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Review

Diffuse Large B-Cell Lymphoma: Recognition of Markers for Targeted Therapy

Laura Tomas-Roca [1,†], Marta Rodriguez [1,2,†], Ruth Alonso-Alonso [1,2,†], Socorro M. Rodriguez-Pinilla [1,2] and Miguel Angel Piris [1,2,*]

[1] Pathology Department, Instituto de Investigación Sanitaria Fundación Jiménez Díaz, 28029 Madrid, Spain; laura.tomasr@quironsalud.es (L.T.-R.); martarodmo@gmail.com (M.R.); ruthalonsoalonso@gmail.com (R.A.-A.); smrodriguez@fjd.es (S.M.R.-P.)
[2] Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), 28029 Madrid, Spain
* Correspondence: miguel.piris@quironsalud.es
† These authors contributed equally to this work.

Abstract: Diffuse large B-cell lymphomas (DLBCL)s, the most common type of Non-Hodgkin's Lymphoma, constitute a heterogeneous group of disorders including different disease sites, strikingly diverse molecular features and a profound variability in the clinical behavior. Molecular studies and clinical trials have partially revealed the underlying causes for this variability and have made possible the recognition of some molecular variants susceptible of specific therapeutic approaches. The main histogenetic groups include the germinal center, activated B cells, thymic B cells and terminally differentiated B cells, a basic scheme where the large majority of DLBCL cases can be ascribed. The nodal/extranodal origin, specific mutational changes and microenvironment peculiarities provide additional layers of complexity. Here, we summarize the status of the knowledge and make some specific proposals for addressing the future development of targeted therapy for DLBC cases.

Keywords: large B-cell lymphoma; targeted therapy; molecular classification

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is one of the most frequent non-Hodgkin's Lymphoma types. In recent decades, considerable effort has been made to clarify its molecular pathogenesis, which has led to several DLBCL subclasses being identified and specific therapeutic approaches proposed for some of these variants [1].

The clinical variability of DLBCL is overwhelming; B-cell lymphoma cases with the same morphology (large cells) may originate in the lymph nodes or in any conceivable extranodal localization. They quite often respond to first-line immunochemotherapy, but eventually, some of them relapse and/or progress, with a final 5-year overall survival (OS) probability of around 75%. Standardized protocols for DLBCL staging and treatment have been approved, but in spite of this, the OS and time to progression (TTP) probabilities are still disappointingly low for cases with advanced clinical staging. In contrast to the progress made in the understanding of the molecular basis of these tumors, the therapeutic approach is still mainly based on a combination of immunochemotherapy and cytotoxic therapy [2].

Molecular studies of DLBCL, using a variety of complementary techniques, have produced a massive amount of information (Figure 1 and Supplementary Table S1). DLBCL cells have been shown to carry on multiple combinations of chromosomal translocations involving the *BCL2*, *BCL6* and *MYC* genes translocated with immunoglobulin heavy or light-chain genes or a myriad of other genes, together with somatic mutations involving several hundred genes regulating the B-cell survival pathways, cell cycle, apoptosis, chromatin conformation, cell metabolism, immune response, DNA repair and others. Combinations of these multiple genetic alterations give rise to a complex scenario in which

the identification of precise combinations underlying specific clinicopathological sites of presentation, evolution and response to treatment continues to be a challenge that has so far only been partially addressed.

In the spirits of this Special Issue dedicated to Tom Grogan, and following his extenses contributions to lymphoma understanding and classification, here, we have reviewed the status of the knowledge and made specific proposals for simplifying DLBCL sub-classification, clustering DLBCL with similar pathogenetic mechanisms and histogenetic differentiation.

	PMBL	ABC						GCB				
Lymphoma type	**PMBL**	**Immune privileged sites (Gonads, PCNSL, breast)**	**PCDLBCL**	**MCD**	**EBV**	**Other ABC**	**N1**	**EZB**	**Other GCB**	**BN2**	**Unclassified**	**PBL: EBV/MYC/ALK/HHV8**
Mutated genes	STAT6 SOCS1 CIITA	MYD88 CD79B CARD11	MYD88 CD79B TNFAIP30 CARD11 STAT3	MYD88 CD79B PRDM1 CD58, MHC	MYC RHOA PIM1 MEF2B MYD88 CD79B	PRMD1 CARD11 TNFAIP3 NOTCH1	NOTCH1 TNFAIP3 IRF4 ID3	BCL2t, EZH2, CREBBP/EP300 KMT2D Sp1PR2/GNA13 MTOR TNFRSF14	SGK1 TET2	BCL6t NOTCH2 SPEN DTX1 TNFAIP3 BCL10	NOTCH2 SPEN	MYC STAT3 CD79B CARD11
Targets	PDL1/PDL2 JAK/STAT CD30	MDM2/4 IRAK NF-κB PDL1/PDL2 BTK PI3K	NF-κB PDL1/PDL2	NF-κB BCR PI3K BCL2 IRAK4 BTK IRF4 mTORC	BCL6 MYC NF-κB CD20 EBV	BCL2 NF-κB BTK BCR	PDL1/PDL2 NOTCH1	BCR PI3K BCL2 EZH2 mTORC	BCL2 PI3K JAK2	NF-κB BCR PI3K BCL2 NOTCH2 mTORC1		ALK MYC BCL6 PDL1/PDL2 EBV

Figure 1. Diffuse large B-cell lymphoma classification and molecular alterations. Subgroups of diffuse large B-cell lymphoma (DLBCL), including its molecular subgroups activated B cell-like (ABC) DLBCL and germinal center B cell-like (GCB) DLBCL defined by gene expression and genetic analysis. Each column represents one subtype. Abbreviations: DLBCL, diffuse large B-cell lymphoma; PTL, primary testicular diffuse large B-cell lymphoma; PCNSL, primary DLBCL of the central nervous system; PMBL, mediastinal large B-cell lymphoma; PCDLBCL, primary cutaneous diffuse large B-cell lymphoma leg-type; MCD, cooccurrence of *MYD88*^{L265P} and *CD79B* mutations; EBV, Epstein–Barr virus; N1, *NOTCH1* mutations; EZB, *EZH2* mutations and *BCL2* translocations; BN2, *BCL6* fusions and *NOTCH2* mutations; PBL, plasmablastic lymphoma; BTK, Bruton's tyrosine kinase inhibitors; BCR, B-cell receptors; PI3K, phosphoinositide 3-kinase; BCL6t, BCL6 translocation.

