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The Role Of Genes Related To The Apoptosis And Neddylation Pathway In Patients With Acute Myeloid Leukemia

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INTRODUCTION

The prognosis of patients with acute myeloid leukemia (AML) is related to the genetic profile of the disease. Abnormalities involving the apoptosis and neddylation pathway, responsible for regulated cell death, may contribute to the selection of progressively aggressive clones and disease progression (Figure 1). Therefore, the apoptosis and neddylation pathway is highlighted in hematooncology as important for the search for new targeted molecules.

AIM

Evaluation of the expression and significance of genes regulating apoptosis and neddylation pathway in AML patients.

METHODS

- A prospective study of 86 newly diagnosed AML patients (Table 1).
- The expression of *BIM (BCL2L11), BID, BIK, PUMA (BBC3), NOXA, BAD, BAX, BAK, BCL2, BCLX, MCL1, SMAC/DIABLO, CASP3, CASP7, TP53, NEDD8*, and cullin genes was determined in duplicate in samples from bone marrow.
- Real-Time PCR was carried out using theTaqMan chemistry and the QuantStudio™7 thermal cycler (Applied Biosystems-Thermo Fisher Scientific).
- Normalization was performed by ΔCt = Ct(reference) – Ct(mRNA of interest). The $\Delta\Delta Ct$ method was used to calculate fold changes (FC) in mRNA expression.

Patients, n	86
• female, n (%)	39 (45)
• male, n (%)	47 (55)
Age, median (range)	66 (25-80)
Treatment approach, n (%)	
• intensive	32 (37)
• azacitidine+venetoclax	21 (25)
• non-intensive	33 (38)
Cytogenetic-molecular risk (ELN2022), n (%)	
• no data	5 (6)
• favorable	12 (14)
• intermediate	35 (41)
• adverse	34 (39)
Peripheral blood blasts %, median (IQR)	17 (3-57)
Bone marrow blasts %, median (IQR)	44 (24-68)
WBC G/l, median (IQR)	16(3-73)
ANC G/l, median (IQR)	3 (0.6-6)
Hemoglobin g/dl, median (IQR)	9 (8-10)
Platelets G/l, median (IQR)	54 (28-105)

Table 1. Patients' characteristics.

RESULTS

- The median follow-up was 10.3 months (95% CI: 7.8-14.4). The median OS in the study cohort was 12.9 months (95% CI: 6.7-16.1).
- Uregulation of antiapoptotic genes compared to proapoptotic and neddylation genes (FC=11.0, p<0.001, FC=2.7, p<0.001, respectively) was found.
- In univariate Cox regression analysis, *BIK* expression (HR 1.2, 95%CI: 1.01-1.43, p=0.041), and *TP53*^{wt} expression (HR 0.61, 95%CI: 0.42-0.86, p=0.005) were factors influencing the outcome.
- In the multivariate model for OS, higher expression of *BIK* (HR 1.27, 95%CI: 1.06-1.53, p=0.011) retained its significant negative impact, while *TP53*^{wt} maintained the protective effect on OS (HR 0.56, 95%CI: 0.38-0.87, p=0.008) (Figure 2).
- In high-risk patients, according to ELN2022, significant differences were detected in the change in mRNA expression multiplicity for the proapoptotic genes: *BAK* (FC=0.44, p=0.028), *PUMA (BBC3)* (FC=0.45, p=0.001), *BIM (BCL2L11)* (FC=0.44, p=0.024), and *CUL1* (FC=0.58, p=0.002), whose expressions were downregulated (Figure 3). Therefore, the presence of lower expression of the above-mentioned proapoptotic genes may result in impaired apoptosis in high-risk patients.

