BIRC3 mutations in chronic lymphocytic leukemia – uncommon and unfavorable

Eugen Tausch and Stephan Stilgenbauer

Department of Internal Medicine III, Ulm University, Ulm, Germany

E-mail: STEPHAN STILGENBAUER - stephan.stilgenbauer@uniklinik-ulm.de

doi:10.3324/haematol.2019.238691

Chronic lymphocytic leukemia (CLL) is characterized by recurrent genomic aberrations as well as gene mutations, and *BIRC3* (Baculoviral IAP Repeat Containing 3, also called *cIAP2*) can be affected by both. *BIRC3* is located on chromosome 11 in proximity to *ATM* and 11q deletions include the *BIRC3* locus in approximately 80% of cases.[1] In addition, *BIRC3* can be affected by mutations, mainly nonsense and frameshift variants, with an incidence of 3-5% in untreated patients, making such mutations rare in comparison to *TP53*, *NOTCH1*, *SF3B1* or *ATM* defects.[1-5] However, as the frequency in fludarabine-refractory cohorts is higher, *BIRC3* abnormalities were discussed to define a high-risk group of CLL patients. Indeed *BIRC3* did turn out to have an adverse prognostic impact in some chemotherapy-treated CLL cohorts.[1,6] Furthermore, *BIRC3* abnormalities are associated with worse outcome in other lymphomas, acute lymphoblastic leukemia and solid tumors, including brain tumors in which *BIRC3* is reported to induce malignant transformation of low-grade gliomas to glioblastomas.[6-8]

While some studies have provided evidence of a clinical impact of mutated *BIRC3* and others have not, the functional implications of *BIRC3* deletion or mutation are partially unexplored. BIRC3 induces proteasomal degradation of MAP3K14, which is the major driver of non-canonical nuclear factor kappaB (NFκB) activation. Therefore, disrupted BIRC3 could result in a ligand-independent activation of the constitutive NFκB pathway, inducing cell proliferation and survival.[7,8] At this point Diop and colleagues began their functional characterization of *BIRC3* mutations in CLL as described in this issue of *Haematologica*.[9] First they confirmed the importance of