Gene expression profiling (GEP) studies led to the identification of different DLBCL molecular subtypes based on the cell of origin (COO) (Figures 1 and 2): germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes [3,4]. The COO variability has been found to explain a significant part of the DLBCL molecular heterogeneity [5,6], but data concerning its clinical applicability have been controversial [6–11]. The possibility of using COO as a predictor of response to lenalidomide, ibrutinib or bortezomib, when associated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), is still contentious [12–14]. Parallel efforts have revealed that a variety of molecular events leading to the deregulation of *MYC* and *BCL2* expression, or the simultaneous expression of both protein markers, have also prognostic value, regardless of the COO [11,15–21]. Most of these studies used immunohistochemistry (IHC) to assess the BCL2 and MYC expression, while COO is widely determined using the NanoString platform. Other

prognostic markers have been found, including the Epstein–Barr virus (EBV), P53, CD5, CD30, PDL1 and others [22–28], mostly using IHC or in situ hybridization (ISH) (e.g., EBER) markers.

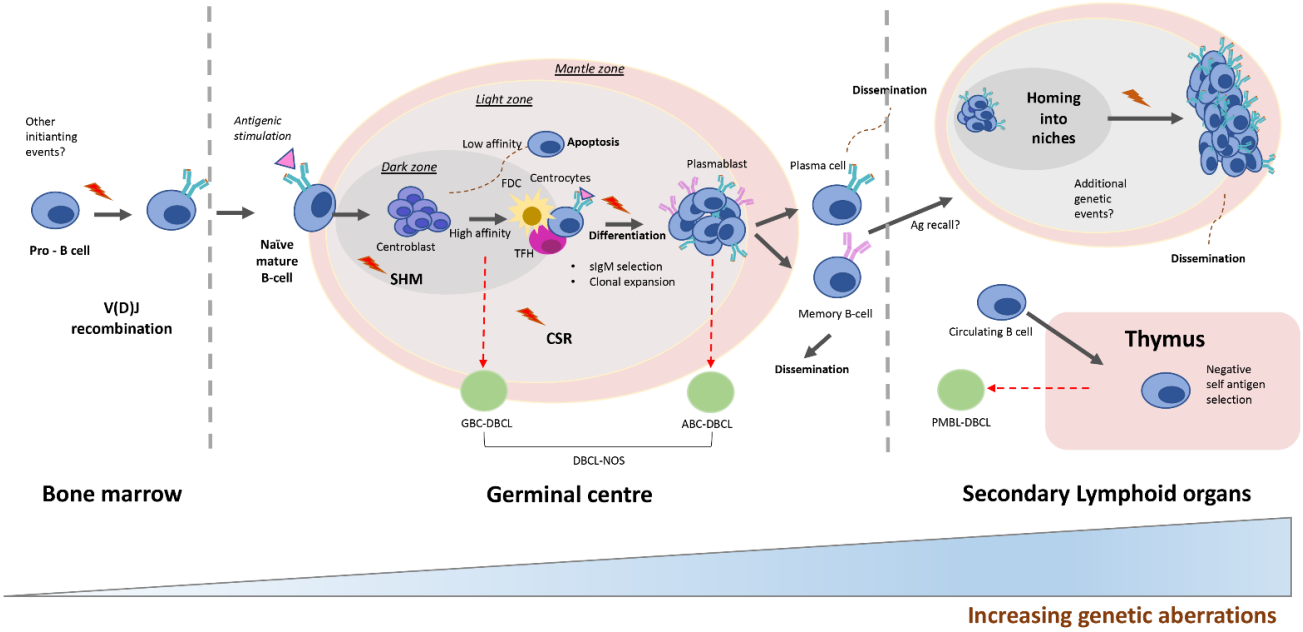

Figure 2. Diffuse large B-cell lymphoma development. Upon stimulation with an antigen (Ag), naive B cells enter the germinal center (GC) reaction, where they undergo rounds of somatic hypermutation (SHM), class-switch recombination (CSR) and proliferation. The initiation of GBC-DLBCL may derive from the transformation of light zone cells. ABC-DLBCL is thought to originate from light zone cells poised to undergo plasma cell differentiation. PMBL is thought to develop from a thymic post-GC B cell or from a GC B cell that has migrated to the thymus. Abbreviations: GBC, germinal center B cell-like; ABC, activated B cell-like; PMBL, mediastinal large B-cell lymphoma; Ag, antigen.

2. Molecular Alterations Defining Aggressive DLBCL

2.1. DLBCL Subclassification

The term "diffuse large B-cell lymphoma" was initially coined to encompass all diffuse B-cell lymphomas with a large cell cytology independently of the organ of origin, molecular history and other prognostic or predictive data. This lymphoma has subsequently been subclassified to recognize the diverse molecular alterations and to integrate the striking differences in survival probability and response to specific targeted therapies. Mediastinal large B-cell lymphoma (PMBL) has emerged as a distinct clinicopathological entity in which different studies coincide in showing that large B-cell lymphomas arising in the mediastinum have a peculiar clinical presentation and histological features, reflecting the underlying characteristic molecular events and bearing important therapeutic implications (Figure 1). Additionally, GEP studies have confirmed that PMBL is a separate entity from DLBCL at the molecular level and confirmed their similarities with Hodgkin's lymphoma (HL) [29]. These results have consolidated PMBL as a distinct entity and have fueled additional efforts to subclassify DLBCL cases.

Besides the attempts to classify DLBCL, the official classification of the World Health Organization (WHO) is based on the work of Alizadeh et al. [3], which established the ABC, GBC and NOS groups. In addition to these three major subtypes, the WHO recognizes others based on their location or peculiar morphological features [30]: cutaneous "leg-type" DLBCL (LBCL leg-type) [31,32], primary testicular diffuse large B-cell lymphoma (PTL), primary DLBCL of the central nervous system (PCNSL) [33], T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) [34] and EBV-positive DLBCL [35] (Figure 1).

In recent years, some authors have divided DLBCL into several subgroups on the basis of additional GEP findings. Monti et al. [34] defined three groups: "B-cell recep-

tor/proliferation", "oxidative phosphorylation" and "host response" (HR). The B-cell receptor/proliferation group contains *BCL6* translocations. The oxidative phosphorylation group includes tumors carrying t(14;18) and apoptotic pathway defects. The HR group is characterized by a T-cell and dendritic signature.

The integration of exome sequencing data, copy number analysis and structural variants enabled Chapuy et al. to identify five DBCL subsets (Supplementary Table S1) [36], each of which possesses specific genetic features: (C1), low-risk ABC-DLBCLs of extrafollicular/marginal zone origin; (C2), tumors with biallelic inactivation of *TP53, 9p21.3/CDKN2A* and associated genomic instability; (C3), high-risk GCB-DLBCLs with *BCL2* structural variants and alterations of the PTEN and epigenetic enzymes; (C4), low-risk GCB-DLBCLs with alterations in the B-cell receptor (BCR)/PI3K, JAK/STAT and BRAF pathway components and multiple histones; (C5), tumors containing *18q* gain, including frequent *BCL2* gain.

More recently, Schmitz et al. classified DLBCL into four groups, according to the presence of genetics aberrations [37]: MCD (cooccurrence of $MYD88^{L265P}$ and *CD79B* mutations), BN2 (*BCL6* fusions and *NOTCH2* mutations), N1 (*NOTCH1* mutations) and EZB (*EZH2* mutations and *BCL2* translocations). Lacy et al. established five molecular subtypes, termed MYD88, BCL2, SOCS1/SGK1, TET2/SGK1 and NOTCH2, also based on the study of genetic alterations, in a cohort of 928 patients (Figure 1) [38].

