma. *Proc. Natl Acad. Sci. USA* **110**, 1398–1403 (2013).
77. Wang, X. et al. Clinical significance of PTEN deletion, mutation, and loss of PTEN expression in de novo diffuse large B-cell lymphoma. *Neoplasia* **20**, 574–593 (2018).
78. Lenz, G. et al. Molecular subtypes of diffuse large B cell lymphoma arise by distinct genetic pathways. *Proc. Natl Acad. Sci. USA* **105**, 13520–13525 (2008).
79. Pfeifer, M. et al. PTEN loss defines a PI3K/AKT pathway-dependent germinal center subtype of diffuse large B cell lymphoma. *Proc. Natl Acad. Sci. USA* **110**, 12420–12425 (2013).
80. Jardin, F. et al. Diffuse large B cell lymphomas with CDKN2A deletion have a distinct gene expression signature and a poor prognosis under R-CHOP treatment: a GELA study. *Blood* **116**, 1092–1104 (2010).
81. Xu-Monette, Z. Y. et al. Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies. *Blood* **119**, 3668–3683 (2012).
82. Xu-Monette, Z. Y. et al. Mutational profile and prognostic significance of TP53 in diffuse large B cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. *Blood* **120**, 3986–3996 (2012).
83. Li, Y. et al. Single nucleotide variation in the TP53 3' untranslated region in diffuse large B cell lymphoma treated with rituximab-CHOP: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood* **121**, 4529–4540 (2013).
84. Monti, S. et al. Integrative analysis reveals an outcome-associated and targetable pattern of p53 and cell cycle deregulation in diffuse large B cell lymphoma. *Cancer Cell* **22**, 359–372 (2012).
85. Xu-Monette, Z. Y. et al. MDM2 phenotypic and genotypic profiling, respective to TP53 genetic status, in diffuse large B cell lymphoma patients treated with rituximab-CHOP immunotherapy: a report from the International DLBCL Rituximab-CHOP Consortium Program. *Blood* **122**, 2630–2640 (2013).
86. Karube, K. & Campo, E. MYC alterations in diffuse large B cell lymphomas. *Semin. Hematol.* **52**, 97–106 (2015).
87. Copie-Bergman, C. et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunotherapy: a GELA/LYSA study. *Blood* **126**, 2466–2474 (2015).
88. Stasik, C. J. et al. Increased MYC gene copy number correlates with increased mRNA levels in diffuse large B cell lymphoma. *Haematologica* **95**, 597–603 (2010).
89. Quesada, A. E. et al. Increased MYC copy number is an independent prognostic factor in patients with diffuse large B cell lymphoma. *Mod. Pathol.* **30**, 1688–1697 (2017).
90. Ennishi, D. et al. Genetic profiling of MYC and BCL2 in diffuse large B cell lymphoma determines cell-of-origin-specific clinical impact. *Blood* **129**, 2760–2770 (2017).
91. Xu-Monette, Z. Y. et al. Clinical and Biologic Significance of MYC Genetic Mutations in De Novo Diffuse Large B cell Lymphoma. *Clin. Cancer Res.* **22**, 3593–3605 (2016).
92. Visco, C. et al. Patients with diffuse large B cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL rituximab-CHOP Consortium Program Study. *Haematologica* **98**, 255–263 (2013).
93. Iqbal, J. et al. BCL2 translocation defines a unique tumor subset within the germinal center B cell-like diffuse large B cell lymphoma. *Am. J. Pathol.* **165**, 159–166 (2004).
94. Kridel, R., Sehn, L. H. & Gascoyne, R. D. Pathogenesis of follicular lymphoma. *J. Clin. Invest.* **122**, 3424–3431 (2012).
95. Monni, O. et al. BCL2 overexpression associated with chromosomal amplification in diffuse large B cell lymphoma. *Blood* **90**, 1168–1174 (1997).