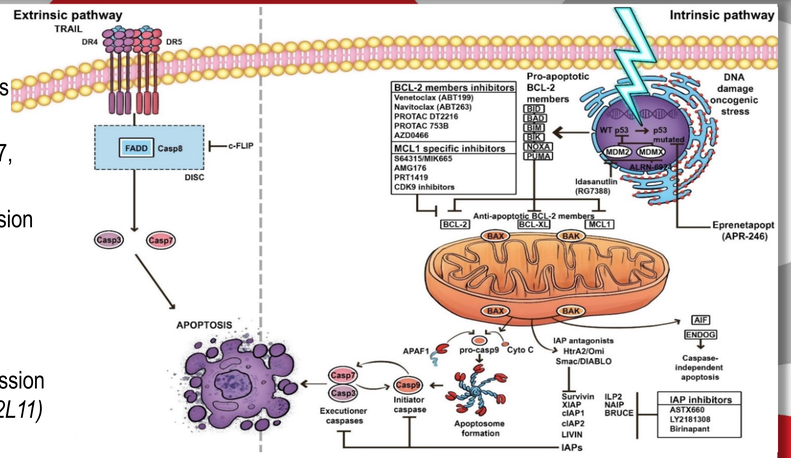


Figure 1. The pathways of apoptosis. Arrows represent activation and T bars represent inhibition.
Krawiec K et al. TargetingApoptosisin AML: Where Do We Stand? Cancers(Basel). 2022 Oct12;14(20):4995.

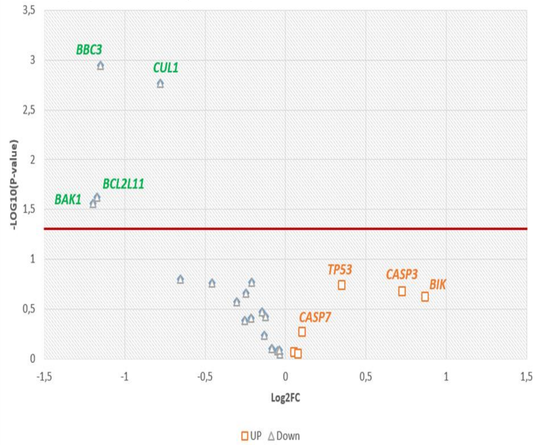


Figure 3. Changes in the expression multiplicity of selected genes in the high-risk group. Up – higher; down - lower expression. The red line indicates the cut-off for *p*-value significance (p<0.05). The p-values are given with Benjamini-Hochberg correction.

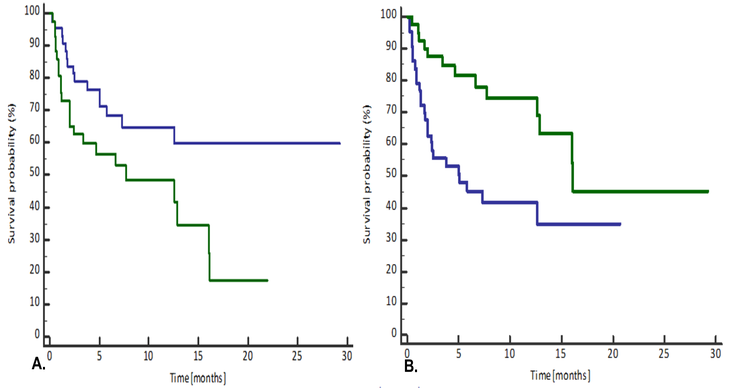


Figure 2. Kaplan-Meier curves for overall survival depending on *BIK* expression (A), and *TP53*^{wt} expression (B); blue line – expression below median, green line – above median.

CONCLUSIONS

This study revealed dysregulation of apoptosis, as well as neddylation genes and indicated that *BIK*, and *TP53*^{wt} may be potential prognostic factors in AML.

Downregulation of certain proapoptotic genes is marked in high-risk patients, which may be reflected in future decisions regarding the choice of targeted treatment.

Our preliminary results did not prove significant differences in the effect of neddylation gene expression levels on the prognosis of AML patients, thus further research is needed.

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