It is of note that some subgroups of DLBCL cases arising in extranodal localizations reproduce the molecular alterations and phenotype that define the MCD subgroup. PCNSL has a particular molecular profile characterized by a predominance of the ABC subtype and the presence of *MYD88/CD79B* mutations and PD-1/PD-2 pathway alterations [39,40]. Similar observations have been made for cutaneous LBCL leg-type and DLBCL arising in immune-privileged sites such as the testis and breast, among others, and which resemble the ABC subtype [41], with 60% of mutations occurring in $MYD88^{L265P}$ [42] and 20% in *CD79B* [43].

2.2. Relevant Genes and Pathways

The pathogenesis of DBCL is a good example of a multistep process involving the accumulation of genetic alterations, including somatic mutations, copy number changes, chromosomal translocations and epigenetic changes (Figure 1 and Supplementary Table S1) [44–47]. These changes are closely linked to two main physiological mechanisms that operate during the immunoglobulin (IG) DNA remodeling processes in B lymphocytes: chromosomal translocations, which arise from errors in V(D)J recombination, somatic hypermutation (SHM) and immunoglobulin class-switch recombination (CSR) [46] (Figure 2) and activation-induced cytidine deaminase (AID)-mediated SHM [47]. Additionally, different B-cell lymphoma genetic alterations affect the crosstalk between malignant B cells and the surrounding cells, including follicular dendritic cells and follicular helper T cells [48].

The introduction of next-generation sequencing (NGS) technologies and functional genomic analysis has revealed an unexpectedly high degree of diversity of the mutational landscape of DBCL. Somatic mutations have been identified in more than 700 genes [44] (Supplementary Table S1), with an average of 50–100 alterations in the coding regions per case (including mutations and copy number alterations) [36,37,49,50]. Around 150 of these genes are mutated driver genes, including some that occur at low frequencies [51]. Notably, Chapuy et al. showed that 80% of the observed mutations are associated with the spontaneous deamination of cytosines at CpGs and involve a switch from cytosine to thymine (C > T) [52].

Here, we review some of the most relevant genes and pathways involved in DLBCL pathogenesis, drawing particular attention to the therapeutic opportunities.

3. BCL6, MYC and BCL2

3.1. BCL6

BCL6 is known as the "master regulator" of the germinal center (GC) reaction (Figure 2). It negatively modulates the expression of the genes involved in a variety of biological

programs [53]. It acts by recruiting distinct corepressor complexes, like the SMRT–NCOR complex, resulting in the recruitment of HDAC3 (Figure 3) [54]. BCL6 is involved in several key functions in GC formation and antibody affinity maturation [55]. It regulates the complex balance between preserving genomic integrity and allowing the production of high-affinity class-switched antibodies during the SHM and CSR steps. It also mediates T-cell-mediated B-cell activation [56], BCR and CD40 signaling [57], NOTCH2 signaling [58] and plasma cell differentiation [59]. A raised BCL6 expression, a hallmark of GC differentiation, can also be found in scattered activated B cells outside the GC, where it is always associated with the expression of proliferation markers.

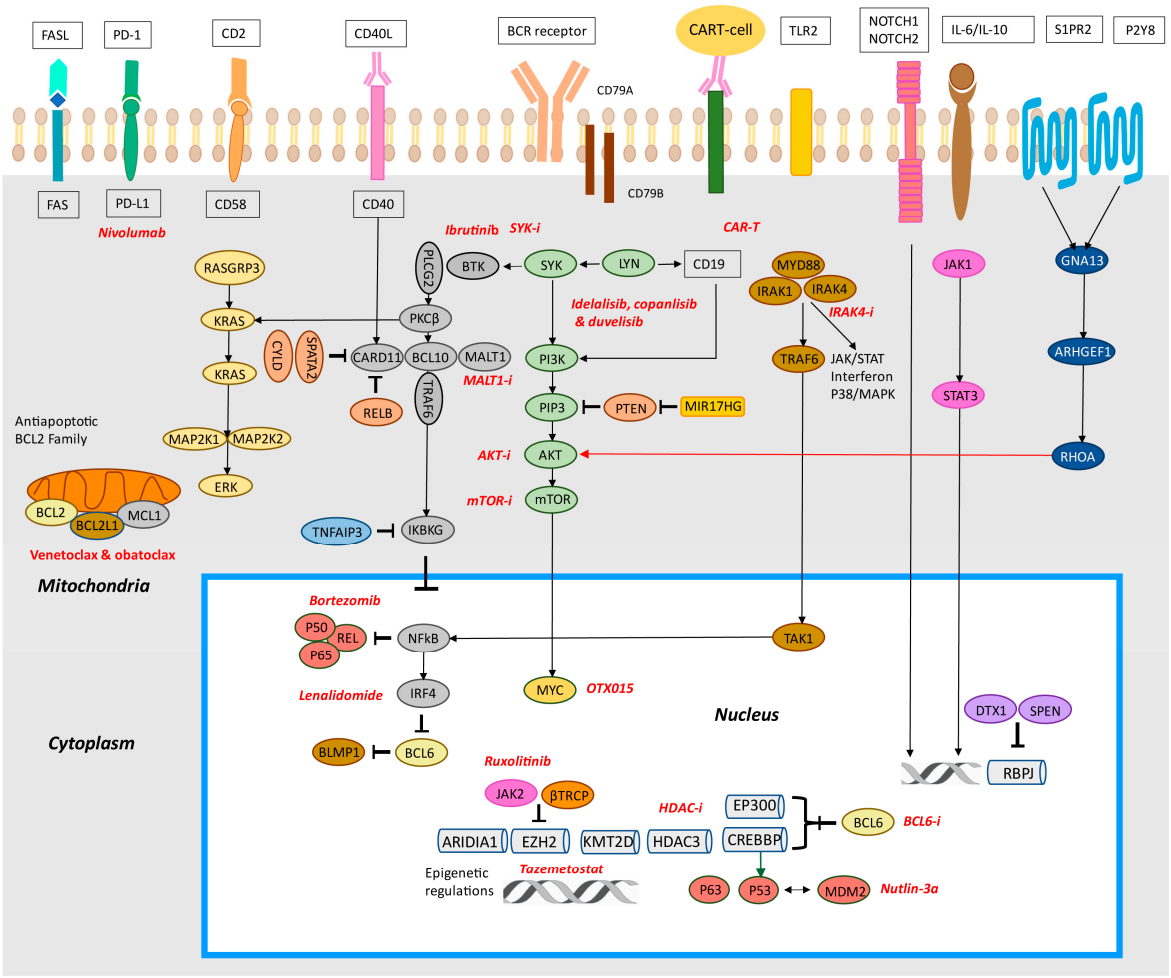

Figure 3. Main pathways involved in the proliferation and survival of DLBCL lymphoma and their potential inhibitors.