96. Rantanen, S., Monni, O., Joensuu, H., Franssila, K. & Knuutila, S. Causes and consequences of BCL2 overexpression in diffuse large B cell lymphoma. *Leuk. Lymphoma* **42**, 1089–1098 (2001).
97. Kusumoto, S. et al. Diffuse large B cell lymphoma with extra Bcl-2 gene signals detected by FISH analysis is associated with a "non-germinal center phenotype". *Am. J. Surg. Pathol.* **29**, 1067–1073 (2005).
98. Schuetz, J. M. et al. BCL2 mutations in diffuse large B cell lymphoma. *Leukemia* **26**, 1383–1390 (2012).
99. Saito, M. et al. BCL6 suppression of BCL2 via Miz1 and its disruption in diffuse large B cell lymphoma. *Proc. Natl Acad. Sci. USA* **106**, 11294–11299 (2009).
100. Monaco, G. et al. Selective regulation of IP3-receptor-mediated Ca²⁺ signaling and apoptosis by the BH4 domain of Bcl-2 versus Bcl-Xl. *Cell Death Differ.* **19**, 295–309 (2012).
101. Deng, X., Gao, F., Flagg, T., Anderson, J. & May, W. S. Bcl2's flexible loop domain regulates p53 binding and survival. *Mol. Cell. Biol.* **26**, 4421–4434 (2006).
102. Grandgirard, D. et al. Alphaviruses induce apoptosis in Bcl-2-overexpressing cells: evidence for a caspase-mediated, proteolytic inactivation of Bcl-2. *EMBO J.* **17**, 1268–1278 (1998).
103. Souers, A. J. et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat. Med.* **19**, 202–208 (2013).
104. Lee, S. Y. et al. Gain-of-function mutations and copy number increases of Notch2 in diffuse large B cell lymphoma. *Cancer Sci.* **100**, 920–926 (2009).
105. Arcaini, L. et al. The NOTCH pathway is recurrently mutated in diffuse large B cell lymphoma associated with hepatitis C virus infection. *Haematologica* **100**, 246–252 (2015).
106. Green, J. A. et al. The sphingosine 1-phosphate receptor S1P(2) maintains the homeostasis of germinal center B cells and promotes niche confinement. *Nat. Immunol.* **12**, 672–680 (2011).
107. Muppidi, J. R., Lu, E. & Cyster, J. G. The G protein-coupled receptor P2RY8 and follicular dendritic cells promote germinal center confinement of B cells, whereas S1PR3 can contribute to their dissemination. *J. Exp. Med.* **212**, 2213–2222 (2015).
108. Muppidi, J. R. et al. Loss of signalling via Galpha13 in germinal centre B cell-derived lymphoma. *Nature* **516**, 254–258 (2014).
109. Morin, R. D. et al. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature* **476**, 298–303 (2011).
110. Kirmizis, A. et al. Silencing of human polycomb target genes is associated with methylation of histone H3 Lys 27. *Genes Dev.* **18**, 1592–1605 (2004).
111. Caganova, M. et al. Germinal center dysregulation by histone methyltransferase EZH2 promotes lymphomagenesis. *J. Clin. Invest.* **123**, 5009–5022 (2013).
112. Velichutina, I. et al. EZH2-mediated epigenetic silencing in germinal center B cells contributes to proliferation and lymphomagenesis. *Blood* **116**, 5247–5255 (2010).
113. Beguelin, W. et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. *Cancer Cell* **23**, 677–692 (2013).
114. Morin, R. D. et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B cell lymphomas of germinal-center origin. *Nat. Genet.* **42**, 181–185 (2010).
115. Sneider, C. J. et al. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B cell lymphomas. *Proc. Natl Acad. Sci. USA* **107**, 20980–20985 (2010).
116. Yap, D. B. et al. Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3K27 trimethylation. *Blood* **117**, 2451–2459 (2011).
