Expression of Sirtuin Genes and Associated microRNA Affects Prognosis in Patients With Acute Myeloid Leukemia

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Introduction

- **Sirtuins** (SIRTs) have the potential to affect the expression of both tumor suppressors and protooncogenes through histone deacetylation [1].
- **MicroRNAs** (miRNAs) can silence key genes of carcinogenesis including SIRTs [2].
- The impact of SIRTs and associated miRNAs on **acute myeloid leukemia** (AML) is yet to be fully discovered.

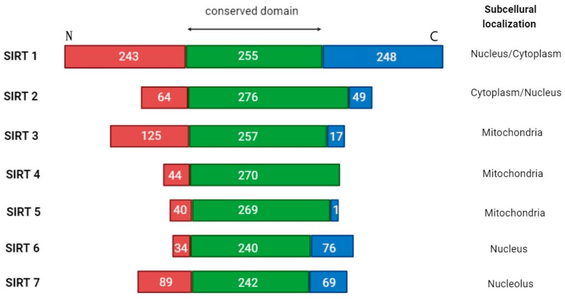


Figure 1. The overall architecture of SIRT1-7 domains [3].

Aim

→ Search for prognostically relevant **SIRTs** and **miRNAs** in AML patients.

Methods

- A prospective study on 98 newly diagnosed AML patients.
- The control group comprised marrow samples from 13 orthopedic patients without hematological malignancies.
- ***SIRT1-7*** and ***TP53*** genes, **14 selected miRNAs**, and reference genes expression was determined in bone marrow using RT-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.
- Median follow-up: **22.8** months (95% CI: 18.6–25.8).

Table 1. Patients' characteristics.

Characteristics	Total
Patients, N	98
Sex, N (%)	F: 42 (43) M: 56 (57)
Age at diagnosis, median (IQR)	65 (55-73)
Blasts % with LAIPs, median (IQR)	47.5 (21-74.5)
BM blasts at diagnosis, median (IQR)	44.5 (24-68)
PB blasts at diagnosis, median (IQR)	17 (3-61)
CBC, median (IQR)	
WBC [G/l]	15 (3-75)
ANC [G/l]	2.7 (0.6-6.5)
Hb [g/dl]	8.9 (7.7-10)
PLT [G/l]	55 (28-105)
ELN2022 risk, N (%)	
favorable	11 (11.6)
intermediate	36 (37.9)
adverse	48 (50.5)
no data	3 (3.1)
Treatment, N (%)	
intensive chemotherapy	38 (38.8)
azacitidine + venetoclax	27 (27.6)
other non-intensive/BSC	33 (33.7)
AlloHSCT	30 (31)

N – number, F – female, M – male, IQR – interquartile range, y – years, LAIPs – leukemia-associated immunophenotypes, BM – bone marrow, PB – peripheral blood, CBC – complete blood count, ELN2022 – European LeukemiaNet 2022, BSC – best supportive care, AlloHSCT – allogeneic hematopoietic stem cells transplantation

Results

- ***SIRT1*** & ***SIRT3*** were up-, while ***SIRT4*** downregulated in AML patients compared to control group (Figure 2).

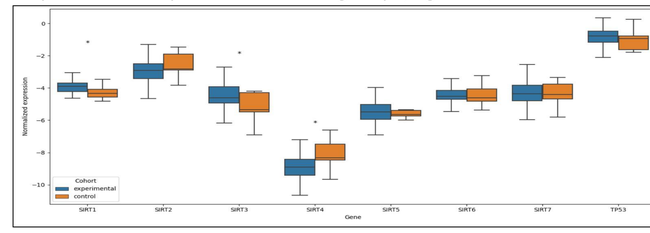


Figure 2. Box & whisker plot. Comparison of *SIRTs* and *TP53*^{wt} normalized genes expression between the study (blue) and control (orange) groups. * p<0.05

- ***SIRT1*** was significantly downregulated in favorable/intermediate vs. adverse ELN2022 risk (p=0.038), while **miR-10a-5p** was upregulated (p<0.001) (Figure 3).