The complexity of the DLBCL genetic landscape is complex and involves many genes and pathways. The major biological programs include epigenetic modifiers such as EZH2, KMT2D, CREBBP, EP300, AR and ARIDIA1. Alterations are also common in other biological pathways such as: BCR (SYK, PI3K and MTOR); TLR (MYD88); JAK-STAT (JAK1 and STAT3) and NF-κB (TNFAIP3). The potential inhibitors of each component or pathway in follicular lymphoma are indicated in red. Abbreviations: BCR, B-cell receptor; *-i*, inhibitor.

BCL6 translocations are more frequently present in the ABC subtype (24–57%) than in GCB-DLBCLs (10–31%) and, per se, do not imply differences in the survival probability (10–31%) [60,61]. BCL6 fusions (and NOTCH2 mutations) are distinctly more frequent in a group of DLBCLs known as BN2 (Figure 1) [37]. These arise more frequently in an extranodal localization and are associated with a better survival probability [37] than patients in the MCD and N1 subgroups.

Double-/triple-hit lymphomas (DHLs/THLs) with translocations in *BCL6* are less common than with BCL2, although they present a slightly different clinical course than other DHLs/THLs. They present a high international prognostic index (IPI), extranodal involvement and an aggressive clinical course in most studies. Their GEP profile also differs substantially [62], and they could have a GCB or non-GCB cell of origin [63].

Recurrent mutations in *BCL6* are also reported in ~16% of DLBCLs [64]. Although genetic aberrations affect *BCL6*, alterations in the genes regulating BCL6 can modify its expression by an indirect mechanism. Mutations have been identified in some of the most important BCL6 regulators, including *CREBBP*/*EP330*, *MEF2B* and *FBXO11* [49,65,66].

DHLs with translocations in *BCL6* and *MYC* are less common than BCL2/MYC DHs, and they do not seem to follow an unfavorable clinical course [61]. They usually present a high IPI and extranodal involvement. Their GEP profile also differs substantially [62].

3.2. MYC

MYC encodes a proto-oncogene transcription factor that regulates a wide range of genes at the cellular level that are involved in the control of cell proliferation, metabolism, cell growth and DNA replication (Figure 3) [67]. MYC expression, which occurs in benign tissues only in scattered GC cells, occurs at a higher level in 29–47% of DLBCLs as a consequence of *MYC* rearrangements but is more often independent of them [68]. Although a very high level of MYC expression has been associated in DLBCLs with the presence of high levels of MYC mRNA and, more frequently, *MYC* translocation, there are many exceptions to this general rule. MYC protein expression is associated with lower OS and progression-free survival (PFS) but only when co-expressed with the BCL2 protein [21]. The unfavorable behavior of DLBCL patients with the increased expression of both MYC and BCL2, after treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), has been reproduced in several studies of protein or RNA expression and has led "double expressers" to be recognized as consistent prognostic markers [11,28,69].

This double MYC/BCL2 expression does not necessarily depend on double-gene translocation, which is a more restricted phenomenon that is recognized in de novo DLBCL or associated with progression from follicular lymphoma (FL).

The DHL/THL-harboring translocations in *MYC* and *BCL2* and/or *BCL6* are present in around 4–8% of DLBCLs, 65% of which are MYC/BCL2 DHLs [70]. Although the majority of these tumors are of the GCB subtype, which is usually associated with a more favorable clinical course, the presence of DHL/THL identifies a subgroup of DLBC-GC cases with an aggressive clinical course and poor outcome [71]. Conversely, patients with single translocations in *MYC* have variable clinical courses, except for those who also carry either *BCL2* or *TP53* mutations and who have an unfavorable prognosis [72]. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and and rituximab; DA-EPOCH-R), an intensive infusion treatment regimen, has been proposed for use against untreated aggressive B-cell lymphoma with an *MYC* rearrangement [73].

There is still much debate about the definition of DHL/THL cases, and it remains an open issue. Some of the useful contributions to this topic have shown that:

- B-cell lymphomas with concurrent MYC and BCL2 abnormalities other than translocations behave similarly to MYC/BCL2 double-hit lymphomas [74].
- This group can be better defined through the recognition of the double-hit gene expression signature (27% of DLBCL-GC patients), which identifies a distinct subgroup of GC-like DLBCLs with a 5-year time to progression rate of 57% [75].
- A molecular high grade, defined using GEP, identifies 9% of DLBCL cases with shorter PFS, in which an analysis of the treatment effects suggested a positive effect of bortezomib [17].
- Double-hit MYC/BCL6 has different biological and clinical implications than the MYC/BCL2 combination.

3.3. BCL2

BCL2 is a key antiapoptotic protein involved in GC B-cell apoptosis inhibition (Figures 2 and 3). The translocations in this gene occur in around 30% of the DLBCL-GBC subset [6], the t(14;18) being identified almost exclusively in GBC. The presence of translocations in *BCL2* is related to a poor outcome, especially when associated with *MYC* translocations [76]. On the other hand, *BCL2* gains are mostly observed in the ABC subtype, where they are mostly associated with overexpression (~14%) [77,78]. Somatic mutations located at the promoter and coding regions are due to SHM, and they are present in ~35% of DBCLs overall but are especially abundant in the GBC subtype [79].

4. B-Cell Receptor Signaling and Toll-Like Receptor Pathways

4.1. BCR

During the GC reaction, T-follicular helper (T_{FH}) cells positively select only centrocytes whose BCRs have a high affinity for antigen(s) so that they can enter the CSR process, having been activated by AID (Figure 2). The BCR is a transmembrane signaling complex composed of an antigen recognition unit and a signaling unit (Figure 3). The signaling unit comprises a heterodimer of CD79A and CD79B proteins and transduces the signal to a gene complex (denominated by the My-T-BCR supercomplex) [80] once the BCR has recognized the antigen. This signal ultimately regulates B-cell survival. The pathway is recurrently deregulated as a consequence of somatic mutations. These pathway alterations are much more frequent in cases of the DLBCL-ABC type that depend on BCR signaling. Thus, mutations targeting the immunoreceptor tyrosine-based activation motifs (ITAMs) in *CD79A* and *CD79B* are present in ~20% of ABC patients but only in ~3% of GBC patients [81]. ABC cases have been shown to carry PRDM1-truncating mutations (~20%) and homozygous deletions (~4%) [37,82]. *PRDM1* is one of the key genes involved in regulating the BCR pathway, wherein its function is to inhibit BCR signaling [83]. CARD11 encodes a scaffold protein that, following its activation by PKCβ, recruits BCL-10 and MALT1 to activate the JNK pathway [81]. Mutations in *CARD11* result in a gain-of-function phenotype that activates the NF-κB pathway [84]. On the other hand, BCL-10 is overexpressed in ~25% of GBC and ~11% of ABC cases, mostly due to the presence of translocations [85]. Most potential pathogenic mutations in *BCL10* are located in the carboxy-terminal domain. These also affect both subtypes: ~10% of ABC and ~6% of GBC cases [37]. Amplifications in MALT1 are mainly detected in ABC-DLBCL (~7% of cases) and GBC (~1%) [37]. These multiple mutations interact to induce lymphomagenic CARD11/BCL10/MALT1 signaling, which drives malignant B-cell proliferation via cooperative NF-κB and JNK activation [86].

