The molecular biology of diffuse large B-cell lymphoma

Mareike Frick, Bernd Dörken and Georg Lenz

Ther Adv Hematol

(2011) 2(6) 369–379

DOI: 10.1177/

2040620711419001

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Abstract: Diffuse large B-cell lymphoma (DLBCL) represents the most common type of malignant lymphoma. In the last few years, significant progress has been achieved in the understanding of the molecular pathogenesis of this entity. Gene expression profiling has identified three molecular DLBCL subtypes, termed germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL). In this review, we summarize our current understanding of the biology of these DLBCL subtypes with a special emphasis on novel diagnostic and therapeutic approaches.

Keywords: biology, DLBCL, gene expression profiling, malignant lymphoma, molecular pathogenesis

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of malignant lymphoma, is characterized by heterogeneity with respect to clinical presentation, morphology, and molecular pathogenesis [Coiffier, 2001]. The introduction of gene expression profiling revealed the existence of at least three distinct molecular subtypes of DLBCL that differ in the expression of thousands of genes and that seem to arise from B cells at different stages of differentiation [Rosenwald *et al.* 2003, 2002; Savage *et al.* 2003; Wright *et al.* 2003; Alizadeh *et al.* 2000]. According to their gene expression profiles these subtypes were termed germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, and primary mediastinal B-cell lymphoma (PMBL). These subtypes do not only differ with respect to their gene expression profiles, but they depend on different oncogenic pathways and are characterized by significant differences in overall survival following standard treatment [Lenz *et al.* 2008b, 2008c; Monti *et al.* 2005; Rosenwald *et al.* 2002]. Whereas patients with GCB DLBCL respond favorably to a combined approach of the anti-CD20 antibody rituximab and chemotherapy, more than 50% of ABC DLBCL patients will succumb to their disease [Lenz *et al.* 2008b]. This implies that novel therapeutic strategies are critically warranted to improve prognosis of affected patients. However, this can only be achieved by a better

understanding of the underlying molecular mechanisms that drive lymphomagenesis.

Molecular pathogenesis of GCB DLBCL

GCB DLBCLs seem to originate from germinal-center B-cells (Figure 1) [Rosenwald *et al.* 2002; Alizadeh *et al.* 2000]. Accordingly, these lymphomas characteristically express many genes such as *BCL6* or *LMO2* that are expressed by normal germinal-center B-cells [Alizadeh *et al.* 2000]. Further evidence for their germinal-center derivation is provided by the fact that GCB DLBCLs frequently show ongoing somatic hypermutation of their variable immunoglobulin heavy chain gene that is mediated by AID, an enzyme that is characteristically expressed at high levels in germinal-center B-cells [Lossos *et al.* 2000].

Various oncogenic pathways are deregulated in GCB DLBCL that contribute to the molecular pathogenesis of this entity (Figure 1). In approximately 45% of GCB DLBCL patient samples, a t(14;18) translocation juxtaposing the *BCL2* gene and the *IgH* locus is detectable. This leads to constitutive activation of the anti-apoptotic BCL2 protein. Intriguingly, this abnormality is not detectable in ABC DLBCL patient samples [Rosenwald *et al.* 2002].

Another hallmark of GCB DLBCL biology is the deregulation of the phosphatase and tensin homologue (PTEN)– phosphatidylinositol 3-kinase

Correspondence to:

Georg Lenz, MD

Department of Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin Berlin, Molecular Cancer Research Center, Augustenburger Platz 1, 13353 Berlin, Germany
georg.lenz@charite.de

Mareike Frick

Bernd Dörken
Department of Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin Berlin, Germany

Figure 1. Germinal-center B-cell-like (GCB) diffuse large B-cell lymphoma (DLBCL) derived from normal germinal-center centroblasts. BCL2 is deregulated by t(14;18) translocations. *PTEN* deletions and amplification of miR-17-92 lead to deregulation of the PI3K/mTOR pathway. *ING1* deletions, *p53* mutations, and *MDM2* gain/amplification are associated with genomic instability. Addition to these signaling pathways conveys vulnerability to specific inhibitors.