117. Sahasrabudhe, A. A. et al. Oncogenic Y641 mutations in EZH2 prevent Jak2/beta-TrCP-mediated degradation. *Oncogene* **34**, 445–454 (2015).
118. Ortega-Molina, A. et al. The histone lysine methyltransferase KMT2D sustains a gene expression program that represses B cell lymphoma development. *Nat. Med.* **21**, 1199–1208 (2015).
119. Zhang, J. et al. Disruption of KMT2D perturbs germinal center B cell development and promotes lymphomagenesis. *Nat. Med.* **21**, 1190–1198 (2015).
120. Pasqualucci, L. et al. Analysis of the coding genome of diffuse large B cell lymphoma. *Nat. Genet.* **43**, 830–837 (2011).

121. Lohr, J. G. et al. Discovery and prioritization of somatic mutations in diffuse large B cell lymphoma (DLBCL) by whole-exome sequencing. *Proc. Natl Acad. Sci. USA* **109**, 3879–3884 (2012).
122. Horton, S. J. et al. Early loss of Crebbp confers malignant stem cell properties on lymphoid progenitors. *Nat. Cell Biol.* **19**, 1093–1104 (2017).
123. Zhang, J. et al. The CREBBP acetyltransferase is a haploinsufficient tumor suppressor in B cell lymphoma. *Cancer Discov.* **7**, 322–337 (2017).
124. Hashwah, H. et al. Inactivation of CREBBP expands the germinal center B cell compartment, down-regulates MHCII expression and promotes DLBCL growth. *Proc. Natl Acad. Sci. USA* **114**, 9701–9706 (2017).
125. Jiang, Y. et al. CREBBP inactivation promotes the development of HDAC3-dependent lymphomas. *Cancer Discov.* **7**, 38–53 (2017).
126. Grossman, S. R. p300/CBP/p53 interaction and regulation of the p53 response. *Eur. J. Biochem.* **268**, 2773–2778 (2001).
127. Challa-Malladi, M. et al. Combined genetic inactivation of beta2-microglobulin and CD58 reveals frequent escape from immune recognition in diffuse large B cell lymphoma. *Cancer Cell* **20**, 728–740 (2011).
128. Steimle, V., Siegrist, C. A., Mottet, A., Lisowska-Groszperle, B. & Mach, B. Regulation of MHC class II expression by interferon-gamma mediated by the transactivator gene CIITA. *Science* **265**, 106–109 (1994).
129. Georgiou, K. et al. Genetic basis of PD-L1 overexpression in diffuse large B cell lymphomas. *Blood* **127**, 3026–3034 (2016).
130. Kataoka, K. et al. Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers. *Nature* **534**, 402–406 (2016).
131. Wang, X. et al. Tumor suppressor miR-34a targets PD-L1 and functions as a potential immunotherapeutic target in acute myeloid leukemia. *Cell Signal* **27**, 443–452 (2015).
132. Cortez, M. A. et al. PDL1 regulation by p53 via miR-34. *J. Natl Cancer Inst.* **108**, djv303 (2016).
133. Boice, M. et al. Loss of the HVEM tumor suppressor in lymphoma and restoration by modified CAR-T cells. *Cell* **167**, 405–418 (2016).
134. Young, K. H. et al. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B cell lymphoma: an international collaborative study. *Blood* **112**, 3088–3098 (2008).
135. Young, K. H. et al. Mutations in the DNA-binding codons of TP53, which are associated with decreased expression of TRAILReceptor-2, predict for poor survival in diffuse large B cell lymphoma. *Blood* **110**, 4396–4405 (2007).
136. Zenz, T. et al. TP53 mutation and survival in aggressive B cell lymphoma. *Int. J. Cancer* **141**, 1381–1388 (2017).
137. Wang, X. J. et al. P53 expression correlates with poorer survival and augments the negative prognostic effect of MYC rearrangement, expression or concurrent MYC/BCL2 expression in diffuse large B cell lymphoma. *Mod. Pathol.* **30**, 194–203 (2017).