4.2. Toll-Like Receptor Signaling

MYD88 is a signal adaptor protein that mediates the activation of the NF-κB pathway after the stimulation of the Toll-like receptor (TLR) and the interleukin IL-1 and IL-18 receptors (Figure 3) [87,88]. MYD88 is frequently activated in DLBCL-ABC and other B-cell lymphoma types, most often as a consequence of a redundant L265P mutation [37,89]. The $MYD88^{L265P}$ mutation, located in the Toll/IL-1 receptor domain of MYD88, intensifies the interaction and consecutive phosphorylation of the IRAK1 and IRAK4 complex, activating downstream targets, including NF-κB and JAK–STAT signaling [87]. A subset of DLBCLs presents concomitant $MYD88^{L265P}$mutations and *CD79B* or *CD79A* (34% of the cases with a $MYD88^{L265P}$ mutation had a coincident *CD79B/A* mutation; these are termed MCD) (Figure 1) [87], providing evidence of the cooperative role of these mutations in the ABC subgroup pathogenesis.

4.3. NF-κB Pathway

NF-κB is a transcription regulator that, after activation by various intra- and extracellular stimuli, translocates to the nucleus and stimulates the expression of the genes involved in a wide variety of biological functions, including cell growth and apoptosis inhibition (Figure 3). The inappropriate activation of NF-κB is associated with several

inflammatory and lymphoproliferative disorders. The raised level of expression of an NF-κB signature is a specific defining feature of the ABC subtype [90]. The ABC-DLBCL subtype shows a constitutive activation of the NF-κB signaling cascade as a consequence of the genetic alterations in NF-κB modifiers and/or EBV infection [90]. Ultimately, genetic abnormalities that activate the BCR and TLR pathways bring about NF-κB activation. For example, the mutations in *CARD11* enhance its capacity to transactivate the NF-κB genes [91], while inactivating mutations of the negative regulator *TNFAIP3*, found in ~30% of the cases, may cause an increase of the NF-κB response and subsequent neoplastic transformation [92,93]. *TNFAIP3*, which is more frequent in the BN2 group, cooccurs with $MYD88^{L265P}$ mutations in around 7% of ABC patients, suggesting that they may cooperate in ABCL pathogenesis [94,95].

4.4. PI3K/AKT/mTOR Pathway

The PI3K signaling pathway is located downstream of BCR signaling and is activated by CD19 and the SYK kinase (Figure 3) [96]. PI3K activates AKT, which sends the signal to mTOR and the other signaling pathways [97]. Genetic aberrations are present in several genes of the PI3K pathway genes (*RHOA*, *GNA13* and *SGK1*) in around 34% of DLBCLs [37]. PTEN is a negative regulator of PI3K signaling, and mutational deletions in the *PTEN* gene facilitate activation of the PI3K/AKT pathway [98]. The microRNA *MIR17HG* that targets the mRNA of *PTEN* is amplified mostly commonly in GCB-DLBCLs (~8% of cases) [37], leading to a reduced PTEN expression. Mutations in PI3K itself occur only in ABC cases (6%) [37]. Furthermore, mutations in the PI3K/AKT pathway can indirectly activate the NF-κB pathway, causing a malignant transformation [99].

FOXO1 is a transcription factor that acts as a tumor suppressor. It is phosphorylated by AKT, resulting in cytoplasmic sequestration and suppression of its activity [100]. Mutations in *FOXO1* have been observed in around 8% of DLBCL cases [65,101] and exhibit aberrant nuclear localization [101].

5. Epigenetic Regulators Histone/Chromatin Modifiers Pathway

The chromatin regulation status is important during B-cell differentiation, and a wide repertoire of genetic aberrations has been identified in genes involved in epigenetic and chromatin regulation [37,51]. Many alterations in chromatin conformation have been found, mainly in tumors derived from the GC, such as FL and the DLBCL-GBC type.

5.1. EZH2

EZH2 is a histone N-methyltransferase responsible for the mono-, di- and trimethylation of lysine 27 of the histone H3 subunit (H3K27), regulating the gene transcription as a component of the PRC2 complex. EZH2 blocks the expression of genes that act to improve B-cell proliferation, inducing apoptosis after genotoxic damage and the restriction of plasma cell differentiation (Figure 3) [102–104]. As an example, *PRDM1* and *IRF4*, both of which are target genes of *EZH2*, as well as the cell cycle inhibitor target genes *CDKN1A* and *CDKN1B*, are required for the differentiation of GC B cells into memory and plasma cells [103,104].

Around 6% of DLBCL cases, all of which are members of the GBC subgroup (~22%) [105], present mutations in *EZH2* (Figure 1) [51]. The majority of *EZH2* mutations are located at the tyrosine residue 641 (Y641N), which is situated within the enzyme catalytic site [106]. As a consequence, there is a switch in the catalytic function that favors trimethylation and leads to higher levels of trimethylated histones [107]. Additionally, the $EZH2^{Y641N}$ mutation suppresses *CDKN1A* and *PRDM1* expression, resulting in hyperproliferation of the GC of B cells and blockade of plasma cell differentiation, respectively [104].

5.2. CREBBP and EP300

CREBBP and EP300 are major acetylation regulators that positively regulate the expression of multiple genes in the GC. They both mediate H3K27 acetylation, which is

required for gene enhancer activation during the GC reaction. However, they are also involved in acetylating other nonhistone molecules, including BCL6 and p53 (Figure 3). Therefore, the inactivation of CREBBP or EP300 impairs the acetylation-mediated inactivation of BCL-6 [49] and the acetylation of p53, thereby preventing post-transcriptional activation [108].

Genetic aberrations in *CREBBP* are identified in these genes in ~25–30% of DLBCL cases, and the mutations in CREBBP are most commonly reported in the GBC subtype. CREBBP loss is associated with increased GC B-cell proliferation and GC expansion and facilitates the loss of immune surveillance of the tumor [109]. They also affect cell-intrinsic engraftment and growth promotion [50,110]. *EP300* mutations are described in ~10% of DLBCL patients and affect the GBC and ABC subtypes [49]. Notably, inactivation of the *CREBBP* and *EP300* genes is mutually exclusive, perhaps due to their high degree of functional and structural homology [51].

