Cell of origin in diffuse large B-cell lymphoma: the way to targeted therapy?

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SUMMARY

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma type worldwide, but the treatment still remains challenging because only 60-70% of the patients can be cured with the standard immunochemotherapy (rituximab, cyclophosphamide-doxorubicin-vincristine-prednisone) scheme. In the last twenty years, several molecular-genetic studies showed that DLBCL comprises at least two distinct molecular subtypes: the activated B-cell-like and the germinal centre B-cell-like subtype. The two groups have different genetic mutation landscapes and outcomes following treatment, with the ABC subtype having the worst prognosis. Gene expression profiling seems to be the gold standard method to subdivide DLBCL into ABC and GCB subtypes, but it is difficult to include this technology in clinical practice because it relies on fresh frozen tissue and microarray technology. To facilitate the DLBCL classification in daily clinical practice, other technologies have been developed allowing analysis of formalin-fixed paraffine embedded tissue biopsies. The unique genetic and epigenetic features of both DLBCL subtypes make targeted therapy a promising approach in the future.

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INTRODUCTION

Lymphomas are malignant proliferations of different cell types belonging to the lymphoid tissue. The classification is complex because of the variable physiologic immune functions of lymphocytes, which vary by lineage and differentiation stage. Lymphomas can basically be divided in two broad categories: Hodgkin' lymphoma (HL) and non-Hodgkin' lymphoma (NHL). HL is a well-defined entity with unique pathological features, marked by the presence of typical Reeds-Sternberg cells. NHL encompasses a very diverse group of lymphoproliferative disorders, which are currently classified according to the WHO 2016 classification. NHLs can further be divided depending on the type of lymphocyte the malignant cell is derived from, making distinction among B-cell NHL, T-cell NHL and natural killer (NK) cell NHL. In addition, these lymphomas can develop at any stage during maturation of normal lymphocytes. Mature B-cell neoplasms constitute >90% of lymphoid neoplasms worldwide. The most common lymphoma type is diffuse large B-cell lymphoma (DLBCL) with a relative frequency of 37%.[1,2]

DLBCL is a heterogeneous disease that can arise *de novo* or from the histologic transformation of more indolent lymphomas such as follicular lymphoma and chronic lymphocytic leukaemia. DLBCL is an aggressive disorder, curable with immunochemotherapy in about 60-70% of patients.[3-5] In patients with relapsed disease, high dose chemotherapy followed by autologous stem cell transplantation leads to durable responses in about 50% of the patients.[6] However, about 20% of patients will develop refractory disease, associated with a very poor outcome.[7] Despite morphological similarities, different molecular-genetic studies have shown that DLBCL is biologically very heterogeneous with several genetic aberrations involving diverse cellular pathways. These

