CEBPA mutations in AML: site matters

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rate-limiting enzyme of cholesterol synthesis (ie, the 3-hydroxy-3methylglutaryl-CoA reductase),[7] inhibit DLBCL xenograft tumorigenesis, especially the DLBCL 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.[6] The synergy between chemotherapy and statins has indeed been explored with encouraging but not definitive results in patients with relapsed acute myeloid leukemia.[10] 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 DLBCL.

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MYELOID NEOPLASIA

Comment on Taube et al, page 87

CEBPA mutations in AML: site matters

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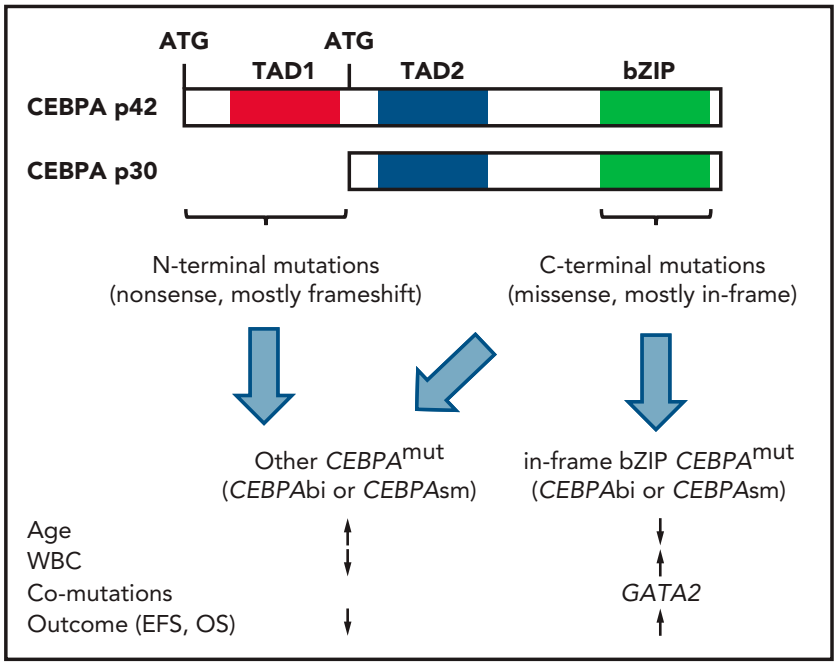
In this issue of *Blood*, based on a retrospective analysis of 4708 acute myeloid leukemia (AML) cases, Taube et al[1] evaluate the impact of *CCAAT/enhancer binding protein* α (*CEBPA*) mutations and show that it is especially in-frame mutations affecting the basic leucine zipper region (bZIP) of CEPBA that confer a favorable outcome, irrespective of their occurrence as biallelic (*CEBPA*bi) or single mutation (*CEBPA*sm). 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,[3] 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 *CEBPA*sm 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 CEPBA did not have the power to detect the impact of bZIP mutations. Nevertheless, already a decade ago, Taskesen et al[5] could show that in-frame insertion or deletion mutations affecting the bZIP domain were not associated with *NPM1* mutations and that *CEBPA*sm 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



Schematic overview of *CEBPA* mutations in AML: impact of *CEBPA* mutation site on disease biology and outcome. bi, biallelic; bZIP, basic leucine zipper region; EFS, event-free survival; mut, mutation; OS, overall survival; sm, single mutation; TAD, transactivation domain; WBC, white blood cell count.

patients. However, *GATA2* mutations were also detected in *CEBPA*sm cases, albeit at a lower frequency, as bZIP and TAD mutations were not considered individually.[6] 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.[1,4] Besides *GATA2* mutations, the study by Taube et al also reported *WT1* mutations as frequent co-occurring events in *CEBPA* mutant AML. In contrast to the pediatric study, *CSF3R* mutations are only seen in a minority (~3%) of adult patients with *CEBPA* mutant AML.[1,4]

Regarding cooperating *GATA2* mutations in *CEBPA* mutant AML, a recent study demonstrated allele-specific expression of *GATA2* caused by epigenetic dysregulation, especially in *CEBPA*bi mutant AML.[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*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.[8] 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* mutant 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*sm cases can now be considered prognostically favorable, whereas the approximate 10% of non-bZIP *CEBPA*bi should be more cautiously managed in the future.

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