5.3. Other Genes Associated with Epigenetics and Chromatin Regulation

Other genetic drivers in DLBCL development related with epigenetic and chromatin regulation include: *KMT2D*, *SUZ12*, *HIST1H1E*, *TET2*, *HIST1H1E*, *ARID1A*, *ARID1B*, *SMARCA4*, *CHD1*, *NCOR1*, *DNMT3A*, *DDX3X*, *SETD1B*, *SETD2* and *INO80* (Figures 1 and 3 and Supplementary Table S1) [49,51,111]. *KMT2D*, which encodes a lysine methyltransferase 2D, is the most commonly mutated gene in DLBCL, occurring in around 25% of cases [51]. The majority of these mutations correspond to truncating variants that remove the C-terminal cluster of highly conserved domains, including the SET domain [65], although missense mutations at the same domains have also been described [112]. Although they can be observed in ABC-DLBCL, they are more frequently found in GBC [113]. Multiple studies have attempted to elucidate the role of *KMT2D* mutations in DLBCL pathogenesis and concluded that the *KMT2D* gene is a tumor-suppressor gene whose early loss facilitates lymphomagenesis by remodeling the epigenetic landscape of the lymphoma precursor cells [112,114], perturbing the expression of the CD40, JAK-STAT, Toll-like receptor and the B-cell receptor signaling pathways [115].

6. p53 Pathway

TP53 is a tumor-suppressor gene that responds to diverse cellular stresses regulating the expression of multiple genes that induce cell cycle arrest, apoptosis, senescence, DNA repair and metabolic changes [116]. The presence of *TP53* somatic mutations in DLBCL is a marker of a negative prognosis [117]. Mutations in this gene are present in 20–25% of DLBCL patients, the frequencies being similar in the two subtypes [111]. *TP53* mutations also occur in DHL *MYC*/*BCL2* cases but rarely in *MYC*/*BCL6* [118]. The activity of *TP53* can also be affected by a variety of genetic alterations in other genes that can hamper TP53 expression, such as the loss of *CDKN2A* or *KDM6B* [119].

7. Escape from Immune Surveillance

Mutations in genes with immune recognition and antigen-presenting functions recur in DLBCL, affecting ~74% of patients with the condition [120,121]. Genetic alterations in these genes are expected to evade immune system recognition and malignant cell elimination.

7.1. MHC Class

The MHC class I complex is encoded by human leukocyte antigen genes (*HLA-A*, *HLA-B* and *HLA-C*) and β2-microglobulin (B2M). Deletions or inactivating mutations of the MHC-I occur in 55–75% of DLBCLs [122], and they are more commonly seen in ABC than in GBC cases. They are notably more frequent in *HLA-A* (~6% of cases) and *HLA-B A* (~7%) than in *HLA-C* (~4%), probably due to their higher level of expression at the cell surface [37]. Mutations in *B2M* have been described in around 29% of DLBCL cases affecting the GBC subtype [122]. The loss or downregulation of *B2M* results in disruption

of the cell surface MHC class I expression, thereby contributing to the evasion of $CD8^+$ T-cell cytotoxicity [51,111,122].

Around 40–50% of DLBCL patients show a reduced expression of the MHC class II complex, which has been associated with poor outcomes [6]. This complex is epigenetically regulated by CREEB/EP300 through CIITA transcription, so genetic alterations affecting those genes can modify the MHC class II expression at the cell surface [110], disabling its recognition by $CD4^+$ T cells [123]. CIITA is a transcriptional coactivator that regulates genes encoding MHC class II proteins, which play a key role in the $CD4^+$ T-cell immune response [124]. Notably, *CIITA* is commonly targeted by ASHM in 21% of DLBCL patients. Several types of genetic aberrations in *CIITA* have been identified in DLBCL, such as mutations, deletions and chromosomal rearrangements; these occur in both subtypes but more frequently in GBC (~10%) than in ABC (~4%) cases [37].

7.2. CD58

CD58 is a member of the superfamily of immunoglobulins. It functions as a ligand of the CD2 receptor present in natural killer (NK) cells (Figure 3). A range of genetic aberrations occur in *CD58*, including biallelic deletions, truncating mutations and in-frame deletions (Supplementary Table S1) [111]. CD58 alterations are more commonly seen in the ABC subtype (~68% of cases) than in the GBC subtype (~32%) [122]. CD58 is involved in regulating the adhesion and activation of NK cells, and its alterations lead to a loss of CD58 at the cell surface, thereby impairing cytolysis by the NK cells.

7.3. CD70

CD70 is a ligand of the CD27 receptor, which can activate the NF-κB pathway to produce a proliferation of B cells [125]. Notably, CD70 activates T cells through the CD27 receptor, which is essential for $CD8^+$ T-cell proliferation [126]. Mutations in *CD70* have been reported in around 10% of DLBCLs in the ABC (6%) and GBC (4%) subtypes [51].

7.4. Other Genes Involved in Immune Escape

A low incidence of somatic mutations has been identified in other genes associated with immune surveillance in DLBCL, such as *FAS, TNFRSF14*, *TNFSF9*, *CD70 MCL1*, *NLRC5*, *SOCS3*, *TAP1*, *FOXP1, IL6ST*, *CD274 (PDCD1LG1)*, *JAK2*, *HGF*, *MRC1*, *CD86*, *UNC13D*, *IL-10*, *RFXAP*, *MSR1*, *TAP2*, *LAIR1*, *CD163*, *PDCD1*, *IDO1*, *TNFRSF25*, *TAPBP*, *CD273 (PDCD1LG2)*, *VEGFA*, *CSF1*, *CD83*, *CTLA-4*, *LAG3*, *NLRC4*, *GDF15*, *CD28*, *CD27*, *RFXANK*, *HAVCR2*, *IDO2*, *LGALS3*, *CD80*, *CD276*, *LGALS1*, *PVR*, *CCL2*, *HLA-DR* and *TIGIT* (Supplementary Table S1) [37,113].

PDCD1LG1 and PDCD1LG2 both code for programmed death ligands (PDLs). Different genetic aberrations, including copy number gains, amplifications and chromosomal rearrangements, have been described in *PDL1* and *PDL2* (Figure 3) [127]. They have been reported most often in cases of non-GCB subtype (27%), in which *PDL1* alterations are associated with higher levels of PD-L1 but not of PD-L2 [127,128]. Moreover, chromosomal rearrangements in *CIITA* and amplifications and rearrangements in *PD-L1* and *PDL-2* have been reported in PMBL [120,129].

Amplifications at the 9p24.1 region are not exclusive to PMBL; Wang and coworkers reported that 3.5% of non-mediastinal LBCL patients exhibit amplifications of this region, with an increased expression of PD-L1, PD-L2 and JAK2; younger age; an ABC phenotype; a mutational profile similar to that of the PMBL cases and a trend towards better event-free survival [130].