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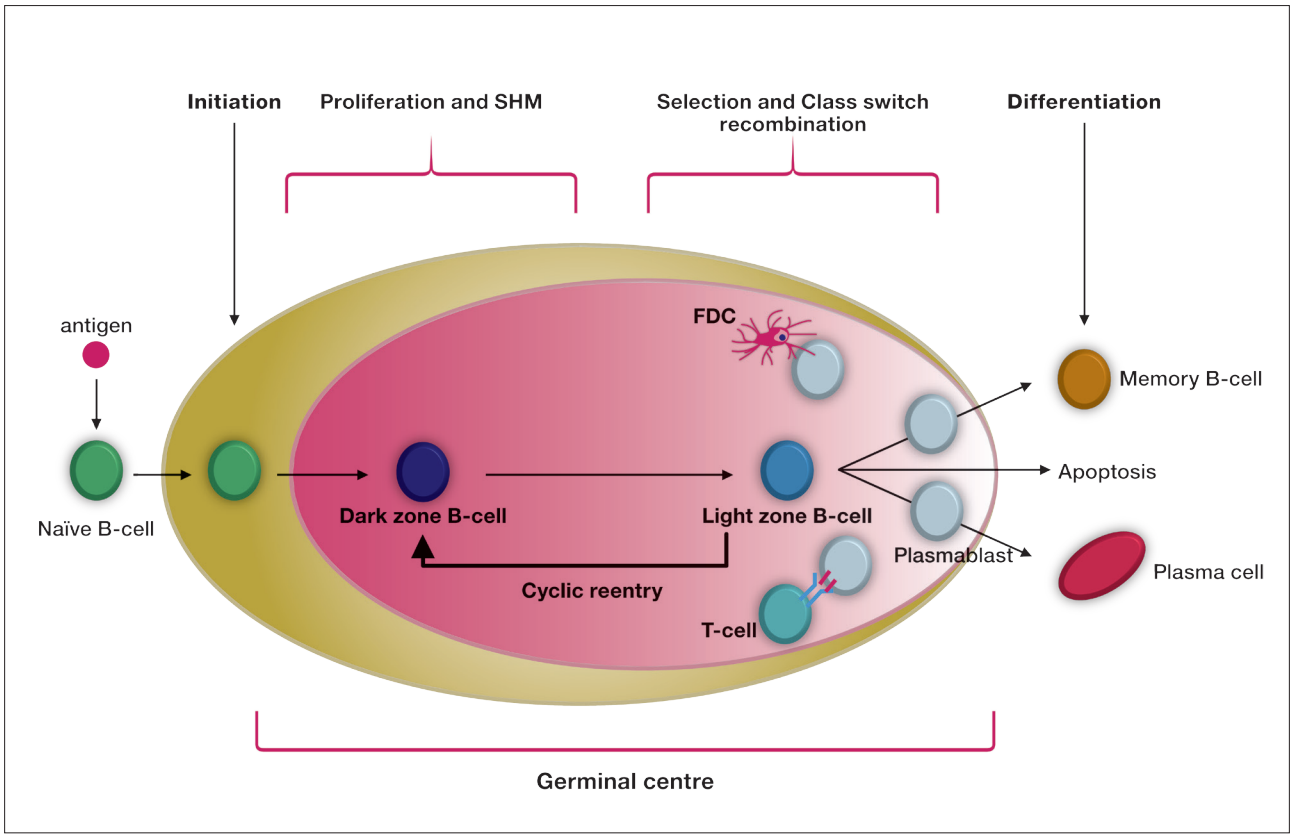

FIGURE 1. Normal B-cell development. *SHM: somatic hypermutation, FDC: follicular dendritic cell.*

new findings have led to improved insights in molecular and genetic pathogenesis of these disorders and to the development of targeted therapies and may be used for detection of early diagnostic and/or prognostic biomarkers. In this review, the most important and relevant transcriptomic and genomic findings in DLBCL during the last years are summarised.

THE NORMAL B-CELL DEVELOPMENT

Lymphocyte development occurs in the specialised environment of the central lymphoid organs, in particular in the bone marrow for B-cells and the thymus for T-cells. Normal B-cell differentiation starts with B-lymphoblasts, undergoing recombination-activating gene (RAG)-mediated V(D)J rearrangement, which produces clonally unique immunoglobulin variable regions, able to bind specific antigen. Mature B-cells will then leave the bone marrow as 'naïve' or 'virgin' B-cells (this means they have not been exposed to antigens yet) and circulate through the bloodstream. Finally, they will be delivered to the secondary or peripheral lymphoid organs (including the spleen, lymph nodes and mucosa-associated lymphoid tissues).

Lymph nodes (LN) are essential structures for the initiation of immune responses by creating an environment in which B lymphocytes, T lymphocytes and antigen-presenting cells (APCs) can interact in a surprisingly efficient and organised way. Distinction can be made between mobile APCs that bring antigens from the periphery to the LN and stationary APCs that reside in the LN, called follicular dendritic cells (FDC). The T-cells in the LN are activated by the antigen-bearing APCs and will proliferate and differentiate into helper cells that interact with adjacent B-cells. A minority of B-cells differentiate into antibody-secreting short-lived plasma cells. The majority of B-cells migrate to the primary follicles and initiate a germinal centre (GC) reaction. The GC is a histological zone that exists of a dark zone and a light zone. Within the GC dark zone, further diversification of immunoglobulin genes will occur through activation-induced cytidine deaminase (AID)-initiated somatic hypermutation (SHM) and class switch recombination (CSR). B-cells expressing high-affinity antibodies will further develop in the light zone of the GC, finally differentiating in antibody-secreting plasma cells and memory B-cells (*Figure 1*).[8,9] Multiple transcription factors and modulators are involved in the regulation of the GC initiation, expansion and exit. Paired Box 5 (PAX 5) is expressed throughout the life of mature B-cells but lost when committed to plasma cell differentiation. In the dark zone, MYC is repressed by B-cell