(PI3K) signaling pathway (Figure 1) [Lenz *et al.* 2008c]. The PI3K signaling cascade is initiated with the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP₂) to phosphatidylinositol 3,4,5-trisphosphate (PIP₃), resulting in cellular processes such as proliferation, cell survival, and cell growth [Chalhoub and Baker, 2009; Salmena *et al.* 2008]. The conversion of PIP₂ into PIP₃ is tightly regulated by the opposing activities of the lipid phosphatase PTEN and class I PI3K family members. Whereas the PI3Ks catalyze the conversion from PIP₂ to PIP₃, PTEN hydrolyzes the 3-phosphate to generate PIP₂ [Salmena *et al.* 2008]. Upon PTEN loss, PIP₃ accumulates and AKT and mTOR are activated, further promoting cell survival, proliferation, and growth [Salmena *et al.* 2008]. Roughly 15% of GCB DLBCLs harbor heterozygous or homozygous deletions of *PTEN*. As an alternative mechanism of deregulating PTEN, 15% of GCB DLBCLs have amplifications of the miR-17-92 locus resulting in PTEN suppression [Lenz *et al.* 2008c; Xiao *et al.* 2008]. These findings implicate an important role of the PTEN–PI3K pathway in the biology of GCB DLBCL. Strikingly, these abnormalities are not detectable in either ABC DLBCL or PMBL samples.

GCB DLBCLs are furthermore characterized by gain or amplification of *MDM2*, a negative

regulator of the tumor suppressor p53, as well as deletions of the known tumor suppressor genes *TP73* and *ING1* (Figure 1) [Lenz *et al.* 2008c]. Finally, in both GCB DLBCL and PMBL, a locus on the chromosomal arm 2p is recurrently amplified [Lenz *et al.* 2008c; Bea *et al.* 2005]. *Rel*, coding for a subunit of the nuclear factor kappa B (NF-κB) transcription factor, is among the most upregulated genes within this abnormality. Whereas the NF-κB signaling pathway is constitutively activated in virtually all ABC DLBCL cases, GCB DLBCLs do not seem to depend on this pathway. Thus, the functional role of this abnormality in the pathogenesis of GCB DLBCL needs to be elucidated.

Molecular pathogenesis of ABC DLBCL

The gene expression profiles of ABC DLBCL patient samples suggest that this subtype is derived from B cells that are in the process of differentiating into plasma cells (Figure 2) [Rosenwald *et al.* 2002]. In contrast to GCB DLBCL, most genes characteristically expressed by normal germinal-center B-cells are downregulated in ABC DLBCL. However, these samples exhibit an upregulation of many genes normally expressed in plasma cells [Wright *et al.* 2003]. Specifically, ABC DLBCLs express XBP-1, a key regulator of the secretory phenotype of plasma cells [Shaffer *et al.* 2004; Wright *et al.*

Figure 2. Activated B-cell-like (ABC) diffuse large B-cell lymphomas (DLBCLs) are derived from plasmablasts that are characterized by a block in differentiation. ABC DLBCLs show constitutive activation of the oncogenic nuclear factor kappa B (NF-κB) signaling pathway as well as deregulation of the anti-apoptotic *BCL2* protein. The molecular mechanisms by which NF-κB is activated will determine responsiveness to specific inhibitors.

2003]. However, full plasmacytic differentiation is blocked by different genetic abnormalities (Figure 2). Approximately 25% of ABC DLBCL patient samples harbor inactivating mutations of *PRDM1* which encodes BLIMP1 [Pasqualucci *et al.* 2006; Tam *et al.* 2006]. BLIMP1 promotes plasmacytic differentiation by terminating the expression of most mature B-cell differentiation genes [Shaffer *et al.* 2002]. Recently, overexpression of microRNAs such as let-7 has been postulated as an alternative mechanism of BLIMP1 deregulation [Nie *et al.* 2010]. Plasmacytic differentiation is blocked in ABC DLBCL additionally by translocations affecting the *PRDM1* repressor *BCL6* that are detectable in roughly 25% of patients [Iqbal *et al.* 2007; Tunayaplin *et al.* 2004; Shaffer *et al.* 2000]. Finally, 26% of cases show gain/amplification and consecutive overexpression of the ETS family transcription factor *SPIB* that also represses Blimp-1 expression [Lenz *et al.* 2008c; Schmidlin *et al.* 2008]. In summary, the

inactivation of *PRDM1* by different genetic aberrations provides direct evidence that a block in differentiation is a hallmark of ABC DLBCL biology.