138. Jia, Z. et al. P53 deletion is independently associated with increased age and decreased survival in a cohort of Chinese patients with diffuse large B cell lymphoma. *Leuk. Lymphoma* **53**, 2182–2185 (2012).
139. Cao, Y. et al. Mutations or copy number losses of CD58 and TP53 genes in diffuse large B cell lymphoma are independent unfavorable prognostic factors. *Oncotarget* **7**, 83294–83307 (2016).
140. Le Guillou, S. et al. The clinical presentation and prognosis of diffuse large B cell lymphoma with t(14;18) and 8q24/c-MYC rearrangement. *Haematologica* **92**, 1335–1342 (2007).
141. Klapper, W. et al. Structural aberrations affecting the MYC locus indicate a poor prognosis independent of clinical risk factors in diffuse large B cell lymphomas treated within randomized trials of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). *Leukemia* **22**, 2226–2229 (2008).
142. Niitsu, N., Okamoto, M., Miura, I. & Hirano, M. Clinical features and prognosis of de novo diffuse large B cell lymphoma with t(14;18) and 8q24/c-MYC translocations. *Leukemia* **23**, 777–783 (2009).
143. Barrans, S. et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B cell lymphoma treated in the era of rituximab. *J. Clin. Oncol.* **28**, 3360–3365 (2010).
144. Kuhn, A. et al. Outcome of elderly patients with diffuse large B cell lymphoma treated with R-CHOP: results from the UK NCRI R-CHOP14v21 trial with combined analysis of molecular characteristics with the DSHNHL RICOVER-60 trial. *Ann. Oncol.* **28**, 1540–1546 (2017).
145. Cuccini, W. et al. MYC+ diffuse large B cell lymphoma is not salvaged by classical R-ICE or R-DHAP followed by BEAM plus autologous stem cell transplantation. *Blood* **119**, 4619–4624 (2012).
146. Lai, C. et al. MYC gene rearrangement in diffuse large B cell lymphoma does not confer a worse prognosis following dose-adjusted EPOCH-R. *Leuk. Lymphoma* **59**, 505–508 (2018).
147. Landsburg, D. J. et al. Sole rearrangement but not amplification of MYC is associated with a poor prognosis in patients with diffuse large B cell lymphoma and B cell lymphoma unclassifiable. *Br. J. Haematol.* **175**, 631–640 (2016).
148. Testoni, M. et al. Gains of MYC locus and outcome in patients with diffuse large B cell lymphoma treated with R-CHOP. *Br. J. Haematol.* **155**, 274–277 (2011).
149. Lu, T. X. et al. MYC or BCL2 copy number aberration is a strong predictor of outcome in patients with diffuse large B cell lymphoma. *Oncotarget* **6**, 18374–18388 (2015).
150. Juskevicius, D. et al. Mutations of CREBBP and SOCS1 are independent prognostic factors in diffuse large B cell lymphoma: mutational analysis of the SAKK 38/07 prospective clinical trial cohort. *J. Hematol. Oncol.* **10**, 70 (2017).
151. Dubois, S. et al. Next-generation sequencing in diffuse large B-cell lymphoma highlights molecular divergence and therapeutic opportunities: a LYSA study. *Clin. Cancer Res.* **22**, 2919–2928 (2016).
152. Scott, D. W. et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J. Clin. Oncol.* **33**, 2848–2856 (2015).
153. Hu, S. et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B cell subtype of diffuse large B cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood* **121**, 4021–4031 (2013).
154. Zhang, L. H. et al. Lenalidomide efficacy in activated B cell-like subtype diffuse large B cell lymphoma is dependent upon IRF4 and cereblon expression. *Br. J. Haematol.* **160**, 487–502 (2013).