lymphoma 6 (BCL6). MYC expression is reactivated in the light zone in a small subset of B-cells that are primed for re-entry in the dark zone where they undergo further cycles of proliferation. The role of MYC has been shown to be important in maintaining the GC structure. Nuclear factor-κB (NF-κB) and interferon-regulatory factor 4 (IRF4) are expressed during GC initiation, are absent in the dark zone B-cells and appear again in the light zone B-cells. In the GC initiation, NF-κB leads to activation of IRF4 that contributes to BCL6 induction. In the light zone B-cells, activation of IRF4 by NF-κB downregulates BCL6 and promotes post-GC differentiation. This event releases also the repression on BCL6 targets, including PRDM1 (positive regulatory domain-containing 1), which encodes the plasma cell master regulator BLIMP1 (B lymphocyte-induced maturation protein 1). Downregulation of BCL6 in combination with strong expression of BLIMP1 and IRF4 (interferon-regulatory factor 4= MUM1) will finally lead to terminal differentiation of GC B-cells into antibody-secreting plasma cells.[10-12]

BCL6 appears to be the master regulator of the GC reaction. This nuclear phosphoprotein represses more than 1200 genes mainly involved in growth, apoptosis and differentiation by affecting multiple signalling pathways. One of these is the direct regulation of tumour protein 53 (tp53), which is associated with the apoptotic response that would normally occur in other cell types associated with very high proliferation rates and DNA breaks. In addition, BCL6 causes transcriptional repression of ataxia telangiectasia and RAD3-related protein (ATR), an important sensor of DNA damage.[10]

In conclusion, the GC provides a strictly regulated but dynamic environment, essential for adaptive immunity. However, the drawback of these complex interactions in the GC is the increased risk for B-cell lymphoma development, due to the rapidly proliferating cells, decreased DNA damage responses and AID-induced double strand breaks, all facilitating (driver) mutations and chromosomal translocations.

THE CELL OF ORIGIN

Each lymphoma subtype possesses a phenotypic similarity to B-cells at a particular site of (frozen) differentiation, often referred to as the 'normal B-cell counterpart' or the 'cell of origin' (COO). In this classification, tumour profiles are compared with normal B-cell profiles. Although this classification is not always correct, it is used by many researchers and clinicians in an attempt to better understand pathogenesis of B-cell lymphomas.[13,14] In DLBCL, COO classification based on gene expression profiling has paved the way for different transcriptomic and genomic studies leading to a substantial improvement of the understanding of the pathobiology of DLBCL.

CELL OF ORIGIN CLASSIFICATION IN DIFFUSE LARGE B-CELL LYMPHOMA

In 2000, Alizadeh *et al.* used gene expression profiling (GEP) on DLBCL samples, identifying several signature patterns resembling normal B-cell signalling. Within DLBCL, at least two distinct groups could be identified. The first group showed high expression of genes expressed in normal GC B-cells and hence was designated as GCB (germinal centre B-cell-like)-DLBCL. On the other hand, the other group was characterised by low expression of GC B-cell genes but high expression of genes expressed by normally activated B-cells and was named ABC (activated B-cell-like)-DLBCL. The DLBCL gene expression subgroups define prognostic categories witch GCB-DLBCL having a significant better prognosis compared with the ABC subtype.[15] The same approach was used by Rosenwald *et al.* in the Leukemia Lymphoma Molecular Profiling Project (LLMPP) in a larger cohort of patients, identifying the previously described gene-expression subgroups in DLBCL but also a third group termed type 3 DLBCL, which did not express either set of genes at a high level. This heterogeneity of expression indicates that it may consist of more than one type of DLBCL. Interestingly, in this study, type 3 DLBCL patients had a similar outcome compared with the ABC subtype when treated with CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) chemotherapy. In hindsight, there were probably cases in this group that had low tumour content and cases that were later identified as primary mediastinal B-cell lymphoma.[16] In later studies, they were labelled as 'unclassified'.[17] The prognostic difference between ABC- and GCB-DLBCL was further confirmed in a new GEP study for patients treated with rituximab (R)-CHOP, the current standard of care for patients presenting with DLBCL.[18]

