Editorial

miRNAs as prognostic predictors in acute myeloid leukemia

João Agostinho Machado-Neto[1], Jorge Antonio Elias Godoy Carlos[1], Keli Lima[1,2]

[1]Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil; [2]Laboratory of Medical Investigation in Pathogenesis and Targeted Therapy in Onco-Immuno-Hematology (LIM-31), Department of Internal Medicine, Hematology Division, Faculdade de Medicina, University of São Paulo, São Paulo, Brazil

Correspondence to: João Agostinho Machado-Neto, PhD. Department of Pharmacology, Institute of Biomedical Sciences, University of São Paulo, Av. Prof. Lineu Prestes, 1524, CEP 05508-900, São Paulo, SP, Brazil. Email: jamachadoneto@usp.br.

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Acute myeloid leukemia (AML) comprises a heterogeneous group of hematological malignancies characterized by proliferation and accumulation of blasts in the bone marrow, peripheral blood, and other organs, failure of terminal cell differentiation (ineffective hematopoiesis) and resistance to apoptosis (1). The etiology of the disease is still poorly understood, but the accumulation of genetic (some recurrent), epigenetic and metabolic alterations participate in the pathogenesis of AML (2). In recent years, there have been great advances in understanding the molecular basis of the disease, which has resulted in the development of the identification of therapeutic targets and the approval of selective treatment targets for certain molecular subtypes. Despite advances in the pharmacological treatment of AML, allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains an important healing option for eligible patients (3). Recently, some pathognomonic molecular alterations have been highlighted in the review of the diagnostic criteria for AML [i.e., *PML::RARA*, *RUNX1::RUNX1T1*, *CBFB::MYH11*, *MLLT3::KMT2A*, *MT2A* rearrangements, *DEK::NUP214*, *GATA2*, *MECOM* (*EVI1*), *MECOM* rearrangements, mutated *NPM1*, in-frame bZIP *CEBPA* mutations, and others], and when present, the presence of ≥10% of blasts in the bone marrow is enough to close the diagnosis of the disease (4). Thus, a better understanding of the molecular basis of AML has contributed to the identification of new targets and prognostic markers.

In the field of AML epigenetics, microRNAs (miRNAs) have emerged as relevant markers for the prognosis and contribute to the biology of the disease (5). miRNAs are small non-coding RNAs, approximately 20–24 nucleotides, capable of regulating the expression of specific genes (i.e., acting under mRNA stability or protein translation), and in this way impact a great diversity of biological processes.

In the present issue, Liu *et al.* (6) reported that high expression of miR-107 and miR-17 is associated with worse clinical outcomes in patients with AML who received chemotherapy, which was not observed in the group of patients who received allo-HSCT. When analyzed together, patients with high expression of both miR-107 and miR-17 had the worst clinical outcomes (entire cohort and chemotherapy group). From the biological point of view, analysis of differentially expressed genes revealed a potential association of these miRNAs with the dysregulation of multiple metabolic processes (6).

Despite the study by Liu *et al.* (6) being a pioneer in the study of miR-107 and miR-17 in AML, the role of miRNAs has been widely explored in the field of oncology, and their contribution has been reported for different types of cancers. Among the solid tumors that show increased miR-107 expression gastric cancer, breast cancer, penile cancer, hepatocellular carcinoma, and colorectal cancer stand out (7-11). Similarly, increased miR-17 has been associated with pancreatic cancer, prostate cancer, Burkitt lymphoma, colorectal cancer, esophageal adenocarcinoma,

