ELSEVIER

Blood 142 (2023) 5699

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

602.MYELOID ONCOGENESIS: BASIC

Lncrna Rmrp Regulate Mitochondrial Function in Relapsed and Refractory Acute Myeloid Leukemia

Yijing Zhao[1], *Hanfei Guo*[2,3], *Li-Ting Niu*[1], *Yalan Zhou*[1], *Meng Lv, MDPhD*[1]

[1] Peking University Institute of Hematology, Peking University People's Hospital, Beijing, China
[2] Stanford University Medical School, Changchun, China
[3] The First Hospital of Jilin University, Changchun, China

Background: The prognosis of relapsed and refractory acute myeloid leukemia (R/R AML) is extremely poor, primarily due to the development of chemotherapy resistance during the treatment, which leads to its relapse and refractory disease. Extensive studies have established that various dysfunctions in the mitochondria of AML cells play a significant role in promoting chemotherapy resistance and the recurrence of the disease. In our previous investigation, we successfully demonstrated the substantial enrichment of the long non-coding RNA (lncRNA) RMRP in the mitochondria. However, the specific function of RMRP in the mitochondria of R/R AML remains unexplored. The objective of this project is to uncover the function of RMRP in R/R AML mitochondria, aiming to provide innovative insights and a theoretical foundation for surmounting chemotherapy resistance in R/R AML.
Methods: In order to investigate the factors that play a crucial role in R/R AML, we employed mass spectrometry (MS) to conduct a screening of factors associated with AML chemoresistance. We utilized quantitative real-time polymerase chain reaction (RT-qPCR) to assess the expression of lncRNA RMRP in both newly diagnosed AML (ND AML) and R/R AML patients. Furthermore, we knocked down the RMRP expression level by transfection with siRNA-NC and siRNA-RMRP. Additionally, we analyzed the correlation between lncRNA RMRP and mitochondria. To explore the involvement of lncRNA RMRP in regulating mitochondrial function in R/R AML, we performed mitochondrial oxidative phosphorylation metabolic function assays subsequent to the inhibition of lncRNA RMRP. Moreover, Western blot analysis was employed to evaluate the relative protein expression levels in AML cell lines.
Results: We enrolled 23 AML patients (ND AML, n=12; R/R AML, n=11), and the result of MS shows that R/R AML group expressed higher level of mitochondria related protein. The qPCR results showed that R/R AML had higher expression level of RMRP ($P<0.0001$) and mitochondrial genome genes ($P<0.0001$) than ND AML patients. The result of co-cultured of BMSCs and AML suggests that mitochondrial transmission of BMSCs to AML existed in AML patients with high RMRP expression level($P<0.0001$). The Seahorse metabolomics results suggest that RMRP knock down attenuated Spare Respiratory Capacity ($P=0.01$) and Maximal Respiration ($P=0.01$), increased the Cytarabine and Doxorubicin sensitivity, and induced alterations in the mitochondrial CpG1 and CpG9 methylation. Knockdown of RMRP is also accompanied by a decrease in mtDNA copy number ($P=0.10$, 0.42, and 0.0074, respectively for mtDNA gene MT-ND2, MT-ND3, and MT-CO1), and mitochondrial genome transcription. Under transmission electron microscope (TEM), mitochondria were engulfed by lysosomes in RMRP knockdown AML cells. And results of Western blot showed that the autophagy markers such as LC3B, BNIP3L/Nix, NDP52 was upregulated, and SQSTM1, Parkin was downregulated in RMRP knockdown AML cells, suggesting that RMRP may induce mitophagy through the BNIP3L/Nix pathway, PINK1/Parkin pathway, and NDP52 pathway.
Conclusion: In R/R AML, RMRP increased chemotherapy resistance and RMRP high expression was associated with multiple mitochondrial function abnormalities, including altered mitochondrial metabolism, reduced mitophagy, and altered mtDNA epigenetics.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-180453