It is clear that gene expression can separate tumours in the two COO groups, and evidence has emerged that these are distinct biological groups. Targeted genomic examination and genome-wide studies have revealed an array of aberrations that can be exclusive to either ABC- or GCB-DLBCL.[19]

Although GEP-defined COO classification has been confirmed as a powerful predictive biomarker, it is difficult to include this technology in clinical practice because it relies on fresh frozen tissue (FFT) and microarray technology. Because of the importance of COO classification, a lot of efforts have been made to approximate the results of GEP, in particular immunohistochemistry (IHC) based assays and RNA based gene expression quantitation tests, both on formalin fixed paraffin embedded tissue (FFPET).

Different investigators have tried to translate the findings made by GEP to an IHC expression pattern. It soon became

TABLE 1. Most frequent genetic aberrations in the different cell-of-origin subtypes and their frequency.[5]

GCB-DLBCL	ABC-DLBCL	GCB-DLBCL and ABC-DLBCL
BCL2 translocations/mutations (34%)	*MYD88* mutations (30%)	*CREBBP/EP300* mutations (30%)
MYC translocations (10%)	*CARD11* mutations (9%)	*MLL2* mutations (35%)
EZH2 mutations (22%)	*PRDM1* mutations/deletions (25%)	*B2M* mutations/deletions (25%)
PTEN deletions (6-11%)	*TNFAIP3* mutations/deletions (30%)	*BCL6* translocations (25%)
GNA13 mutations (21%)	*CD79A/CD79B* (20%)	*TP53* mutations (20%)

BCL2: B-cell lymphoma 2, MYC: myelocytomatosis oncogene cellular homologue, EZH2: enhancer of zeste homologue 2, PTEN: phosphatase and tensin homologue, MYD88: myeloid differentiation primary response 88, CARD11: caspase recruitment domain-containing protein 11, PRDM1: positive regulatory domain-containing 1 (with zinc finger protein) TNFAIP3: tumour necrosis factor alpha-induced protein 3, CREBBP: cAMP-response element-binding binding protein, EP300: E1A-associated protein p300, MLL2: mixed lineage leukaemia 2, B2M: beta-2-microglobulin, BCL6: B-cell lymphoma 6, TP53: tumour protein 53.

clear that no single IHC staining could reliably subdivide DLBCL samples into ABC or GCB subtypes, when compared with the gold (GEP) standard method. However, it was believed that combining different IHC staining in an algorithm would solve the problem. Hans *et al*. developed an IHC based algorithm applicable to FFPET by producing a tissue microarray (TMA) – the Hans algorithm. Based on antibodies against three different proteins highly differentially expressed between ABC and GCB (BCL6, CD10 and MUM1), separation of GCB and non-GCB (combination of ABC and 'type 3' cases) subtypes was possible, with a concordance rate of 79% compared with GEP findings.[20] In the following years, many other IHC based algorithms have been proposed by different groups.[21] However, several studies comparing the algorithms with each other and with GEP findings showed often very poor reproducibility and accuracy, leading to the conclusion that currently IHC based COO assays cannot be used to guide management of DLBCL outside clinical trials.[19,21,22]