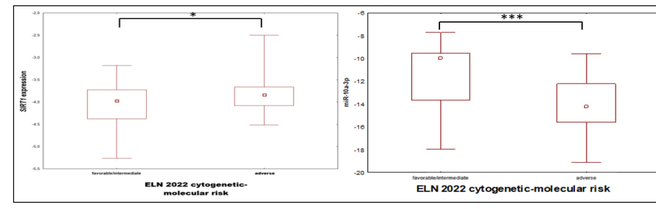


Figure 3. Box & whisker plots. Comparison of *SIRT1* and miR-10a-3p expression between favorable/intermediate vs adverse ELN2022 risk patiens. * p<0.05, *** p<0.001

- All ***SIRTs*** showed **a positive** correlation with each other, but no strong correlation with ***TP53*** was found (Figure 4).

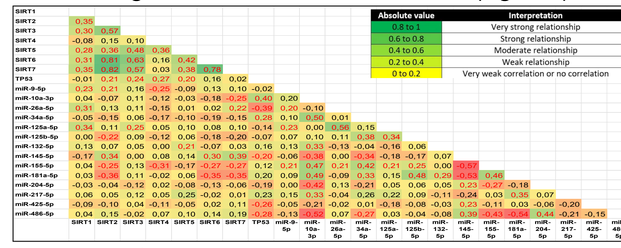


Figure 4. Spearman's correlation between genes tested.

- Median overall survival (OS) in the experimental cohort was **12.9 months** (95% CI: 6.1-17.6), while median event-free survival (EFS) **6.6 months** (95% CI: 43.-9.9).

Table 2 & 3. Multivariable Cox regression assessing *SIRTs* impact for **EFS**.

Variable	HR	95% CI Lower	95% CI Upper	p-value
SIRT6	1.55	1.00	2.40	0.049
Intensive treatment	0.36	0.19	0.71	0.003
Aza+Ven	0.62	0.34	1.15	0.131
Favorable risk	0.65	0.24	1.73	0.388
Intermediate risk	0.87	0.52	1.46	0.592
BM blasts %	1.01	1.00	1.02	0.052

Variable	HR	95% CI Lower	95% CI Upper	p-value
SIRT7	1.48	1.04	2.09	0.028
Intensive treatment	0.40	0.20	0.78	0.008
Aza+Ven	0.62	0.34	1.15	0.130
Favorable risk	0.62	0.23	1.63	0.328
Intermediate risk	0.93	0.55	1.57	0.779
BM blasts %	1.01	1.00	1.02	0.049

Table 4 & 5.. Multivariable Cox regression assessing miRNA impact for **OS**.

Variable	HR	95% CI Lower	95% CI Upper	p-value
miR-9-5p	1.16	1.05	1.29	0.003
Intensive treatment	0.18	0.08	0.39	<0.001
Aza+Ven	0.53	0.27	1.02	0.059
Favorable risk	0.58	0.17	1.97	0.384
Intermediate risk	0.73	0.40	1.33	0.306
BM blasts %	1.01	1.00	1.03	0.061

Variable	HR	95% CI Lower	95% CI Upper	p-value
miR-34a-5p	0.77	0.67	0.89	<0.001
Intensive treatment	0.18	0.08	0.41	<0.001
Aza+Ven	0.62	0.32	1.22	0.167
Favorable risk	0.66	0.19	2.26	0.508
Intermediate risk	0.92	0.50	1.67	0.776
BM blasts %	1.02	1.01	1.03	0.004

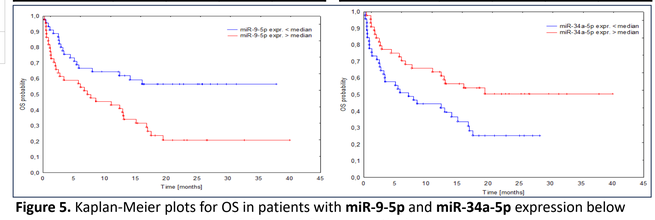


Figure 5. Kaplan-Meier plots for OS in patients with **miR-9-5p** and **miR-34a-5p** expression below median vs above. Log-rank test: p=0.003, p=0.015, respectively.

Acknowledgments

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References

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Conslusions

- Baseline *SIRTs* and related miRNA expression **affects** the prognosis in AML patients.
- No strong correlation between *SIRTs* and *TP53* was found.
- miR-9a-5p and miR-34a-5p emerge as promising **biomarkers** for prognostic stratification in AML.