ABC DLBCL is characterized by additional genetic abnormalities that play an important role in its pathogenesis (Figure 2). The *INKA/ARF* tumor suppressor locus is deleted in approximately 30% of ABC DLBCLs [Lenz *et al.* 2008c; Tagawa *et al.* 2005]. Another characteristic abnormality is gain or amplification of 18q that is associated with overexpression of the anti-apoptotic *BCL2* protein [Lenz *et al.* 2008c; Bea *et al.* 2005]. In addition, trisomy 3 is frequently detected in ABC DLBCL, but not in other subtypes [Lenz *et al.* 2008c; Bea *et al.* 2005]. *FOXP1* emerged as a potential target gene of trisomy 3. Previously, *FOXP1* has been implicated as an oncogene based on translocations in MALT lymphoma and DLBCL [Lenz *et al.* 2008c; Haralambieva *et al.* 2006;

Streubel *et al.* 2005]. However, its role in the molecular pathogenesis needs to be validated experimentally.

Another pathogenetic feature of ABC DLBCLs is the constitutive activation of the NF- κ B signaling pathway that promotes cell survival and proliferation and inhibits apoptosis (Figure 2) [Davis *et al.* 2001]. NF- κ B is a family of inducible transcription factors consisting of five members, RelA (p65), RelB, c-Rel, NF- κ B1 (p50 and its precursor p105), and NF- κ B2 (p52 and its precursor p100) [Jost and Ruland, 2007]. These proteins form different homodimers and heterodimers that are kept inactive by binding to inhibitory proteins of the I κ B family. Activation of NF- κ B through various stimuli leads to phosphorylation and proteosomal degradation of the I κ B proteins by the multiprotein I κ B kinase (IKK) resulting in nuclear translocation of the NF- κ B subunits and transactivation of their target genes [Jost and Ruland, 2007]. ABC DLBCLs are characterized by constitutive activation of the NF- κ B pathway. Inhibition of this pathway using either a dominant active form of I κ B α or a specific IKK inhibitor is toxic to ABC but not to GCB DLBCL cell lines indicating the importance of NF- κ B signaling in ABC DLBCL biology [Lam *et al.* 2005; Davis *et al.* 2001].

Insights which upstream molecular mechanisms lead to the constitutive activity of NF- κ B in ABC DLBCL were obtained by a small hairpin RNA (shRNA) screen that revealed toxicity of shRNAs directed against CARD11, BCL10, and MALT1 in ABC DLBCL cell lines [Ngo *et al.* 2006]. In normal B and T cells these three proteins form a transient signaling complex (the CBM complex) following stimulation that activates IKK [Rawlings *et al.* 2006]. In contrast, in ABC DLBCL the CBM complex is constitutively activated due to different mechanisms. Resequencing revealed that approximately 10% of ABC DLBCL patients harbor activating *CARD11* mutations leading to NF- κ B pathway activation [Lenz *et al.* 2008a]. ABC DLBCLs with wildtype *CARD11* depend on chronic active B-cell receptor (BCR) signaling. Roughly 20% of ABC DLBCLs have mutations in the signaling molecules *CD79B* and less frequently in *CD79A*. These mutations predominantly affect the ITAM signaling motifs, resulting in reduced activation of LYN, a negative regulator of BCR signaling and increased BCR cell surface expression. These findings implicate chronic

BCR signaling in the biology of ABC DLBCLs with wildtype *CARD11* [Davis *et al.* 2010].

Additional mechanisms for the constitutive activation of NF- κ B have been reported. Approximately one third of ABC DLBCL patients carry biallelic inactivation of the negative NF- κ B regulator A20 [Compagno *et al.* 2009; Kato *et al.* 2009]. Reintroduction of A20 into A20-deficient cell lines resulted in inhibition of NF- κ B signaling and induced apoptosis and cell growth arrest [Compagno *et al.* 2009]. Alternatively, a recent study showed that activating mutations affecting the adaptor protein *MYD88* that mediates toll and interleukin-1 receptor signaling results in constitutive NF- κ B signaling [Ngo *et al.* 2011].

