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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

PGK1 Represents a Therapeutic Target for Pediatric Acute Myeloid Leukemia Via Regulating c-Myc/SLC7A5/mTOR Pathway

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Acute myeloid leukemia (AML) is a clonal disorder of hematopoietic stem and progenitor cells characterized by abnormal growth, differentiation blockade, and accumulation of immature myeloblasts, which accounts for 15-20% of pediatric leukemia. Emerging literature has shown that metabolism disorder and their related pathways, play pivotal roles in leukemogenesis and disease progression. Phosphoglycerate kinase 1 (PGK1), an essential enzyme in glycolysis pathway, has been demonstrated to be up-regulated in several malignancies, and was related with tumor stage and poor prognosis. This study aimed to investigate the correlation between PGK1 expression and tumorigenesis of AML, explore the possible underlying mechanism as well as provide a potential therapeutic target for pediatric AML.

The research included 64 AML patients and 10 healthy donors recruited from July, 2012 to June, 2020 in Children's Hospital of Soochow University. Expression of PGK1 mRNA in bone marrow of newly-diagnosed AML patients was higher than normal group ($p<0.001$). Based on median expression of PGK1, 64 patients were divided into PGK1high group (n=32) and PGK1low group (n=32). Patients in PGK1high group had lower complete remission (CR) rate after first course of chemotherapy (65.6% vs 75.0%, p=0.027), overall survival (OS) (53.1%±8.8% vs 84.4%±6.4%, p=0.004) and relapse-free survival (RFS)(63.5%±10.4% vs 90.1%±5.4%, p=0.018). PGK1-knockdown cell lines were constructed to figure out the correlation between PGK1 expression and AML development in vitro. Knockdown of PGK1 inhibited the proliferation, suppressed colony formation and promoted apoptosis of AML cells. In addition, PGK1KD AML cells became more sensitive to Cytarabine (Ara-C) and daunorubicin (DNR). AML model was established by injecting PGK1KD P388-D1 cells of BALB/c mice via tail veins. The results indicated that growth of PGK1KD cells in vivo was significantly suppressed compared to negative control group. Moreover, the median survival time of PGK1 ^{KD} group was shorter (10 days vs 13 days, p=0.035). NG52, a newly reported small molecule kinase inhibitor of PGK1, could block glycolysis pathway by suppressing the kinase activity of PGK1. NG52 promoted MV4-11 and Kasumi-1 apoptosis in a dose-dependant manner, and showed synergism with Ara-C and DNR in MV4-11 and Kasumi-1. To identify downstream targets of PGK1, RNA-sequencing analysis was performed in PGK1 ^{KD} cell lines. SLC7A5 was found to be the most significant down-regulated gene of differentially expressed genes (DEGs). Meanwhile, c-Myc, p-S6 and p-4EBP1 expression were reduced in PGK1 ^{KD} cell lines, indicating that c-Myc/SLC7A5/mTOR pathway was suppressed in PGK1 ^{KD} AML cells. We subsequently established SLC7A5 ^{KD} cells. Inhibition of proliferation and increased apoptosis was found in SLC7A5 ^{KD} cells, which was consistent with the results in PGK1 ^{KD} cells. Expression of c-Myc and activation of mTOR pathway were observably decreased in SLC7A5 ^{KD} cells, which supported the hypothesis above. We found that SLC7A5 expression level was also higher in AML patients than in healthy donors.

In conclusion, our study indicated that PGK1 is a molecular biomarker of poor prognosis and a potential therapeutic target of pediatric AML. Inhibition of PGK1 suppressed progression of AML by regulating c-Myc/SLC7A5/mTOR pathway, providing a promising intervention for AML precision medicine.

Disclosures No relevant conflicts of interest to declare.

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