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Blood 142 (2023) 7141

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Epigenetic Modulation Enhances the Therapeutic Potential of All-Trans Retinoic Acid in Acute Myeloid Leukemia

Lukasz Szymanski, PhD[1], *Rafal Skopek*[2], *Malgorzata Palusinska*[2], *Karolina Maslinska-Gromadka*[2], *Leszek Kraj, MD PhD*[3,2], *Tino Schenk, PhD*[4,5], *Arthur Zelent, PhD*[2]

[1] Institute of Genetics and Animal Biotechnology, Polish Academy of Sciences, Magdalenka, Poland
[2] Department of Molecular Biology, Institute of Genetics and Animal Biotechnology, Polish Academy of Sciences, Magdalenka, Poland
[3] Department of Oncology, Medical University of Warsaw, Warsaw, Poland
[4] Department of Hematology and Oncology, University Hospital, Jena, Germany
[5] Institute of Molecular Cell Biology, Center for Molecular Biomedicine Jena (CMB), Jena University Hospital, Jena, Germany

Epigenetic dysregulation has been strongly associated with the development and progression of acute myeloid leukemia (AML). While all-trans retinoic acid (ATRA), a derivative of vitamin A, has demonstrated significant anti-cancer effects in acute promyelocytic leukemia (APL-AML), its clinical efficacy in non-APL AMLs has been limited. This limited response can be attributed, in part, to the epigenetic silencing of genes targeted by or involved in the ATRA pathway, rendering them unresponsive to the drug. Consequently, our research aims to overcome the epigenetic barriers in AML by combining ATRA with small molecules that possess epigenetic modulating properties.

To investigate the activation of the retinoic acid pathway in response to ATRA and a library of over 650 small molecules with epigenetic activity, we transduced HEK-293 cells with the p-GreenFire-RARE-Tk-Luc reporter construct. Through the screening process, we have identified 11 compounds that show promise as potential candidates for combination therapy with ATRA in non-APL AML. Notably, when combined with ATRA, two specific compounds, a dual PI3K HDAC inhibitor, and a pan-PKC inhibitor, demonstrated a significant 4-5 fold increase in RARE activity, indicating a synergistic effect.

To determine the impact of selected compounds on the functional level, we evaluated the viability, differentiation, and phosphorylation status of ERK1/2, AKT1, MAPK9, p38, and MAPK9 in various cell lines, including HL-60, KG1a, BMNC, and primary MSC and AML cells. The dual PI3K HDAC inhibitor and a pan-PKC inhibitor were noncytotoxic to HL60, BMNC, and primary MSC. Interestingly, dual PI3K HDAC inhibitor with and without ATRA reduced the viability of KG1α by more than 95%. Moreover, dual PI3K HDAC inhibitor and a pan-PKC inhibitor, when combined with ATRA, lead to a 2-3 fold increase in the differentiation of HL60 cells and a 2-4 fold increase in the differentiation of AML cells *ex vivo* compared to ATRA in combination with the LSD1 inhibitor TCP (treatment control protocol) and untreated cells from AML subtypes M1, M2, and M4. PI3K HDAC inhibitor combined with ATRA significantly reduced p-MAPK and p-p38 levels while increasing the phosphorylation of p53 in HL-60 cells. Furthermore, RNA sequencing and chromatin profiling by Cleavage Under Targets and Tagmentation (CUT&Tag) were performed to gain additional insights into the molecular mechanisms involved.

Based on obtained results, the combination of ATRA with specific dual PI3K HDAC and pan-PKC inhibitors holds promise as a potential therapeutic approach for AML. Nevertheless, further investigations, including studies utilizing patient-derived xenograft models, are warranted to validate the efficacy and feasibility of this proposed treatment strategy.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-174217