Over the last decade, different technologies have been developed allowing GEP with highly degraded DNA extracted from FFPET. Although different technology platforms have been used, one of the most promising is the NanoString platform. This is a 20-gene (15 discriminating and 5 housekeeping genes) RNA-based assay (called Lymph2Cx), applicable to FFPET, that is routinely obtained for diagnosis and with a rapid turnover time (<36 hours). In 2015, a study from Scott *et al*. including 344 patients with *de novo* DLBCL treated with R-CHOP showed a high concordance between the Lymph2Cx assay and the so-called gold standard of COO assignment using GEP on fresh frozen tissue. The Lymph2Cx assay confirmed the prognostic impact of COO subgrouping without any frank misclassification (ABC-DLBCL to GCB-DLBCL or *vice versa*) and independent of IPI score and MYC/BCL2 dual expression.[19] In 2017, Yoon *et al*. published a study in which the Lymph2Cx assay was applied to 82 pre-treatment FFPE samples from patients with DLBCL who were treated with R-CHOP and was compared with the Hans algorithm. The authors showed that there was a discordancy rate of 26.4% between the Hans algorithm and the Lymph2Cx assay and hence confirmed the poor accuracy and reproducibility of the IHC based assays. Similar to all other previous reports, this study could confirm the better prognosis of the GCB-DLBCL compared with the ABC-DLBCL. However, the 'unclassified' group had the worst outcome, which was inconsistent with previous Lymph2Cx results where the 'unclassified' patient group had an intermediate prognosis.[23]

In conclusion, DLBCL risk stratification according to COO has prognostic value in patients treated with the current R-CHOP based regimen showing that GCB-DLBCL has a more favourable course than ABC-DLBCL.[5]

GENETIC AND EPIGENETIC LANDSCAPE OF DIFFUSE LARGE B-CELL LYMPHOMA

The molecular mechanisms underlying lymphomagenesis

in *de novo* DLBCL are well characterised. Although DLBCL shares some common abnormalities across COO types, the mutation type and/or frequency of some genes are different in each subtype (see *Table 1*).

ABERRATIONS OBSERVED BOTH IN GCB-DLBCL AND ABC-DLBCL

A consistent theme in DLBCL genomic analyses has been the discovery of recurrent mutations in genes that encode for histone/chromatin modifiers, which is found in 85% of all DLBCL cases. In 30% of the DLBCL cases, somatic mutations of the methyltransferase KMT2D are found. The *KMT2D* gene (also known as MLL2 or mixed lineage leukaemia 2) encodes a member of the SET1 family of histone methyltransferases and plays a role in apoptosis, CD40 and B-cell receptor (BCR) signalling and the control of cell migration. It is the most frequent genetic aberration found in DLBCL.[24]

Inactivation of the acetyltransferase genes *CREBBP* and *EP300* is also frequently seen, with a significant prevalence in the GCB-DLBCL subgroup. Of importance is the ability of CREBBP to oppose the proto-oncogenic activity of BCL6. Apart from that, CREBBP-mediated acetylation is also required for the activation of the p53 tumour suppressor, which is itself a target of BCL6. Knowing this, drugs targeting acetylation/de-acetylation mechanisms could be effective in patients with *CREBBP/EP300* mutant DLBCL, but the efficacy of these drugs has to be further evaluated.[5,25]

Given the critical role of BCL6 during the GC reaction, it's not surprisingly that BCL6 deregulation is an important finding in B-cell transformation. Indeed, translocation and somatic hypermutation of the *BCL6* gene are two major types of molecular alterations in DLBCL. *BCL6* translocations at the major breakpoint region (both with IgH and non-IgH fusion partners) are more common in ABC-DLBCL compared with GCB-DLBCL (24% *vs* 10%), whereas *BCL6* somatic hypermutations (mostly single-base substitutions) are more frequent in the latter group (44% *vs* >70%).[26] In contrast to alterations that directly involve the *BCL6* locus, there are also several other genetic lesions that deregulate the expression of BCL6 by indirect mechanisms such as the deleterious mutations of *CREBBP/EP300* as already mentioned before, somatic mutations in the MEF2B transcription factor, which eventually enhance BCL6 expression and finally loss-of-function mutations and/or deletions of FBXO11, a protein that normally targets BCL6 for proteasomal degradation.[25] BCL6 is an attractive therapeutic target in DLBCL. Promising results have been obtained *in vitro* and in pre-clinical models.[5,27]

