rate-limiting enzyme of cholesterol synthesis (ie, the 3-hydroxy-3-methylglutaryl-CoA reductase), inhibit DBCL xenograft tumorigenesis, especially the DBCL cell lines with higher SOX9 expression (see figure). These results are in accordance with studies demonstrating that the treatment of myeloid leukemia samples with statins enhances chemotherapy-induced leukemic cell apoptosis, by counteracting the cytoprotective increase of the cellular cholesterol levels induced by chemotherapy. The synergy between chemotherapy and statins has indeed been explored with encouraging but not definitive results in patients with relapsed acute myeloid leukemia. In this context, the study by Shen et al suggests exploring the combination of statins and standard treatments in advanced stage patients affected by SOX9 overexpressing DBCL.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

DOI 10.1182/blood2021014300 © 2022 by The American Society of Hematology

MYELOID NEOPLASIA

Comment on Taube et al, page 87

CEBPA mutations in AML: site matters

Lars Bullinger | Charité – Universitätsmedizin Berlin; German Cancer Consortium

In this issue of Blood, based on a retrospective analysis of 4708 acute myeloid leukemia (AML) cases, Taube et al1 evaluate the impact of CCAAT/enhancer binding protein α (CEBPA) mutations and show that it is especially in-frame mutations affecting the basic leucine zipper region (bZIP) of CEBPA that confer a favorable outcome, irrespective of their occurrence as biallelic (CEBPAbi) or single mutation (CEBPAsm). Compared with transactivation domain (TAD) mutations, this study strongly supports a previously undefined role of CEBPA bZIP mutations, which is reflected in a distinct disease biology including younger age, higher white blood cell counts, the presence of GATA2 mutations, and high complete remission rates and long median event-free and overall survival.

This observation not only refines the current genomic risk stratification of AML, which thus far only links CEBPA bi cases to a favorable prognosis,2 but it may also impact the current World Health Organization classification,2 changing the category “AML with biallelic mutations of CEBPA” into “AML with bZIP mutations of CEBPA.”

Although the observation of Taube et al warrants additional validation in independent cohorts, their findings are in line with a recent report in 2958 pediatric AML cases also demonstrating that CEBPA bZIP domain mutations are associated with favorable clinical outcomes, regardless of mono- or biallelic mutational status.4 Transcriptome analysis performed in both studies further supports a unique bZIP mutation biology, as bZIP CEBPAsm and CEBPA bi cases are characterized by similar expression profiles.

Both studies also nicely demonstrate the power of analyzing large leukemia cohorts and open the possibility of further refining clinically relevant AML subgroups. A better understanding of the molecular mechanisms underlying AML with CEBPA mutation has been of longstanding interest as a prerequisite for improved patient management (see figure). The first studies looking at the impact of CEBPA did not have the power to detect the impact of bZIP mutations. Nevertheless, already a decade ago, Taskesen et al5 could show that in-frame insertion or deletion mutations affecting the bZIP domain were not associated with NPM1 mutations and that CEBPAsm cases did not show a unique gene expression signature, thereby supporting their distinct biology, in line with the recent data. In addition, the large study by Taube et al now demonstrates that 90% of CEBPA bi mutant cases carry bZIP in-frame mutations, which explains why this cohort demonstrated unique profiles in most previous analyses.

Regarding cooperating events contributing to leukemogenesis in CEBPA mutant AML, several studies reported concurrent GATA2 mutations, which are often associated with the CEBPA bi subgroup of
patients. However, GATA2 mutations were also detected in CEBPA\textsl{sm} cases, albeit at a lower frequency, as bZIP and TAD mutations were not considered individually.\textsuperscript{a} Although GATA2 mutations did not affect clinical outcome in previous studies, GATA2 mutation co-occurrence also did not significantly impact outcome in the 2 recent adult and pediatric studies.\textsuperscript{1,4} Besides GATA2 mutations, the study by Taube et al also reported WT1 mutations as frequent co-occurring events in CEBPA\textsl{mut} AML. In contrast to the pediatric study, CSF3R mutations are only seen in a minority (~3\%) of adult patients with CEBPA\textsl{mut} AML.\textsuperscript{1,4}

Regarding cooperating GATA2 mutations in CEBPA\textsl{mut} AML, a recent study demonstrated allele-specific expression of GATA2 caused by epigenetic dysregulation, especially in CEBPA\textsl{bi} mutant AML.\textsuperscript{7} The question is now whether this is also caused by in-frame bZIP mutations, which are found in more than 90\% of patients with CEBPA\textsl{bi} mutation? Thus, future studies must look more closely at the bZIP mutant CEBPA mutation subgroup. Unique expression signatures characterizing this newly identified AML cohort also suggest distinct epigenetic mechanisms cooperating with genetic hits in the pathogenesis of bZIP-mutant CEBPA AML.

However, future studies will not only need to determine the mutation site but will also need explore posttranslational modifications (PTMs). A recent study showed that the myeloid CEBPA interactome was comprised by PTM-regulated interactions with protein machineries involved in regulating epigenetic modifications, as well as gene expression and RNA processing.\textsuperscript{5} This study shows that PTMs can alter the interaction spectrum of CEBPA, thereby rendering it an intrinsically disordered multivalent transcription factor that can interact with multiple components.

Thus, future investigations will not only have to comprehensively study genomic, epigenomic, and transcriptomic aberrations in AML but will also have to use powerful strategies to systematically explore the interactomes of mutant transcription factors. Ultimately, this will allow us to better understand the biology of CEBPA\textsl{mut} AML and to identify additional targets for precision therapies. Until then, the study by Taube et al already provides guidance to further improve management of our patients, because bZIP CEBPA\textsl{mut} cases can now be considered prognostically favorable, whereas the approximate 10\% of non-bZIP CEBPA\textsl{bi} should be more cautiously managed in the future.

Conflict-of-interest disclosure: L.B. has held an advisory role and/or received honoraria from Abbvie, Amgen, Astellas, Bristol-Myers Squibb, Celgene, Daichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer, Roche, Sanofi, and Seattle Genetics, and has received research support from Bayer and Jazz Pharmaceuticals.

REFERENCES