155. Hernandez-Izaliturri, F. J. et al. Higher response to lenalidomide in relapsed/refractory diffuse large B cell lymphoma in nongerminal center B cell-like than in germinal center B cell-like phenotype. *Cancer* **117**, 5058–5066 (2011).
156. Wiernik, P. H. et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. *J. Clin. Oncol.* **26**, 4952–4957 (2008).
157. Witzig, T. E. et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B cell non-Hodgkin's lymphoma. *Ann. Oncol.* **22**, 1622–1627 (2011).
158. Zinzani, P. L. et al. Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B cell lymphoma: a phase 2 trial. *Clin. Lymphoma Myeloma Leuk.* **11**, 462–466 (2011).
159. Wang, M. et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia* **27**, 1902–1909 (2013).
160. Feldman, T. et al. Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B cell lymphoma. *Br. J. Haematol.* **166**, 77–83 (2014).
161. Martin, A. et al. Lenalidomide in combination with R-ESHAP in patients with relapsed or refractory diffuse large B cell lymphoma: a phase 1b study from GELTAMO group. *Br. J. Haematol.* **173**, 245–252 (2016).
162. Hitz, F. et al. Rituximab, bendamustine, and lenalidomide in patients with aggressive B cell lymphoma not eligible for high-dose chemotherapy or anthracycline-based therapy: phase I results of the SAKK 38/08 trial. *Ann. Hematol.* **92**, 1033–1040 (2013).
163. Hitz, F. et al. Rituximab, bendamustine and lenalidomide in patients with aggressive B cell lymphoma not eligible for anthracycline-based therapy or intensive salvage chemotherapy - SAKK 38/08. *Br. J. Haematol.* **174**, 255–263 (2016).
164. Ferreri, A. J. et al. Lenalidomide maintenance in patients with relapsed diffuse large B cell lymphoma who are not eligible for autologous stem cell transplantation: an open label, single-arm, multicentre phase 2 trial. *Lancet Haematol.* **4**, e137–e146 (2017).
165. Czuczman, M. S. et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clin. Cancer Res.* **23**, 4127–4137 (2017).
166. Nowakowski, G. S. et al. Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B cell lymphomas: phase I study. *Leukemia* **25**, 1877–1881 (2011).
167. Chiappella, A. et al. Lenalidomide plus cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab is safe and effective in untreated, elderly patients with diffuse large B cell lymphoma: a phase I study by the Fondazione Italiana Linfomi. *Haematologica* **98**, 1732–1738 (2013).
168. Vitolo, U. et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. *Lancet Oncol.* **15**, 730–737 (2014).
169. Nowakowski, G. S. et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B cell phenotype in newly diagnosed diffuse large B-cell lymphoma: a phase II study. *J. Clin. Oncol.* **33**, 251–257 (2015).
170. Nowakowski, G. S. et al. ROBUST: Lenalidomide-R-CHOP versus placebo-R-CHOP in previously untreated ABC-type diffuse large B cell lymphoma. *Future Oncol.* **12**, 1553–1563 (2016).
171. Thieblemont, C. et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J. Clin. Oncol.* **35**, 2473–2481 (2017).
172. Reddy, N. M. et al. A phase II randomized study of lenalidomide or lenalidomide and rituximab as maintenance therapy following standard chemotherapy for patients with high/high-intermediate risk diffuse large B cell lymphoma. *Leukemia* **31**, 241–244 (2017).
173. Chen, D., Frezza, M., Schmitt, S., Kanwar, J. & Dou, Q. P. Bortezomib as the first proteasome inhibitor anticancer drug: current status and future perspectives. *Curr. Cancer Drug Targets* **11**, 239–253 (2011).
174. Goy, A. et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B cell non-Hodgkin's lymphoma. *J. Clin. Oncol.* **23**, 667–675 (2005).
175. Furman, R. R. et al. Phase I trial of bortezomib plus R-CHOP in previously untreated patients with aggressive non-Hodgkin lymphoma. *Cancer* **116**, 5432–5439 (2010).