Molecular pathogenesis of PMBL

PMBL has been identified as a distinct entity based on clinical and morphological features. PMBL normally affects young women with a median age of 30–35 years with the mediastinum being the predominant site of lymphoma manifestation. Morphologically PMBL tumors are frequently sclerotic and are characterized by diffuse proliferation of medium-sized to large B-cells with a heterogeneous morphology [van Besien *et al.* 2001]. However, PMBL cannot be reliably diagnosed solely by morphologic and clinical parameters. A recent gene expression profiling study showed that approximately one quarter of cases diagnosed as PMBL by conventional criteria did not exhibit the characteristic gene expression signature of PMBL and thus represented other molecular DLBCL subtypes with mediastinal involvement [Rosenwald *et al.* 2003]. Interestingly, PMBLs share many clinical and molecular features with nodular sclerosis classical Hodgkin lymphoma (cHL) [Rosenwald *et al.* 2003; Savage *et al.* 2003]. Similar to PMBL, nodular sclerosis cHL often affects young women with a mediastinal mass that is sclerotic in the histological examination. With respect to gene expression profiling, more than one third of the genes overexpressed in PMBL are also highly expressed in cHL cell lines [Rosenwald *et al.* 2003]. Furthermore, PMBL and nodular sclerosis cHL utilize the same oncogenic pathways such as NF- κ B [Rosenwald *et al.* 2003; Savage *et al.* 2003]. However, despite these similarities PMBL and nodular sclerosis cHL can reliably be distinguished by histology and gene expression profiling.

PMBLs are characterized by gain or amplification of the chromosomal band 9p24 [Lenz *et al.* 2008c]. Roughly 50% of PMBL cases harbor this abnormality. One target gene of this amplicon is JAK2, a tyrosine kinase which regulates cytokine signaling through STAT transcription factors. Interestingly, *SOCS1*, a suppressor of JAK signaling is recurrently deleted in PMBL [Weniger *et al.* 2006; Mestre *et al.* 2005]. *SOCS1* inhibits JAK2 activity by competing with STAT proteins for the JAK2 binding site [Ritz *et al.* 2008]. Thus, deletion of *SOCS1* contributes to the constitutive activation of the JAK2 pathway implying that JAK2 plays an important role in the molecular pathogenesis of PMBL [Melzner *et al.* 2006, 2005].

A recent shRNA library screen revealed that additional genes within the 9p24 amplicon might be involved in the biology of PMBL [Rui *et al.* 2010]. The histone demethylase JMJD2C seems to cooperate with JAK2 to modify the PMBL epigenome and thereby promotes proliferation and survival in PMBL cell lines [Rui *et al.* 2010]. Thus, inhibition of both JAK2 and JMJD2C might represent a novel therapeutic approach for PMBL. PD-L1 and PD-L2 that are ligands for the PD receptor on T-cells are also upregulated by this amplification in PMBL [Rosenwald *et al.* 2003]. Engagement of the PD receptor by its ligands inhibits signaling through the T-cell receptor, suggesting that amplification of these genes modulates the interaction between PMBL cells and the surrounding T cells [Rosenwald *et al.* 2003]. Finally, PMBLs are characterized by constitutive activation of the NF- κ B signaling pathway [Rosenwald *et al.* 2003; Savage *et al.* 2003]. Inhibition of NF- κ B using a specific IKK inhibitor was toxic to PMBL cell lines, indicating that constitutive activation of this pathway is important for PMBL biology [Lam *et al.* 2005]. The molecular mechanisms leading to this constitutive activation are poorly understood. In more than 30% of PMBL cases, the negative NF- κ B regulator A20 is inactivated [Schmitz *et al.* 2009].

Clinical implications

The DLBCL subtypes are characterized by different overall survival rates following standard anthracycline-containing chemotherapy [Monti *et al.* 2005; Rosenwald *et al.* 2002]. GCB DLBCL and PMBL patients have relatively favorable 5-year overall survival rates.

In contrast, the majority of ABC DLBCL patients will succumb to their disease. The introduction of the anti-CD20 antibody rituximab significantly improved the outcome for DLBCL patients [Coiffier *et al.* 2002]. This benefit is observed in both ABC and GCB DLBCL patients. However, GCB DLBCL patients still do significantly better compared with patients diagnosed with ABC DLBCL (Figure 3A) [Lenz *et al.* 2008b].