TNFRSF14 is a member of the tumor necrosis factor family (1p36.32) [131], which acts as a tumor suppressor in DLBCL. Loss-of-function mutations and deletions in *TNFRSF14* have been reported only in GBC cases (~30%) and in FL [37]. The loss of TNFRSF14 results in the activation of B-cell proliferation and promotes the generation of GC lymphomas [132]. FAS is a tumor suppressor from the TNF receptor family. FAS promotes apoptosis through its ligand (FASL), which is expressed on the plasma membrane of T cells and NK cells

(Figure 3) [133]. Loss-of-function mutations are present in around 6% of cases of the GBC subtype and in 5% of those of the ABC subtype [134].

8. JAK-STAT Pathway

The JAK/STAT signaling cascade is composed of Janus-associated kinases and the signal transducer and activator of transcription proteins. STAT3 is a target of BCL6, and its activation is associated with tumor angiogenesis and metastasis [135], and, therefore, with the advanced stages of DLBCL and a poor outcome [136].

The JAK/STAT pathway is often affected in PMBL [137] but is also a feature of ABC-DLBCL. It is a feature of the ABC subtype and is triggered by the autocrine production of interleukin-6 (IL-6) and IL-10, which encourage cancer progression [138,139]. However, somatic mutations have been reported in *SOCS1*, *STAT3* and *STAT6* at higher frequencies in GBC than in ABC cases [140]. Notably, some authors have observed a subset of GBC patients that feature inactivating mutations in *SOCS1* and that have a good prognosis [140,141]. Recurrent mutations have been described in HIV-associated plasmablastic lymphoma, with 42% cases carrying STAT3 mutations and JAK1 (14%) or SOCS1 (10%), which facilitate its constitutive activation.

9. Others

The heterogeneous genetic landscape of DLBCL is reflected by the vast repertoire of genetic aberrations (Figures 1 and 3 and Supplementary Table S1). The implementation and combination of NGS techniques and genome-wide functional studies have revealed multiple mutations and structural alterations of low incidences in DLBCL patients.

MEFB2 is a calcium-regulated gene encoding a transcription factor present in GC B cells that regulates the transcription of several genes, including *BCL6* [142]. Around 15% of DLBCL patients, of both subtypes, present mutations in *MEFB2* [65,142], which enhance the transcriptional activity of *BCL6*, thereby increasing its expression [37,142]. FBXO11 is a ubiquitin-adaptor protein that promotes BCL6 proteasomal degradation. Therefore, loss-of-function mutations and deletions in *FBXO11* also increase the target expression level of BCL6 [66].

Mutations in the NOTCH receptor recur in DLBCLs. Mutations in *NOTCH1* have been reported solely in ABC-DLBCL (~6% of cases), while mutations in *NOTCH2* have a higher incidence in DLBCL-NOS (~21% of cases) [37]. Most mutations of NOTCH1 and NOTCH2 cause a partial or total deletion of the PEST domain, resulting in increased protein stability [143,144]. Loss-of-function mutations in the NOTCH pathway inhibitor, *SPEN*, that lead to NOTCH activation, have also been identified in around 11% of DLBCL cases, particularly in the DLBCL-NOS subtypes (~18% of cases) [37].

Inactivating mutations in components from the GC-specific G protein-coupled receptor pathway have been described solely in GCB-DLBCL, including *S1PR2* and *GNA13*, and at a lower frequencies in the *ARHGEF1* and *P2RY8* genes [144,145].

10. Therapeutic Targeting of Diffuse Large B-Cell Lymphoma

Molecular analysis and clinical trials in DLBCL are progressively revealing multiple therapeutic opportunities that eventually could replace the currently used chemotherapy. These new options are tumor-type specific and, thus, adapted for the GC, ABC, thymic or terminally differentiated phenotypes and, additionally, in many cases, are coupled with precise genetic events or deregulated pathways.

10.1. BCL6 Inhibitors

The *BCL6*-deregulated expression is central to DLBCL and FL molecular pathogenesis and makes the molecule an attractive therapeutic target. Although the direct targeting of BCL6 is difficult, small molecule inhibitors have been generated that bind to BCL6 and block corepressor recruitment [146,147]. These are active in ABC- and GC-DLBCL cases.

10.2. BCL2/MYC Inhibitors

An increased BCL2 expression as a consequence of the *BCL2* gene translocation or the oncogenic activation of multiple cell survival pathways is a frequent finding in DLBCL, especially in the ABC subtype, making this molecule an ideal target for therapy [148].

Venetoclax is a BCL2 inhibitor currently under investigation for the treatment of DLBCL [149], following its approval for use against chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). It targets the BH3 domain, where most BCL2 mutations occur [79]. The use of venetoclax in combination with chemotherapy, including R-CHOP and R-EPOCH, is also being studied for DHL and double-expresser DLBCL [150,151]. Navitoclax is a BCL2 inhibitor resembling BH3 that has a proven activity in CLL and NHL patients. However, the clinical application of this drug is limited due to its dose-dependent thrombocytopenia effect [152].

Gal-3 inhibitors interrupted CD45/Gal-3 interaction and restored apoptotic function in their preclinical models [153].

MYC is under the epigenetic regulation of bromodomain (BRD)-containing proteins that recruit transcription factors to acetylate chromatin, leading to gene transcription [154]. A range of BRD inhibitors have demonstrated some degree of clinical activity in phase I trials [155,156]. However, in spite of these promising findings, much more experimental work and further clinical trials need to be done to explore the possibilities of MYC silencing using bromodomain and extraterminal (BET) inhibitors.

10.3. BTK iInhibition

B-cell receptor signaling has emerged as a key survival factor for normal and neoplastic B-lymphocytes. Thus, the cell viability of large B-cell lymphomas with an ABC phenotype has been shown to depend on NF-κB activation via chronic active BCR signaling [81] through the formation of a complex including $MYD88^{L265P}$ with IRAK kinases that activates NF-κB and JAK-STAT signaling [87]. BTK inhibitors have been developed and tested in diverse experimental and clinical studies, which showed that the tumors with the MCD genetic subtype (*CD79B* and $MYD88^{L265P}$) had a particularly high response rate [18]. Thus, although the ABC phenotype has not been shown to predict the responses to lenalidomide, ibrutinib or bortezomib [12–14,18], a subgroup of these cases defined by the presence of mutations in *CD79B* and $MYD88^{L265P}$ seems to have identified a group of DLBCL cases that may respond to ibrutinib [18], although confirmation of this would require a clinical trial designed specifically for this purpose. This positive result in a subset of the ABC subtype also provides additional useful information about PCNSLs, which are tumors with an ABC phenotype (and frequent *CD79B* and $MYD88^{L265P}$ mutations) that are difficult to treat. Clinical responses to ibrutinib have been noted in 77% of patients with PCNSL, five cases of which were complete responses [157].