An important issue in cancer development and evolution is the concept of immune evasion, mediated by different immunological key players. Both human leucocyte antigen (HLA) class I and II are essential for efficient T-cell activation. Antigens presented by HLA class I antigens can be targets of CD8+ T-cell attack, whereas antigens presented by HLA class II antigens can be recognised by CD4+ T-cells. A common event in DLBCL leading to immune escape is inactivating mutations and deletions of the beta-2-microglobulin (*B2M*) gene, which causes complete loss of HLA class I antigen expression on the surface of affected cells, preventing their recognition by CD8+ T-cells.[25,28] In addition, loss of HLA class II antigen has been observed as well due to mutations, genomic deletions and translocations affecting the HLA class II-regulatory gene *CIITA*.[29] Programmed death-ligand 1(PD-L1) and PD-L2 are important co-stimulatory signalling molecules expressed on the surface of APCs. Following binding with their ligand PD-1 on effector T-cells, a negative regulatory signal is transmitted leading to inhibition of T-cell proliferation. Amplifications and translocations of genes coding for PD-L1 and PD-L2 have been described as genetic mechanisms of PD-L1/2 overexpression in both subtypes of DLBCL, although they are mainly associated with the ABC subtype.[25,30] These findings suggest that these patient groups might benefit from therapy with immune checkpoint inhibitors.

ABERRATIONS ONLY OBSERVED IN GCB-DLBCL

Translocations of *BCL2* (B-cell lymphoma 2) and/or c-*MYC* (myelocytomatosis oncogene cellular homologue) genes are commonly observed in GCB-DLBCL (up to 25-30%), leading to constitutive activation of the proliferating c-MYC and/or anti-apoptotic BCL2 protein respectively.[16,31] Inhibitors of the BCL2 protein (e.g., venetoclax, BH3 mimetic) are currently under investigation in combination with standard immunochemotherapy regimens.[32] MYC inhibition would also be a powerful approach for the treatment of many cancer types, but direct targeting of MYC is a challenge because of the 'undruggable' protein structure. Alternative approaches to indirectly abrogate MYC oncogenic functions have been extensively investigated. One of these is inhibition of the mammalian bromodomain and extra-terminal (BET) family that normally regulates *MYC* transcription. Better therapeutics to target *MYC*-dependent cancers will be required in the future.[33] Five to ten percent of DLBCL is defined as double hit lymphomas (in most cases GCB subtype) with both c-*MYC* and *BCL2* translocations. In contrast to other GCB-DLBCL, they are associated with advanced disease and very poor prognosis.[34]

Loss of the *PTEN* (phosphatase and tensin homologue) gene is another genetic aberration observed in GCB-DLBCL but not in ABC-DLBCL, leading to activation of the PI3K/AKT/

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma type. Sixty percent of the patients can be cured with standard immunochemotherapy (rituximab, cyclophosphamide-doxorubicin-vincristine-prednisone).**

2 **DLBCL is biologically a very heterogeneous disease. Gene expression profile studies have clearly distinguished at least two different subtypes of DLBCL based on the cell of origin: the germinal centre B cell (GCB) and the activated B cell (ABC) subtype with GCB-DLBCL having a significant better prognosis than ABC-DLBCL.**

3 **Both groups have different (epi)genetic features that makes targeted therapy a promising approach, especially in the poor prognosis for the ABC subtype where the response to immunochemotherapy is significantly worse than in the GCB subtype.**

mTORC1 pathway and hence promoting survival, proliferation and cell growth.[18,35]

The GCB-DLBCL also frequently carries additional mutations affecting epigenetic modifications. Morin *et al.* performed a next generation sequencing study in two GCB-derived lymphoma subtypes (follicular B-cell NHL and GCB-DLBCL), identifying a high incidence of gain-of-function mutations of the histone methyltransferase gene *EZH2* (enhancer of zeste homologue 2), a gene responsible for addition of methyl groups to H3K27. Histones associated with trimethylated H3K27 will cause repression of transcription. EZH2 mutations were observed in 21.7% of GCB-DLBCL but not in ABC-DLBCL.[36] Small-molecule inhibitors of EZH2 have shown specific activity in pre-clinical models of GCB-DLBCL, independently of the presence of somatic mutations.[5]

