Editorial Commentary

Long non-coding RNAs emerge as a novel prognostic indicator in pediatric acute myeloid leukemia

Talia Velasco-Hernandez[1,2]^, Pablo Menéndez[1,2,3,4,5]^

[1]Josep Carreras Leukemia Research Institute, Barcelona, Spain; [2]Spanish Network of Advanced Therapies (TERAV)-Carlos III Health Institute (ISCIII) (RICORS, RD21/0017/0029), Madrid, Spain; [3]The Spanish Biomedical Research Centre in Cancer (CIBER-ONC, ISCIII), Barcelona, Spain; [4]Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain; [5]Department of Biomedicine, School of Medicine, University of Barcelona, Barcelona, Spain

Correspondence to: Talia Velasco-Hernandez, PhD. Josep Carreras Leukemia Research Institute, Carrer Casanova 143, 4º Floor, 08036 Barcelona, Spain; Spanish Network of Advanced Therapies (TERAV)-Carlos III Health Institute (ISCIII) (RICORS, RD21/0017/0029), Madrid, Spain. Email: tvelasco@carrerasresearch.org; Pablo Menéndez, PhD. Josep Carreras Leukemia Research Institute, Carrer Casanova 143, 4º Floor, 08036 Barcelona, Spain; Spanish Network of Advanced Therapies (TERAV)-Carlos III Health Institute (ISCIII) (RICORS, RD21/0017/0029), Madrid, Spain; The Spanish Biomedical Research Centre in Cancer (CIBER-ONC, ISCIII), Barcelona, Spain; Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain; Department of Biomedicine, School of Medicine, University of Barcelona, Barcelona, Spain. Email: pmenendez@carrerasresearch.org.

Comment on: Farrar JE, Smith JL, Othus M, *et al.* Long Noncoding RNA Expression Independently Predicts Outcome in Pediatric Acute Myeloid Leukemia. J Clin Oncol 2023;41:2949-62.

Keywords: LncRNAs; acute myeloid leukemia (AML); RNA sequencing; signature

Submitted Jun 27, 2023. Accepted for publication Oct 09, 2023. Published online Oct 20, 2023.
doi: 10.21037/tp-23-351
View this article at: https://dx.doi.org/10.21037/tp-23-351

Acute myeloid leukemia (AML) is a clonal hematological malignant disorder characterized by the accumulation of myeloid cell progenitors with arrested differentiation (blasts). AML is mainly diagnosed in adults, and it shows an increased prevalence in elderly people; however, it can be also diagnosed, although at 1-log lower frequency, during infancy and childhood. This leukemia can originate from a variety of genetic aberrations and chromosomal translocations leading to a very heterogeneous phenotypic and clinical spectrum of patients diagnosed as AML. Several studies published in the last years have attempted to bring order to the very complex classification of the many AML subtypes by establishing different categories and subgroups based on cytogenetics and mutational burden of the blasts, with the aim of tailoring therapy to suit the individual patient.

For example, a recent study by Tazi and colleagues (1) reported on the comprehensive molecular profiling of 3,653 adult patients to characterize and validate 16 different molecular subgroups describing 100% of patients with AML, and associating them with clinical presentation, response to chemotherapy and risk of relapse and death. Also, an extended official classification of myeloid neoplasms and acute leukemias (International Consensus Classification) was developed in 2022 (2), with the aim of using all accumulated data to define real disease entities to facilitate diagnosis and prognostication of these neoplasms and, thus, improve treatment decisions for patients. Here, the authors established 18 different subtypes based on gene mutations and chromosomal translocations.

In the case of pediatric AML, genomes have been characterized in less detail, but existing studies hinted at substantial differences between the genomic landscapes of adult and pediatric AML, the latter showing a more silent mutational landscape (3). Specific studies centred on pediatric patients would be needed to deliver optimal

^ ORCID: Talia Velasco-Hernandez, 0000-0003-2183-7443; Pablo Menéndez, 0000-0001-9372-1007.

therapies for this subgroup of patients.

Actually, in a recent issue of the *Journal of Clinical Oncology*, Farrar and colleagues (4) reported on the use of a 37 long non-coding RNA (lncRNA) signature (lncScore) to classify patients with pediatric AML into risk category subgroups, which yielded a superior stratification to current methods based on cytogenetics or mutational burden. They focused their study on pediatric samples using a relatively large cohort of 1,299 patients from the Children's Oncology Group as part of the TARGET pediatric AML initiative, with representation of the full spectrum of cytogenetic subgroups.

LncRNAs are defined as molecules longer than 200 nucleotides that are transcribed but do not code for any protein. They are involved in multiple biological processes and can exert their functions through diverse modes of action. There is growing evidence of the importance of lncRNAs as prognostic and diagnostic markers in different cancers, but their expression is not yet fully characterized in AML and, in particular, in pediatric AML. Farrar and colleagues examined lncRNAs expression in this cohort of AML patients and, by comparing high- and low-risk patients, established the lncScore based on the expression of 37 lncRNAs that they fully validated.