10.4. Toll-Like Receptor Inhibition

ABC-DLBCL bear mutations, copy number alterations and amplifications in the TLR components involving *MYD88*, *TLR9*, *CNPY3* and *UNC93B1* [80]. Of these, TLR9 has been selected as a therapeutic target in two clinical trials, although it proved to be of limited efficacy [158,159]. MYD88 is an adaptor protein that mediates Toll and IL-1 receptor signaling [88]. Notably, RNAi experiments have revealed that MYD88 and the associated IRAK1 and IRAK4 are indispensable for ABC-DLBCL survival [87]. Due to the great relevance of MYD88 in DLBCL pathogenesis, several inhibitors of IRK4 have been proposed, and experimental studies have shown the pharmacological inhibition of IRAK4 to be a suitable therapeutic strategy for treating ABC-DLBCL, especially in combination with the BTK inhibitor ibrutinib or the Bcl-2 inhibitor ABT-199 [160,161].

A phase I trial study will analyze a third generation of anti-CD19 chimeric antigen receptor T cells, incorporating a TLR2 domain in patients with relapsed or refractory (R/R) B-cell lymphoma [162].

10.5. PI3K Inhibition

Experimental studies have demonstrated that GC and ABC-type DLBCLs are both sensitive to PI3K/AKT inhibition, although for different reasons [163]. AKT signaling is known to be crucial for PTEN-deficient DLBCLs, whereas the PI3Kα/δ-induced activation of NF-κB is critical for ABC-DLBCLs [163]. Clinical trials have yielded interesting results in DLBCLs treated with PI3K/AKT inhibitors. For example, voxtalisib (also known as XL765 or SAR245409), a pan-PI3K/mTOR inhibitor, in patients with relapsed or refractory DLBCL is only slightly clinically active [164], but copanlisib (a PI3K inhibitor with potent activity against the PI3K-α and -δ isoforms) has a higher response rate in ABC-DLBCL than in GCB-DLBCL patients [165].

10.6. NF-κB Inhibition

Several therapeutic strategies employ the NF-κB pathway as a target, mainly in ABC-DLBCL. Small-molecule inhibitors of the IκB kinase (IKK) complex have demonstrated selective inhibition of the ABC-DLBCL cell lines [166]. On the other hand, bortezomib targets the NF-κB pathway through reversible proteasome inhibition and by blocking the degradation of the NF-κB inhibitory protein IκBα [167]. Bortezomib in patients with R/R DLBCL has a lower efficacy when administered alone than when combined with the EPOCH regimen [168,169].

Lenalidomide is a well-known drug that blocks the BCR–NF-κB pathway by targeting the E3 ubiquitin ligase component cereblon, with antineoplastic consequences [170]. The efficacy of lenalidomide maintenance has yielded positive results in DLBCL patients after salvage or frontline therapy [171]. DLBCL demonstrated a substantial activity in patients with R/R, especially in the non-GBC and ABC-DLBCL subtypes. In newly diagnosed DLBCL patients, the administration of lenalidomide with CHOP seems to have positive effects, particularly in non-GBC patients [172]. Additionally, the combination of lenalidomide with a PI3K inhibitor and mTOR in ABC-DLBCL cells had a synergistic cytotoxic effect [173]. The benefits of lenalidomide in combination with R-CHOP, and alone in ABC cases, merit further investigation. Carfilzomib is a second-generation proteasome inhibitor that has shown promising results in DLBCL cell lines, including those resistant to rituximab [174].

The NF-κB pathway can be indirectly dysregulated by genetic alterations in other pathways, such as alterations of the BCR signaling pathway components [81,91]. Additionally, mutations in the adaptor molecule MYD88, which are present in approximately 30% of ABC cases, might alter the signal transduction from the TLR to the NF-κB complex [87]. In a clinical trial study, tumors with concomitant mutations in *MYD88* and *CD79B* responded well to BTK inhibition treatment, unlike those carrying only *MYD88* mutations [18].

10.7. JAK/STAT Inhibition

The JAK/STAT signaling cascade transduces signals to the nucleus, where they regulate key biological functions such as proliferation and cell survival. Recurrent genetic alterations in this pathway are present in DLBCL, making it an interesting therapeutic target [175].

Ruxolitinib is an oral inhibitor of JAK1 and JAK2 that has been approved for the treatment of primary myelofibrosis [176]. It is currently being investigated in the context of R/R DLBCL, although it seems to be more effective in combination regimens. Pacritinib is an oral small-molecule inhibitor that selectively inhibits JAK2 and has shown efficacy in vitro in DLBCL cell lines [177]. It is of note that the constitutive activation of STAT3 is associated with an aggressive disease phenotype and poor overall survival [178]. AZD9150 is a 16-nucleotide next-generation chemistry antisense oligonucleotide [179] that targets STAT3 mRNA and downregulates its expression. Preclinical and phase 1b trial studies have demonstrated its efficacy and safety in patients with refractory/resistant DLBCL [180,181].

10.8. ICIs

Immune checkpoint inhibitors (ICIs) blockading CTLA4, PD1 and PD-L1 have an indisputable role in the treatment of PMBCL and HL [182,183] and in a subset of DLBCL cases.

PDL1 and PDL2 are both frequently expressed in PMBL (~71% of cases) [184], HL (~97%) [185] and ABC-DLCBCL (~36% PDL1 and ~60% PDL2) and GBC-DLBCL (~4% PDL1 and ~26% PDL2) [186]. The causal mechanisms of PDL1 and/or PDL2 overexpression include amplification of the 9p24 genomic area, where PDL1 and PDL2 are located, and Epstein–Barr virus infection. Although the alteration of 9p24 occurs in most of the PMBL patients [129], it is not restricted to PMBL, since it has also been described in HL [185] in around 54% of PTL and 52% of PCNSL cases [187], as well as in a subset of DLBCL (19%) cases with refractory/relapsed DLBCL [188,189]. Consistent with these observations, the PD-1 blockade with nivolumab is clinically active in primary CNS and testicular lymphoma [190].

The potential therapeutic activity of the anti-PD1 antibody (nivolumab and others) has been evaluated in a small number of DLBCL patients [191] who showed a lower response rate (40%) than seen in HL patients (66%) [192]. Preliminary studies of other antibodies involving PDL1, e.g., atezolizumab, have yielded promising results [193,194]. Studies of therapies involving PD-L1 antibodies in combination with other antibodies against different immune checkpoints, or in combination with chemotherapy, are currently being conducted.

A number of clinical trials are also currently assessing the safety and efficacy of different antibodies that target other immune checkpoints, such as varlilumab, which targets the tumor necrosis factor receptor superfamily member 9 (4-1BB).

11. Conclusions

Integrative genomic studies have revealed a complex and heterogeneous landscape of molecular changes in DLBCL. Combination of this information with clinical and morphological data has made it possible to identify different discrete DLBCL subclasses characterized by specific features, where an additional layer of mutational data is starting to offer personalized therapeutic opportunities. Design of future clinical trials should focus on molecularly defined DLBCL subgroups, where the result of targeted therapies may offer an opportunity for learning on the mechanisms of DLBCL survival and therapy escape.

Supplementary Materials: The following are available online link https://www.mdpi.com/article/10.3390/hemato2020017/s1. Table S1: Molecular aberrations in DLBCL.

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