Diffuse large B-cell lymphoma (DLBCL) represents the most frequent lymphoma subtype and is considered a heterogeneous diagnostic category [1]. Using gene expression profiling, two major molecular subtypes termed germinal centre B-cell-like (GCB) DLBCL and activated B-cell-like (ABC) DLBCL can be distinguished [2]. Their gene expression profiles suggest that they arise from B-cells at different stages of differentiation. The GCB DLBCLs appear to originate from germinal centre B-cells, whereas the ABC DLBCLs may arise from post-germinal-centre B-cells that are in transition to being differentiated into plasma cells. Intriguingly, these two subtypes differ not only with respect to the expression of thousands of genes, but also utilise different oncogenic pathways and have significantly different survival rates following therapy [3,4]. ABC DLBCLs are characterised by inferior survival compared with GCB DLBCL patients when treated with a combined approach of the anti-CD20 antibody rituximab and CHOP chemotherapy [5].

Recent advances in the understanding of the biology of these entities lead to the identification of a variety of potentially novel therapeutic targets for the treatment of affected patients. ABC DLBCLs are characterised by constitutive activation of the oncogenic nuclear factor-κB (NF-κB) pathway, which promotes cell proliferation and differentiation and suppresses apoptosis [6]. NF-κB signaling is mediated by a family of transcription factors that are normally kept inactive in the cytoplasm by binding to inhibitory IκB proteins. The constitutive activation of NF-κB in ABC DLBCL is caused in the vast majority of cases by somatically acquired mutations that affect positive (CARD11, CD79B and MYD88) and negative (TNFAIP3) NF-κB regulators [7–10]. Inhibition of NF-κB was toxic to preclinical models of ABC DLBCL [6]. Therefore, targeting the NF-κB pathway seems to be an attractive therapeutic approach. Such a strategy was taken by Dunleavy and colleagues in a recent phase II study in which the efficacy of bortezomib was investigated in DLBCL [11]. Preclinical data suggest that bortezomib inhibits NF-κB by blocking IκB degradation. The efficacy of bortezomib in combination with chemotherapy was evaluated in relapsed/refractory ABC and GCB DLBCL patients [11]. Interestingly, the response rates were significantly higher in ABC compared with GCB DLBCL, and even more importantly, patients with ABC DLBCL had a significantly superior overall survival. These results potentially suggest that inhibition of NF-κB might be a promising approach in ABC DLBCL. This hypothesis was further supported by recently presented data on the efficacy of the Bruton agammaglobulinemia tyrosine kinase (BTK) inhibitor ibrutinib [12]. BTK plays an important role in activating NF-κB following B-cell receptor stimulation. Using this inhibitor, impressive response rates in relapsed and refractory ABC DLBCL could be achieved. Collectively, these data indicate that inhibition of the oncogenic NF-κB pathway might be a future option to overcome the adverse prognosis of patients affected by ABC DLBCL.

While patients with GCB DLBCL are characterised by superior prognosis compared with ABC DLBCL [5], a substantial proportion of GCB DLBCL patients are not cured by standard treatment. GCB DLBCLs frequently express the transcriptional repressor BCL-6 that plays an important role in the germinal centre reaction. BCL-6 therefore might represent a novel target for GCB DLBCLs. In preclinical models, specific BCL-6 inhibitors showed impressive efficacy [13,14]. GCB DLBCLs are furthermore frequently characterised by deregulation of the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway [4]. 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. Various PI3K inhibitors are currently being evaluated in different cancer types and might represent a promising therapeutic approach in GCB DLBCL.

In summary, ABC and GCB DLBCL represent molecular subtypes that are dependent on different oncogenic signaling pathways. In clinical reality this biological diversity is still insufficiently taken into account. Efforts to distinguish these entities using gene expression profiling or next-generation sequencing will pave the way to more specific and less toxic treatment strategies.

Conflict of interest statement

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REFERENCES

[1] Nogai H, Dorken B, Lenz G. Pathogenesis of Non-Hodgkin’s lymphoma. J Clin Oncol 2011;29:1803–11.
[2] Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–11.
[3] Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937–47.
[4] Lenz G, Wright GW, Emre NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A 2008;105:13520–5.
[5] Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 2008;359:2313–23.
[6] Davis RE, Brown KD, Siebenlist U, Staudt LM. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med 2001;194:1861–74.
[7] Lenz G, Davis RE, Ngo VN, et al. Oncogenic CARD11 mutations in human diffuse large B cell lymphoma. Science 2008;319:1676–9.
[8] Compagno M, Lim WK, Grunn A, et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. Nature 2009;459:717–21.
[9] Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature 2010;463:88–92.
[10] Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. Nature 2011;470:115–9.
[11] Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood 2009;113:6069–76.
[12] Wilson W, Gerecitano J, Goy A, et al. The Bruton’s tyrosine kinase (BTK) Inhibitor, ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, phase 2 study. Blood 2012 [ASH Abstract 623].
[13] Cerchietti LC, Yang SN, Shaknovich R, et al. A peptidomimetic inhibitor of BCL6 with potent anti-lymphoma effects in vitro and in vivo. Blood 2009;113:3397–405.
[14] Cerchietti LC, Ghetu AF, Zhu X, et al. A small-molecule inhibitor of BCL6 kills DLBCL cells in vitro and in vivo. Cancer Cell 2010;17:400–11.