Gene expression profiling can provide additional information besides the distinction of ABC and GCB DLBCL. A multivariate gene expression-based survival predictor model that is independent of the International Prognostic Index (IPI) can be used to predict survival upfront at diagnosis in DLBCL patients treated with a combination of rituximab and anthracycline-containing chemotherapy [Lenz *et al.* 2008b]. Three gene expression signatures termed 'germinal-center B-cell', 'stromal-1' and 'stromal-2' are associated with survival (Figure 3B). The prognostically favorable 'germinal-center B-cell' signature parallels the distinction of ABC and GCB DLBCL and consists of genes characteristically expressed in germinal-center B-cells. In contrast, the 'stromal-1' and 'stromal-2' signatures reflect the composition of nonmalignant cells, i.e. the tumor microenvironment [Lenz *et al.* 2008b]. The favorable 'stromal-1' signature reflects extracellular matrix deposition and histiocytic infiltration. In contrast, the prognostically unfavorable 'stromal-2' signature reflects tumor blood-vessel density. A multivariate model for survival was created from these three gene expression signatures. For every patient biopsy, a survival predictor score was calculated. These scores were used to divide the patients into quartiles of 3-year overall survival rates of 89%, 82%, 74%, and 48% and 3-year progression-free survival rates of 84%, 69%, 61%, and 33% (Figure 3B) [Lenz *et al.* 2008b].

A different approach to utilize changes in gene expression to predict outcome in DLBCL patients was taken by Lossos and colleagues [Lossos *et al.* 2004]. A predictor of survival measuring only six genes (*LMO2*, *BCL6*, *FN1*, *CCND2*, *SCYA3*, and *BCL2*) was constructed that divided DLBCL patients into low-, medium-, and high-risk groups according to their overall survival [Lossos *et al.* 2004]. This predictor was recently evaluated and confirmed

Figure 3. (A) Activated B-cell-like (ABC) and germinal-center B-cell-like (GCB) diffuse large B-cell lymphomas (DLBCLs) are characterized by significant differences in overall survival following a combination of rituximab and chemotherapy. (B) A multivariate gene expression-based survival model can be used to predict survival upfront at diagnosis in DLBCL patients treated with a combination of rituximab and chemotherapy. For every patient biopsy, a survival predictor score can be calculated. These scores are used to divide DLBCL patients into quartiles of significantly different 3-year overall survival rates of 89%, 82%, 74%, and 48%.

in its predictive value in DLBCL patients using formalin-fixed paraffin-embedded (FFPE) patient material [Malumbres *et al.* 2008]. Although this approach does not distinguish DLBCL patients into ABC and GCB DLBCL, its application might be helpful for guiding clinical strategies and therefore its implementation could be useful until gene expression profiling techniques are widely available.

In addition to its value in predicting patient outcome, gene expression profiling using DNA microarrays can additionally be applied to distinguish DLBCL from Burkitt's lymphoma (BL). Two recent studies convincingly showed that BL is characterized by a unique gene expression profile [Dave *et al.* 2006; Hummel *et al.* 2006]. Intriguingly, in these analyses a substantial number of cases that were diagnosed as DLBCL by conventional methods showed the gene expression profile of BL, suggesting that they represent BL cases that are difficult to diagnose by current methods. This distinction however is of major clinical importance, as BL requires more intensive treatment strategies.

Future developments

Despite the recognition and acknowledgement of different molecular DLBCL subtypes more than a decade ago, the translation into clinical routine is only slowly progressing and microarray-based technologies are just emerging in the clinical application. Several efforts to use immunohistochemistry to distinguish the molecular subtypes have been undertaken [Choi *et al.* 2009; Hans *et al.* 2004]. A recent report by Meyer and colleagues introduced a novel algorithm (Tally) that seems to be able to distinguish GCB and non-GCB DLBCL subtypes analyzing five immunohistochemical makers (CD10, GCET1, MUM1, FOXP1, and LMO2) [Meyer *et al.* 2011]. This algorithm showed a high concordance with gene expression profiling and the two identified groups of patients had different overall survival rates. However, this algorithm needs to be confirmed by other groups, especially as previous immunohistochemical approaches to determine the molecular DLBCL subtypes could not always be confirmed in additional analyses. This might be due to the limitations of immunohistochemistry, as staining and scoring procedures are

Table 1. Specific inhibitors targeting pathways that play an important role in DLBCL pathogenesis.

