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Assessment of Sirtuin Genes and Related microRNA Expression in Patients with Acute Myeloid Leukemia

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INTRODUCTION

Sirtuins are the group of 7 (SIRT1-7) histone deacetylases with pleiotropic effects on aging and cell survival [1]. They are responsible for the post-translational modification of histones and interact with other molecules, such as microRNA (miRNA) [2]. Another important aspect of their activity is the sirtuin-TP53 axis, which affects the processes of cel apoptosis and DNA repair [3]. Thus, the role of sirtuins and associated molecules in key mechanisms of tumorigenesis makes them a worthwhile topic in acute myeloid leukemia (AML).

AIM

- Evaluation of the expression and role of sirtuin and *wtTP53* genes, and related miRNA in AML patients.

METHOD

- A prospective study was performed on 80 newly diagnosed AML patients.
- The expression of *SIRT1-7*, *wtTP53* genes and 14 selected miRNAs was determined in duplicate in bone marrow samples using real-time PCR.
- Normalization was performed by ΔCycle threshold (Ct)=Ct(reference) – Ct(gene of interest). The ΔΔCt method was used to calculate fold changes (FC) in gene expression. Kaplan-Meier method was used to assess overall survival (OS).

Table 1. Patients' characteristics.

Patients, n	80
- female, n (%)	37 (46)
- male, n (%)	43 (54)
Age, median (range)	67 (25-90)
Treatment approach, n (%)	
- intensive	27 (34)
- azacitidine+venetoclax	22 (27)
- non-intensive	31 (39)
Cytogenetic-molecular risk (ELN2022), n (%)	4 (5)
- no data	6 (7)
- favorable	35 (44)
- intermediate	35 (44)
- adverse	
Peripheral blood blasts %, median (IQR)	19 (3-62)
Bone marrow blasts %, median (IQR)	44 (25-68)
WBC G/l, median (IQR)	15 (3-71)
ANC G/l, median (IQR)	2 (0.6-5)
Hemoglobin g/dl, median (IQR)	9 (8-10)
Platelets G/l, median (IQR)	55 (28-114)

RESULTS

- Median follow-up of the study was 12.1 months (95% CI, 8.8-15.7), and the median overall survival (OS) was 12.6 months (95% CI, 5.8-16.1).

Results concerning *SIRTs*:

- There was no association of sirtuin expression with treatment response or OS of AML patients.
- Expression of sirtuins seems to vary depending on the genetic profile of the disease. In patients with *FLT3* mutations, all sirtuins (*SIRT1-7*) were downregulated, while *wtTP53* was upregulated.
- The significant difference was found in the mRNA expression multiplicity change depending on the presence of *FLT3* mutation for *SIRT7* (FC=0.64, *p*=0.007). The *p*-values were given with Benjamini-Hochberg (BH) correction (Figure 1).

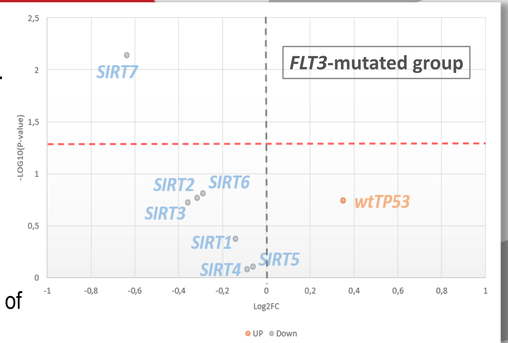


Figure 1. Changes in expression multiplicity of the *SIRT* and *wtTP53* genes in the presence of *FLT3* mutation. Up - higher expression, down - lower expression. The red line indicates the cut-off for *p*-value significance.

Results concerning miRNAs:

- Positive correlation was found between **miR-9-5p** and both *SIRT1* and *SIRT2* (r=0.24, *p*=0.04; r=0.26, *p*=0.02, respectively), and between **miR-34a-5p** and *TP53*, while negative with *SIRT6* (r=0.34, *p*=0.002; r=-0.27, *p*=0.02, respectively).
- **miR-34a-5p** down-regulation was detected in a high-risk group (FC=0.43, *p*=0.05), and an up-regulation in *FLT3*-mutated group (FC=2.64, *p*=0.001).
- In a multivariate Cox regression, **miR-9-5p** negatively affected OS (HR=1.2, 95% CI: 1.05-1.37, *p*=0.006), while **miR-34a-5p** had a significant positive impact on survival (HR=0.76, 95%CI: 0.63-0.92, *p*=0.005) (Figures 2A-B).

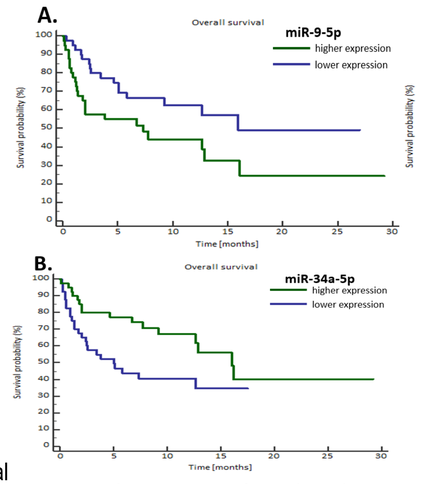


Figure 2. Kaplan-Meier curves for OS depending on miR-9-5p expression (A), and mi-R-34a-5p expression (B); blue line – expression below median, green line – expression above median.

- Clustering was performed, which identified 2 groups of patients depending on the expression of a given miRNA. The most significant differences were seen between sAML and *de novo* patients, and between the *FLT3*-mutated and *FLT3*-wild type groups (Figure 3).

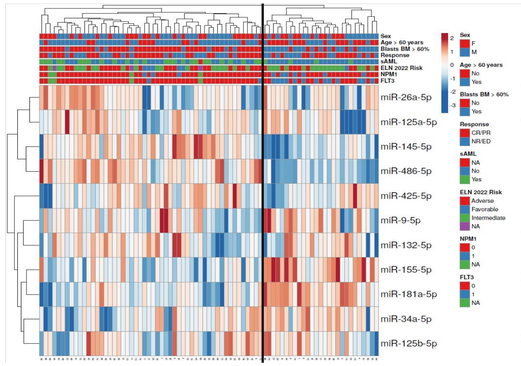


Figure 3. Clustering of miRNA expression according to the selected clinical variables.

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CONCLUSIONS

- Our results indicate **dysregulation of the expression of miRNAs** potentially interacting with sirtuins and *TP53* in AML.
- **miR-9a-5p** and **miR-34a-5p** may act as biomarkers in AML.
- **Sirtuins** expression **did not significantly differ** between the AML risk groups, nor did it affect OS in AML patients.