Distributing patients between negative and positive lncScore, they could recapitulate the classification of patients according to overall survival (OS) and event-free survival (EFS) with an accuracy comparable with traditional classifications. Indeed, they observed that cytogenetic subgroups classically categorized as low-risk, such as CBFB-MYH11 and RUNX1-RUNX1T1, had a negative score, whereas those normally classified as high-risk, such as NUP98-rearranged or CBFA2T3-GLIS2, had a positive lncScore. For cytogenetic subgroups such as KMT2A-rearranged, which are extremely heterogeneous owing to their partnership with different fusion genes, the lncScore was able to subdivide the patient cohort according to the treatment outcomes, with a substantially better allocation of patients to the risk group than when based only on the KMT2A fusion partner.

To test whether the lncScore could also better predict the outcome of patients than post-induction prognostic criteria, they used as a comparator the final risk (FR), a parameter integrating information about cytologic and molecular features at presentation, induction response by minimal residual disease (MRD), and the length and intensity of the consolidative therapy. So, in the multivariable model, the integration of both parameters—FR and lncScore—outperformed both FR and lncScore alone in prediction of patient outcome after treatment.

The 37 lncRNAs used in this signature, shown in *Fig. 1E* of Farrar *et al.*'s study, have not been previously described to have an effect on AML outcomes; however, prior studies with lncRNAs have been already reported. For instance, Garzon and colleagues (5) described a 48 lncRNA signature in adult cytogenetically-normal (CN)-AML from microarray and RNA-sequencing data, which was also used for patient stratification and risk prediction. In this report, the authors also identified individual lncRNAs more associated with specific genetic alterations. Likewise, Mer and colleagues (6) studied the prognostic value of individual lncRNAs in an AML cohort of 274 patients, identifying 33 lncRNAs with prognostic value for OS of the AML patients. They also used the expression of all the lncRNAs detected in the study to classify patients into four different risk groups, although they failed to find any correlation with additional molecular or biological features within the four groups. Both studies used adult cohorts of patients for the analysis. Farrar *et al.* (4) used pediatric samples for modelling, but they also tested the lncScore with a smaller adult cohort of 96 patients, which revealed a similar prognostic potential as pediatric samples, indicating a wider spectrum of ages for which this score would be accurate. However, broader clinical implementation to predict patient's outcome awaits for further validation in an independent patient cohort (7). This would be of special relevance in those patients in need of hematopoietic stem cell transplantation.

In sum, the lncScore, an easily quantifiable parameter following a single blood extraction followed by RNA extraction and RNA-sequencing (in this case), could provide additional information when assigning patients to risk groups at diagnosis to help in treatment decisions. This protocol can be easily implemented in clinical diagnostic and, as the authors discussed, would be highly beneficial to medical institutions with limited resources in place of the numerous molecular and cellular assays currently established for the full-risk classification of patients. It would also be of major clinical relevance to determine whether lncScore can anticipate those cases of AML predicted as low-risk based on current cytogenetics/molecular features who eventually become treatment-resistant or relapse as these patients can benefit from more intensive upfront clinical management. The opposite scenario would apply to those AML cases initially predicted as high-risk who eventually display a favourable, long-term clinical outcome as these

patients may have been overtreated. Further studies will be necessary to test whether the lncScore provides additional biological or therapeutic features in AML.

Acknowledgments

We thank CERCA/Generalitat de Catalunya and Fundació Josep Carreras-Obra Social "la Caixa" for core support.
Funding: Competitive financial support for the group was obtained from the Deutsche José Carreras Leukämie-Stiftung (No. DJCLS15R/2021 to PM and TVH). This research was also supported by the Spanish Ministry of Economy and Competitiveness (No. SAF2016-80481R, PID2019-108160RB-I00/AEI/10.13039/501100011033), "la Caixa" Foundation (No. LCF/PR/HR19/52160011), European Union's Horizon Europe Research and Innovation Programme under Grant Agreement No. 101057250 (CANCERNA), the Leo Messi Foundation, "Heroes hasta la médula" initiative and ISCIII-RICORS within the Next Generation EU program (plan de recuperación, transformación y resiliencia) to PM. TVH is supported by an investigator fellowship from the AECC (No. INVES223069VELA).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Pediatrics*. The article has undergone external peer review.

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-351/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-351/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Tazi Y, Arango-Ossa JE, Zhou Y, et al. Unified classification and risk-stratification in Acute Myeloid Leukemia. Nat Commun 2022;13:4622.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-28.
3. Bolouri H, Farrar JE, Triche T Jr, et al. The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. Nat Med 2018;24:103-12.
4. Farrar JE, Smith JL, Othus M, et al. Long Noncoding RNA Expression Independently Predicts Outcome in Pediatric Acute Myeloid Leukemia. J Clin Oncol 2023;41:2949-62.
5. Garzon R, Volinia S, Papaioannou D, et al. Expression and prognostic impact of lncRNAs in acute myeloid leukemia. Proc Natl Acad Sci U S A 2014;111:18679-84.
6. Mer AS, Lindberg J, Nilsson C, et al. Expression levels of long non-coding RNAs are prognostic for AML outcome. J Hematol Oncol 2018;11:52.
7. McCaw ZR, Richardson PG, Wei LJ. Assessing the Ability of Long Noncoding RNA Expression to Predict Patient Outcomes in Pediatric AML. J Clin Oncol 2023;41:4446-7.

Cite this article as: Velasco-Hernandez T, Menéndez P. Long non-coding RNAs emerge as a novel prognostic indicator in pediatric acute myeloid leukemia. Transl Pediatr 2023;12(10):1913-1915. doi: 10.21037/tp-23-351