Mutations in *SIPR2* (sphingosine-1-phosphate receptor 2), *GNA13* (G protein subunit alpha 13) and, more rarely, *ARHGEF1* (Rho guanine nucleotide exchange factor 1) and *P2RY8* (P2Y receptor family member 8) genes can affect B-cell migration. In mouse, deletions of these genes are associated with disruption of the GC architecture and dissemination of GC B-cells to the peripheral blood and bone marrow. Eventually, this can lead to the formation of lymphoma with features of GCB-DLBCL.[37]

Mutations of *TNFRSF14* (tumour necrosis factor receptor superfamily member 14), which encodes for a member of the TNF-receptor superfamily that is expressed in both T- and B-cells and has a tumour suppressor role, are also found in 9-22% of the GCB-DLBCL cases.[5]

ABERRATIONS ONLY OBSERVED IN ABC-DLBCL

As already mentioned above, expression of BLIMP1 is essential for terminal differentiation of GC B-cells to plasma cells and repression of the GC master genes *PAX5* and *BCL6*. About 25% of ABC-DLBCL cases is associated with inactivating mutations in *PRDM1*, the gene coding for BLIMP1.[38]

A major characteristic hallmark of ABC-DLBCL biology is the constitutive activation of oncogenic NF-κB. This constitutive activation can result from activating mutations in the different components of the NF-κB pathway or from inactivating mutations in negative regulators. Activating mutations include mutations in the *MYD88* (myeloid differentiation primary response 88) and *CARD11* (caspase recruitment domain-containing protein 11) gene. A20 (tumour necrosis factor alpha-induced protein 3[TNFAIP3]) is the most common mutated negative regulator in ABC-DLBCL. In addition, constitutive BCR activation, often due to mutations in *CD79A* and *CD79B*, is another upstream activator of NF-κB signalling, associated with ABC-DLBCL.[39]

Recent clinical studies reported promising results with the use of BTK (Bruton's tyrosine kinase) inhibitors. BTK is a molecule linking BCR signalling to NF-κB. In the study of Wilson *et al.*, ABC-DLBCL subgroups with *BCR* mutations frequently responded to ibrutinib, especially those with concomitant *MYD88* mutations. However, the highest response occurred in the ABC-DLBCL subgroups that lacked *BCR* mutations. This suggests that oncogenic BCR signalling in this group does not require *BCR* mutations and might be initiated by non-genetic mechanisms.[40]

CONCLUSION

DLBCL is the most common malignant lymphoma subtype in adults but still remains a clinical challenge because 30-40% of the patients are not be cured. Despite morphological similarities, several molecular-genetic studies have shown that DLBCL is biologically very heterogeneous with

several genetic aberrations involving diverse cellular pathways. GEP studies at the beginning of this century clearly distinguished at least two different subtypes of DLBCL based on the COO: the GCB and ABC subtype. Multiple studies confirmed inferior survival in patients in the ABC-DLBCL subgroup compared with the GCB-DLBCL subgroup when treated with R-CHOP. Application of the DLBCL classification to the daily clinical practice has been facilitated by the development of novel technologies allowing analysis of FFPET biopsies, such as the GEP based NanoString platform. The distinction in GCB- and ABC-DLBCL has even been officially incorporated into the revised WHO classification of haematological malignancies. Novel technologies have shown that both subtypes possess shared but also unique genetic and epigenetic features, making targeted therapy a promising approach, especially in the poor prognosis for the ABC subtype. Other classification approaches beyond COO may further refine our knowledge on DLBCL pathogenesis, as illustrated by a recent study from Schmitz *et al*., in which the authors described four genetic subtypes (MCD, BN2, N1 and EZB) consisting of recurrent genetic aberrations. Taken together, these new insights may lead to the development of precision therapies.[41]

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