176. Dunleavy, K. et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B cell lymphoma. *Blood* **113**, 6069–6076 (2009).
177. Evens, A. M. et al. A phase I/II trial of bortezomib combined concurrently with gemcitabine for relapsed or refractory DLBCL and peripheral T cell lymphomas. *Br. J. Haematol.* **163**, 55–61 (2013).
178. Ruan, J. et al. Bortezomib plus CHOP-rituximab for previously untreated diffuse large B cell lymphoma and mantle cell lymphoma. *J. Clin. Oncol.* **29**, 690–697 (2011).
179. Offner, F. et al. Frontline rituximab, cyclophosphamide, doxorubicin, and prednisone with bortezomib (VR-CAP) or vincristine (R-CHOP) for non-GCB DLBCL. *Blood* **126**, 1893–1901 (2015).
180. Leonard, J. P. et al. Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. *J. Clin. Oncol.* **35**, 3538–3546 (2017).
181. Wilson, W. H. et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat. Med.* **21**, 922–926 (2015).
182. Younes, A. et al. Combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for treatment-naive patients with CD20-positive B cell non-Hodgkin lymphoma: a non-randomised, phase 1b study. *Lancet Oncol.* **15**, 1019–1026 (2014).
183. Sauter, C. S. et al. A phase 1 study of ibrutinib in combination with R-ICE in patients with relapsed or primary refractory DLBCL. *Blood* **131**, 1805–1808 (2018).

184. Ramchandren, R. et al. The iR² regimen (ibrutinib, lenalidomide, and rituximab) is active with a manageable safety profile in patients with relapsed/refractory non-germinal center-like diffuse large B-cell lymphoma. *Blood* **132**, S402 (2018).
185. Younes, A. et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J. Clin. Oncol.* <https://doi.org/10.1200/JCO.18.02403> (2019).
186. Grommes, C. et al. Ibrutinib unmasks critical role of bruton tyrosine kinase in primary CNS lymphoma. *Cancer Discov.* **7**, 1018–1029 (2017).
187. Lionakis, M. S. et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell* **31**, 833–843 (2017).
188. Grommes, C. et al. Phase Ib trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. *Blood* <https://doi.org/10.1182/blood-2018-09-875732> (2018).
189. Robertson, M. J. et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B cell lymphoma. *J. Clin. Oncol.* **25**, 1741–1746 (2007).
190. Crump, M. et al. Randomized, double-blind, phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. *J. Clin. Oncol.* **34**, 2484–2492 (2016).
191. Hainsworth, J. D. et al. A randomized, phase 2 study of R-CHOP plus enzastaurin versus R-CHOP in patients with intermediate- or high-risk diffuse large B cell lymphoma. *Leuk. Lymphoma* **57**, 216–218 (2016).
192. Friedberg, J. W. et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood* **115**, 2578–2585 (2010).
193. Barr, P. M. et al. Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL. *Blood* **127**, 2411–2415 (2016).
194. Burke, J. M. et al. An open-label, phase II trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in diffuse large B cell lymphoma. *Clin. Lymphoma Myeloma Leuk.* **18**, e327–e331 (2018).
195. Flinn, I. W. et al. A phase II trial to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL). *Eur. J. Cancer* **54**, 11–17 (2016).
196. Brown, J. R. et al. Phase I trial of the pan-PI3K inhibitor pilaralisib (SAR245408/XL147) in patients with chronic lymphocytic leukemia (CLL) or relapsed/refractory lymphoma. *Clin. Cancer Res.* **21**, 3160–3169 (2015).
197. Younes, A. et al. Pan-phosphatidylinositol 3-kinase inhibition with buparlisib in patients with relapsed or refractory non-Hodgkin lymphoma. *Haematologica* **102**, 2104–2112 (2017).