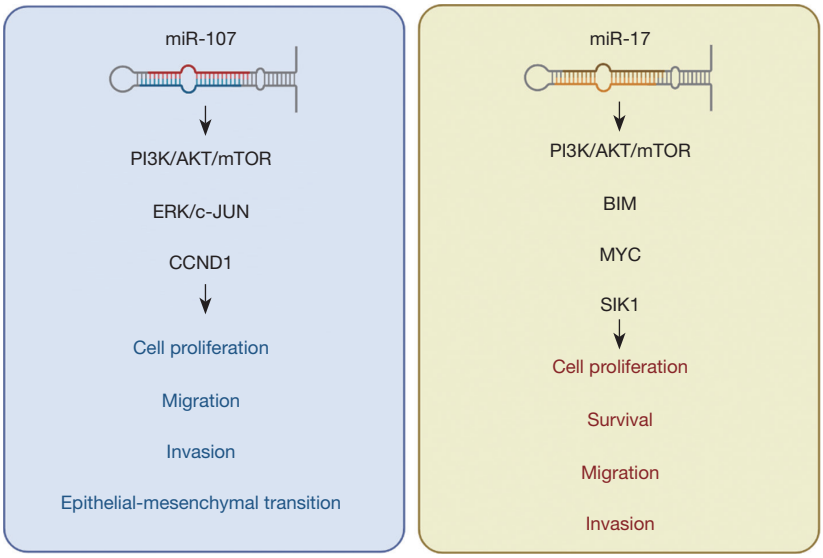

Figure 1 Insights for miR-107 and miR-17 on signaling pathways and cellular processes in cancer. In solid tumors, miR-107 participates in the activation of the PI3K/AKT/mTOR pathway via FAT4 regulation, in the activation of the ERK/c-JUN pathway via regulation of HMGCS2, and regulation of CCND1, which impact the regulation of epithelial-mesenchymal transition, proliferation, migration, and invasion. Similarly, miR-17 has also been associated with the activation of the PI3K/AKT/mTOR pathway through the regulation of PTEN, and in the modulation of BIM, MYC, and SIK1, promoting proliferation, survival, migration, and invasion of cancer cells.

and nasopharyngeal carcinoma (12-17). Performing an analysis of the signaling pathways and cellular processes modulated by these microRNAs in solid tumors, we highlight that miR-107 participates in the activation of the PI3K/AKT/mTOR pathway via FAT4 regulation (7), in the activation of the ERK/c-JUN pathway via regulation of HMGCS2 (10) and regulation of CCND1 (11), which has been associated with modulation of epithelial-mesenchymal transition, proliferation, migration, and invasion. miR-17 has also been associated with the activation of the PI3K/AKT/mTOR pathway through the regulation of PTEN (13), in addition to the modulation of BIM, MYC, and SIK1 (14,15) modulation, acting in a similar way in promoting proliferation, survival, migration and invasion of tumor cells. A summary of the main signaling pathways induced by miR-107 and miR-17 and the related-cellular processes in solid tumors are illustrated in *Figure 1*. These findings suggest the activation of the PI3K/AKT/mTOR pathway as a point in common between the two miRNAs that could be used as a pharmacological target, given a large number of inhibitors (some already approved for clinical use) that act on this signaling pathway (18). Furthermore, the role of this signaling pathway is also widely studied in the field of AML and could be an interesting point for future investigations.

Another point worth mentioning in the study presented by Liu *et al.* is that miR-107 and miR-17 had an impact on AML patients who received only chemotherapy. Indeed, the role of these miRNAs has been associated with chemoresistance in solid tumor models (19-22). For instance, increased expression of miR-17 reduces sensitivity, while inhibition of this miRNA increases response, to oxaliplatin, irinotecan, and fluorouracil in colorectal cancer cells (21). Thus, a better understanding of the molecular basis of resistance induced by these miRNAs may guide the development of more effective therapeutic regimens in miR-107 and/or miR-17 high-expressing cancer patients.

In summary, the initial evidence provided by Liu *et al.* on the contribution of miR-107 and miR-17 in the clinical outcomes of AML highlights the need for future functional and cell signaling studies in experimental models of AML to better elucidate the role of these miRNAs in the response to chemotherapy and potentially identify new therapeutic approaches.

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Footnote

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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.

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