by activating STAT5, which stimulates production of c-MYC, cyclin D and PIM. It also blocks differentiation, at least partially, *via* p27 downregulation, an aspect that requires further investigation (Figure 1C).

Peschel *et al.* now add a further layer of complexity to our understanding. In AML cells, p27 partially co-localizes with FLT3 in extended perinuclear structures. The co-localization is accompanied by enhanced p27 Y88-phosphorylation. Cytoplasmic p27 is susceptible to SCF^{SKP2}-triggered proteolysis but is potentially able to exert proto-oncogenic functions. Although the stabilization of p27 is expected to have a net tumor suppressive effect, the simultaneous increase in the cytoplasmic level of p27 might have unintended consequences that offset the benefits of restoring nuclear p27. Whether AML therapy should aim to stabilize p27 or to degrade it is still unclear (Figure 1D). The importance of learning whether to degrade or not to degrade cannot be overstated. We hope that drug synergy screens will soon provide an answer.

Acknowledgments

We are grateful to Philipp Jodl and Peter Alexander Martinek for their excellent technical help in generating the figures. We are deeply indebted to Graham Tebb for editing the manuscript. This work was supported by the Austrian Science Fund (FWF) Grant SFB F47 (to VS) and by an ERC-advanced grant (to VS).

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Long non-coding RNAs: another brick in the wall of normal karyotype acute myeloid leukemia?

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Acute myeloid leukemia (AML) is a complex malignant neoplasm of the hematopoietic system, characterized by multiple somatically (germline mutations occur in ~5% of AML cases) acquired pathologic (driver) mutations and the presence of coexisting competing malignant clones that frequently evolve under "selective pressure" exerted by antileukemic treatment strategies. Genomic events in AML follow specific patterns of mutual exclusivity and co-occurrence and can be grouped into distinct functional categories of mutational and chromosomal abnormalities, including rearrangements involving transcription factors and mutations in tumor suppressor genes, genes encoding myeloid transcription factor, members of the cohesin complex, genes involved in DNA methylation, genes responsible for activated signaling, chromatin-modifying genes, the *nucleophosmin 1* (*NPM1*) gene and members of the spliceosome complex.[1] These patterns of genomic associations can be used to segregate AML cases into several non-overlapping cohorts, each with a distinct clinical outcome.[2] In addition, these genomic events result in the clustering of AML patients into distinct messenger ribonucleic acid (RNA) expression

signatures and microRNA sequencing profiles.[1] These expression signatures correlate with unique morphological features, baseline clinical characteristics and underlying genomic abnormalities and have a strong association with prognosis, especially in AML patients with normal karyotype.[3]

In this issue of Haematologica, Papaioannou D *et al.* expand on our current understanding of the contribution of a distinct class of RNA molecules to the pathogenesis and prognosis in AML.[4] Along with other regulatory RNA molecules, such as microRNAs, short-interfering RNAs, and others, long non-coding RNAs (lncRNAs) are integral for intracellular homeostasis by exerting specific cellular functions, including regulation of gene transcription, progression through the cell cycle, regulation of post-transcriptional mRNA processing, and others.[5] Using a well-validated cohort of younger *de novo* AML patients with normal karyotype (NK-AML) enrolled into consecutive studies of cytarabine/anthracycline-based first-line therapy on The Alliance for Clinical Trials in Oncology, the authors defined the global expression of lncRNAs in this cohort of patients. They also defined a lncRNA signature associated with response to therapy and risk of relapse and reported on the baseline and genomic characteristics of NK-AML patients with distinct lncRNA expression signatures.

Additionally, the investigators reported several interesting and novel observations. First, it was noted that two-thirds of the lncRNAs belong to 1 of 3 categories of these regulatory RNA molecules (processed pseudogenes, intergenic/intervening lncRNAs or antisense lncRNAs). The investigators also identified a 24 lncRNAs signature that was highly correlated with outcomes, whereas low prognostic lncRNA scores (favorable lncRNA scores) were associated with improvements in different survival endpoints (favorable lncRNA score status also associated with longer overall survival (OS; P=0.002, 5-year rates, 52% *versus* 26%) and longer event-free survival (EFS; P<0.001, 5-year rates, 46% *versus* 16%). Importantly, these differences remained significant in multivariable analyses even after adjustment for other prognostic covariates. In addition, the presence of a low lncRNA prognostic score was associated with other known prognostic variables, such as low white blood cell count at diagnosis, lower frequency of *FLT3*-internal tandem duplication (ITD) and more frequent classification into the favorable risk category according to the European LeukemiaNet (ELN) classification. Next, several lncRNA expression signatures identified had strong correlation with well-defined prognostic molecular mutations in NK-AML, such as biallelic *CEBPA* mutations, mutations in the *NPM1* gene and presence of *FLT3*-ITD. Finally, a strong association between high lncRNA prognostic score expression and specific messenger RNA and microRNA expression profiles was observed.

Despite these unique observations, several questions remain regarding the value of lncRNA profiling in patients with NK-AML. First, only a highly selected cohort of patients was included in these investigations. For example, adult patients younger than 60 years of age represent one-third of all cases of AML (although, more limited data have previously demonstrated the prognostic significance of lncRNA expression profiling in older patients with AML, despite a lack of overlap in these expression signatures).[6] In addition, NK-AML is observed in approximately half of younger adults with AML. These factors limit their generalization of the findings to less than 20% of AML patients and excluded several high-risk cohorts, such as patients with secondary AML (both antecedent hematologic disorders as well as those with therapy-related AML) and those with adverse-risk karyotypes. Recommendations for post-remission treatment include the consideration of allogeneic hematopoietic cell transplant (alloHCT) in patients with high-risk genomic features. The exclusion of patients receiving alloHCT in first complete remission, including those with an increased risk of relapse (such as patients segregated into the intermediate and adverse ELN cohorts),[7] hampers the identification of the optimal post-remission approach in patients with high prognostic lncRNA scores. Also, the study segregates patients with NK-AML according to the updated version of the ELN classification.[8] However, the associations of recurrent gene mutations with lncRNA expression studies reported herein do not account for the updated ELN classification, whereby *FLT3*-ITD patients can be segregated into favorable (mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITDlow), intermediate (wild-type *NPM1* without *FLT3*-ITD or wild-type *NPM1* and *FLT3*-ITDlow or mutated *NPM1* and *FLT3*-ITDhigh) or adverse (wild-type *NPM1* and *FLT3*-ITDhigh) categories. Finally, AML is an oligoclonal malignant disorder where genomic abnormities are acquired serially; the design of the study by Papaioannou D *et al.* limits the assessment of the combinatorial effect of multiple mutations on the lncRNA expression signature and consequently their prognostic significance. For example, the investigators report that mutation in the *NPM1* gene was strongly associated with a lncRNA signature, however, patients with *NPM1* often also have co-associated mutations in *IDH1/2* (improved clinical outcomes),[9] *DNMT3A* (worse clinical prognosis)[10] and *FLT3*-ITD (variable clinical outcomes depending on the allelic ratio of *FLT3*-ITD).[8] This variability in genomic co-associations may explain why the results failed to demonstrate an association between *NPM1* mutational status, *FLT3*-ITD or biallelic mutations in the *CEBPA* genes and lncRNA expression prognostic score.

In summary, the current report identifies a lncRNA expression signature that allows segregation of younger patients with *de novo* NK-AML into 2 separate prognostic cohorts and describes expression signatures associated with specific molecular abnormalities. Overall, these results expand on prior studies and highlight the importance of coding and non-coding RNAs, adding another brick in the wall of understanding of the processes involved in leukemic transformation.

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