198. Dreyling, M. et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann. Oncol.* **28**, 2169–2178 (2017).
199. Oki, Y. et al. CUDC-907 in relapsed/refractory diffuse large B cell lymphoma, including patients with MYC-alterations: results from an expanded phase I trial. *Haematologica* **102**, 1923–1930 (2017).
200. Wang, J. et al. AKT hyperactivation and the potential of AKT-targeted therapy in diffuse large B-cell lymphoma. *Am. J. Pathol.* **187**, 1700–1716 (2017).
201. Oki, Y. et al. Phase II study of an AKT inhibitor MK2206 in patients with relapsed or refractory lymphoma. *Br. J. Haematol.* **171**, 463–470 (2015).
202. Witzig, T. E. et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. *Leukemia* **25**, 341–347 (2011).
203. Smith, S. M. et al. Temsirolimus has activity in non-mantle cell non-Hodgkin's lymphoma subtypes: the University of Chicago phase II consortium. *J. Clin. Oncol.* **28**, 4740–4746 (2010).
204. Barnes, J. A. et al. Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B cell lymphoma. *Haematologica* **98**, 615–619 (2013).
205. Fenske, T. S. et al. A phase 2 study of weekly temsirolimus and bortezomib for relapsed or refractory B cell non-Hodgkin lymphoma: a Wisconsin Oncology Network study. *Cancer* **121**, 3465–3471 (2015).
206. Witzig, T. E. et al. Adjuvant everolimus in high-risk diffuse large B cell lymphoma: final results from the PILLAR-2 randomized phase III trial. *Ann. Oncol.* **29**, 707–714 (2018).
207. Johnston, P. B. et al. Everolimus combined with R-CHOP-21 for new, untreated, diffuse large B cell lymphoma (NCCTG 1085 [Alliance]): safety and efficacy results of a phase 1 and feasibility trial. *Lancet Haematol.* **3**, e309–e316 (2016).
208. Witzig, T. E. et al. High rate of event-free survival at 24 months with everolimus/RCHOP for untreated diffuse large B cell lymphoma: updated results from NCCTG N1085 (Alliance). *Blood Cancer J.* **7**, e576 (2017).
209. Italiano, A. et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol.* **19**, 649–659 (2018).
210. Ribrag, V. et al. Interim results from an ongoing phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *Blood* **132**, 4196 (2018).
211. Sarkozy, C. et al. Results from a phase Ib evaluation of tazemetostat (EPZ-6438) in combination with R-CHOP in poor prognosis newly diagnosed diffuse large B cell lymphoma (DLBCL): a Lyso study. *Blood* **132**, 4191 (2018).
212. Straus, D. J. et al. Phase I/II trial of vorinostat with rituximab, cyclophosphamide, etoposide and prednisone as palliative treatment for elderly patients with relapsed or refractory diffuse large B cell lymphoma not eligible for autologous stem cell transplantation. *Br. J. Haematol.* **168**, 663–670 (2015).
213. Batlevi, C. L. et al. A phase 2 study of mocetinostat, a histone deacetylase inhibitor, in relapsed or refractory lymphoma. *Br. J. Haematol.* **178**, 434–441 (2017).
214. Kelly, W. K. et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. *J. Clin. Oncol.* **23**, 3923–3931 (2005).
215. Crump, M. et al. Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid) in relapsed diffuse large-B cell lymphoma. *Ann. Oncol.* **19**, 964–969 (2008).
216. Budde, L. E. et al. A phase I study of pulse high-dose vorinostat (V) plus rituximab (R), ifosfamide, carboplatin, and etoposide (ICE) in patients with relapsed lymphoma. *Br. J. Haematol.* **161**, 183–191 (2013).
217. Assouline, S. E. et al. Phase 2 study of panobinostat with or without rituximab in relapsed diffuse large B cell lymphoma. *Blood* **128**, 185–194 (2016).