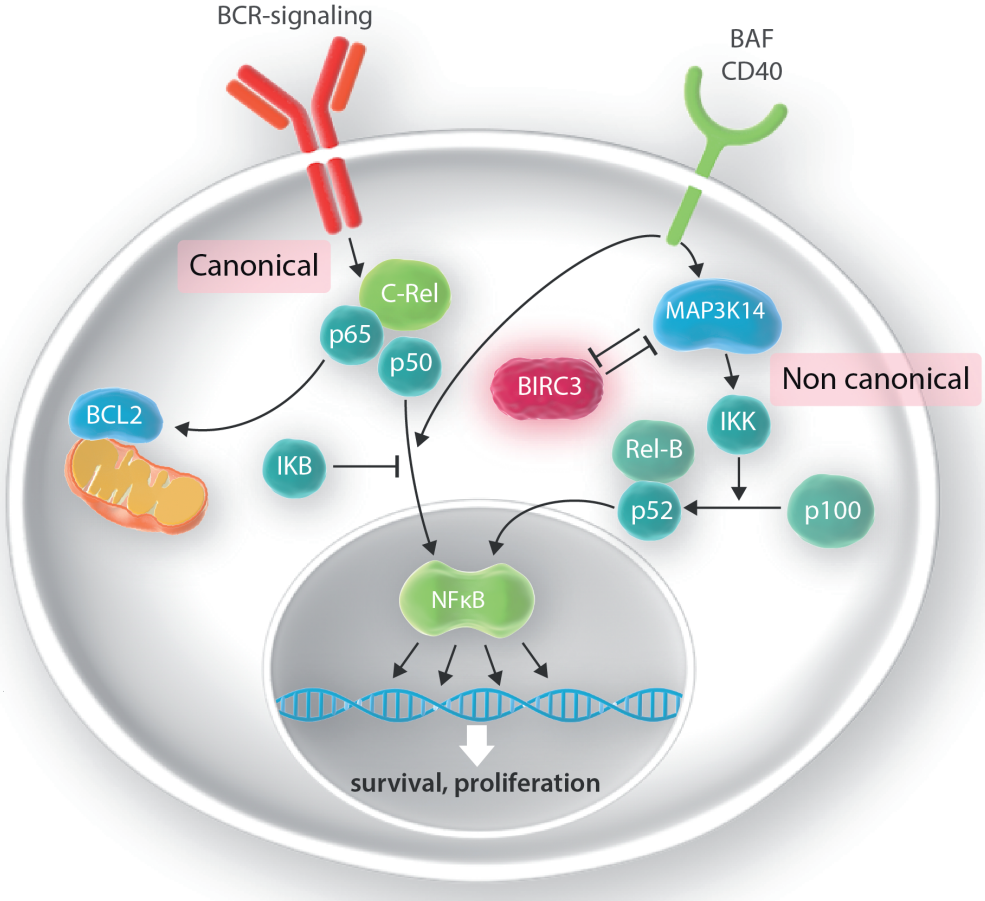

Figure 1. The canonical and non-canonical nuclear factor kappaB pathways. In the canonical nuclear factor kappaB (NFκB) pathway, activation of the B-cell receptor (BCR) results in a shift of the transcription factors c-Rel, p65 and p50 to the nucleus if not sequestered by IKB. In the non-anonical pathway, activation of MAP3K14 results in proteolytic cleavage of p100 to p52, which as a heterodimer with Rel-B serves as a transcription regulator. BIRC3, which is part of the negative regulatory complex, induces proteosomal degradation of MAP3K14, the major driver of activation of the non-canonical NFκB pathway.

the BIRC3-Map3K14 interaction for activation of the non-canonical NFκB pathway. Silencing Map3K14 by short hairpin RNA decreased the levels of NFκB, which was followed by reduced viability of *BIRC3*-mutated cells. MAP3K14 could, therefore, be a potential drug target to overcome mutant *BIRC3*-induced cell proliferation. Next Diop and colleagues evaluated the vulnerability of *BIRC3*-mutated cell lines and primary CLL cells to fludarabine. Viability assays under fludarabine treatment confirmed that *BIRC3*-mutated samples had a higher viability than *BIRC3* wildtype ones, although still lower than that of *TP53*-mutated samples after 48 h. Therefore, refractoriness to fludarabine, which has been consistently assigned to *TP53* defects in previous clinical and biological studies, is also found to a lesser extent in *BIRC3*-mutated cells. This translates into a significantly shorter progression-free survival of patients with *BIRC3*-mutated CLL receiving therapy with fludarabine, cyclophosphamide and rituximab (FCR), as found by the authors in a cohort of 287 previously untreated CLL patients.

This effect on outcome may be different with more modern treatment regimens. Although Diop and colleagues provide some evidence that NFκB in *BIRC3*-mutated patients remains active with ibrutinib therapy, there are more downstream targets of Bruton tyrosine kinase (BTK), including MEK/ERK and MAPK, which should remain inhibited by ibrutinib.[10] In general, *in vitro* cultures are less informative regarding the efficacy of BTK inhibitors for which the microenvironment plays a crucial role. In contrast to ibrutinib, treatment with venetoclax resulted in a similarly low viability of *BIRC3*-mutated and wildtype primary CLL cells.[9] This appears rational, as BCL2 is not involved in the non-canonical pathway affected by BIRC3. However, there is also some evidence that BCL2 levels are higher in *BIRC3*-mutated cases, indicating a greater sensitivity to venetoclax.[11] Although only limited data on the impact of *BIRC3* mutations are available from clinical trials with ibrutinib and venetoclax, an adverse outcome has not been observed, in contrast to del17p/mutated *TP53*.[12,13]

Despite the comprehensive work by Diop and colleagues some questions remain in addition to the unclear impact on outcome with novel compounds. This include the difference between monoallelic and biallelic defects (i.e., mutations and deletions), which considered together should result in a much higher number of affected patients. Furthermore the role of non-truncating missense variants and mutations outside the C-terminal RING-domain found predominantly in solid tumors, but also in lymphomas and CLL, remains unclear. Therefore, further studies, in particular in cohorts of patients from prospective trials evaluating biologically targeted agents, are warranted before *BIRC3* assessment can be put forward as a routine test in general clinical practice.

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