Molecular target	DLBCL subtype specificity	Inhibitor	Status in DLBCL therapy
BCL2 family	DLBCL	(a) ABT-737 [Oltersdorf <i>et al.</i> 2005] (b) ABT-263 [Wilson <i>et al.</i> 2010]	Preclinical and clinical
BCL6	DLBCL	(a) 79-6 [Cerchietti <i>et al.</i> 2010] (b) PU-H71 [Cerchietti <i>et al.</i> 2009]	Preclinical
BTK	ABC DLBCL with wildtype CARD11	(a) Dasatinib [Davis <i>et al.</i> 2010] (b) PCI-32765 [Davis <i>et al.</i> 2010]	(a) Preclinical (b) Preclinical and clinical
IKK	ABC DLBCL, PMBL	PS-1145 and MLX105 [Lam <i>et al.</i> 2005]	Preclinical
JAK	ABC DLBCL, PMBL	(a) Small-molecule pan-JAK inhibitor [Lam <i>et al.</i> 2008] (b) TG101348 [JAK2-inhibitor] [Rui <i>et al.</i> 2010] zVRPR-fmk [Ferch <i>et al.</i> 2009; Hailfinger <i>et al.</i> 2009]	Preclinical
MALT1	ABC DLBCL	(a) LY294002 [Kloo <i>et al.</i> 2011; Uddin <i>et al.</i> 2006] (b) BKM120	Preclinical
PI3K	DLBCL	Sotrastaurin [Naylor <i>et al.</i> 2011] Bortezomib [Dunleavy <i>et al.</i> 2009] R406 [Friedberg <i>et al.</i> 2010]	Preclinical Clinical Preclinical and clinical
PKC Proteasome SYK	ABC DLBCL with CD79A/B mutations DLBCL ABC DLBCL with wildtype CARD11		
DLBCL, diffuse large B-cell lymphoma; ABC, activated B-cell-like; GCB, germinal-center B-cell-like; IKK, I κ B α kinase; PMBL, primary mediastinal B-cell lymphoma.			

variable even between experienced laboratories as shown by a recent study of the Lunenburg Lymphoma Biomarker Consortium. Therefore, technical variations between laboratories should be harmonized, before these algorithms can be reliably implemented into routine diagnostics [de Jong *et al.* 2009].

Recently, a quantitative nuclease protection assay was applied on FFPE tissue to distinguish DLBCL patient samples into ABC and GCB DLBCL [Rimsza *et al.* 2011]. Classification into the molecular subtypes using this assay was compared with results obtained by gene expression profiling applying DNA microarrays. 73% of GCB DLBCLs and 79% of ABC DLBCLs were categorized correctly using this assay (confidence cutoff >0.9) [Rimsza *et al.* 2011]. As the classification into molecular subtypes will be indispensable in the future for the rational design of clinical studies and the application of new pharmacologic agents, the use of this quantitative nuclease protection assay might hold promise due to its applicability on FFPE patient material. However, gene expression profiling remains the gold standard to distinguish the molecular DLBCL subtypes especially as there has been significant progress in the development of microarray protocols that can be performed on FFPE tissue [Williams *et al.* 2010].

In the last couple of years significant progress has been made in the development of novel compounds that specifically target oncogenic pathways (summarized in Table 1). Several of these strategies are currently being evaluated in clinical trials. However, these efforts will only be successful if the molecular target or signaling pathway is indeed expressed or utilized by the malignant cells. Thus, it is important to employ our molecular understanding of these diseases and incorporate techniques such as gene expression profiling that can be used to predict if a specific tumor is addicted to a certain oncogenic pathway.

Due to their dependency on NF- κ B signaling, components of the NF- κ B and/or BCR pathways might represent a promising therapeutic target for ABC DLBCL patients (Table 1). Specific inhibitors targeting PKC and MALT1 showed promising results in preclinical models [Naylor *et al.* 2011; Ferch *et al.* 2009; Hailfinger *et al.* 2009]. It is conceivable that these therapeutic approaches can be translated into the clinic. This was underscored by a recent study in

which ABC and GCB DLBCL patients were treated with a combined approach of chemotherapy and the proteasome inhibitor bortezomib that can inhibit NF- κ B signaling [Dunleavy *et al.* 2009]. Strikingly, only ABC DLBCL patients showed benefit by the addition of bortezomib. GCB DLBCL might preferentially respond to PI3K or mTOR inhibitors due to their dependency on the PTEN-PI3K pathway. Finally, PMBL might benefit from the addition of JAK2 inhibitors (Table 1). These efforts will eventually lead to more specific and effective and less-toxic treatment strategies of DLBCL patients.

Funding

This work was supported by research grants to GL from the German Research Foundation (DFG), the Deutsche Krebshilfe, the Berliner Krebsgesellschaft e.V., and the Else Kröner-Fresenius-Stiftung.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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