218. Oki, Y. et al. Phase I study of panobinostat plus everolimus in patients with relapsed or refractory lymphoma. *Clin. Cancer Res.* **19**, 6882–6890 (2013).
219. Ribrag, V. et al. Safety and efficacy of abexinostat, a pan-histone deacetylase inhibitor, in non-Hodgkin lymphoma and chronic lymphocytic leukemia: results of a phase II study. *Haematologica* **102**, 903–909 (2017).
220. Holkova, B. et al. Phase I trial of carfilzomib (PR-171) in combination with vorinostat (SAHA) in patients with relapsed or refractory B cell lymphomas. *Leuk. Lymphoma* **57**, 635–643 (2016).
221. Nieto, Y. et al. Double epigenetic modulation of high-dose chemotherapy with azacitidine and vorinostat for patients with refractory or poor-risk relapsed lymphoma. *Cancer* **122**, 2680–2688 (2016).
222. Hofmeister, C. C. et al. A phase 1 study of vorinostat maintenance after autologous transplant in high-risk lymphoma. *Leuk. Lymphoma* **56**, 1043–1049 (2015).
223. Nieto, Y. et al. Vorinostat combined with high-dose gemcitabine, busulfan, and melphalan with autologous stem cell transplantation in patients with refractory lymphomas. *Biol. Blood Marrow Transplant* **21**, 1914–1920 (2015).
224. Davids, M. S. et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J. Clin. Oncol.* **35**, 826–833 (2017).
225. de Vos, S. et al. Venetoclax, bendamustine, and rituximab in patients with relapsed or refractory NHL: a phase 1b dose-finding study. *Ann. Oncol.* **29**, 1932–1938 (2018).
226. Morschhauser, F. et al. Venetoclax plus rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) improves outcomes in BCL2-positive first-line diffuse large B-cell lymphoma (DLBCL): first safety, efficacy and biomarker analyses from the phase II CAVALLI study. *Blood* **132**, 782 (2018).
227. Liu, Y. et al. NOXA genetic amplification or pharmacologic induction primes lymphoma cells to BCL2 inhibitor-induced cell death. *Proc. Natl Acad. Sci. USA* **115**, 12034–12039 (2018).
228. Amorim, S. et al. Bromodomain inhibitor OTX015 in patients with lymphoma or multiple myeloma: a dose-escalation, open-label, pharmacokinetic, phase 1 study. *Lancet Haematol.* **3**, e196–e204 (2016).
229. Lesokhin, A. M. et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J. Clin. Oncol.* **34**, 2698–2704 (2016).
230. Ansell, S. M. et al. Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. *J. Clin. Oncol.* **37**, 481–489 (2019).
231. Kline, J. et al. PD-L1 gene alterations identify a unique subset of diffuse large B cell lymphoma that harbors a T cell inflamed phenotype. *Blood* **132**, 673 (2018).
232. Nayak, L. et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood* **129**, 3071–3073 (2017).
233. Greenawalt, D. M. et al. Comparative analysis of primary versus relapse/refractory DLBCL identifies shifts in mutation spectrum. *Oncotarget* **8**, 99237–99244 (2017).
234. Melchardt, T. et al. Clonal evolution in relapsed and refractory diffuse large B cell lymphoma is characterized by high dynamics of subclones. *Oncotarget* **7**, 51494–51502 (2016).
235. Morin, R. D. et al. Genetic landscapes of relapsed and refractory diffuse large B-cell lymphomas. *Clin. Cancer Res.* **22**, 2290–2300 (2016).
236. Mareschal, S. et al. Whole exome sequencing of relapsed/refractory patients expands the repertoire of somatic mutations in diffuse large B cell lymphoma. *Genes Chromosomes Cancer* **55**, 251–267 (2016).
237. Park, H. Y. et al. Whole-exome and transcriptome sequencing of refractory diffuse large B cell lymphoma. *Oncotarget* **7**, 86433–86445 (2016).

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