ELSEVIER

Blood 142 (2023) 5706

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

602.MYELOID ONCOGENESIS: BASIC

Retinoic Acid and Ascorbate Remodel the Epigenome of Leukemia Cells to Improve Therapeutic Efficacy By Enhancing TET Activity

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Ten-eleven translocation (TET) enzymes are commonly mutated in leukemia, leading to aberrant DNA methylation and impaired hydroxymethylation. All-trans retinoic acid (ATRA) is a vitamin A derivative and cofactor of retinoic acid receptors (RARs) which, in combination with arsenic trioxide, can curatively treat acute promyelocytic leukemia. ATRA has also been shown to upregulate expression of *Tet2* and *Tet3* in murine embryonic stem cells, and retinol and ascorbic acid (vitamin C) have been shown to enhance pluripotent stem cell reprogramming through increasing hydroxymethylcytosine and promoting DNA demethylation. Our previous work has demonstrated ascorbate can slow disease progression *in vivo* and, combined with the PARP inhibitor Olaparib, promote cell cycle dysregulation and induce cellular differentiation in acute myeloid leukemia (AML) models both *in vitro* and *in vivo*.

Here, we show ATRA can induce TET2 and/or TET3 expression in AML cells, and, combined with ascorbate, increase genome-wide oxidized methylcytosine in a TET-dependent manner. Combination treatment with ATRA and ascorbate also induces transcriptional reprogramming, leading to upregulation of DNA repair genes and pathways leading to increased expression of myeloid differentiation markers. Additionally, we observe chromatin remodeling associated with an enrichment for ETS motifs including genes and regions regulated by the transcription factor PU.1, an essential modulator of hematopoietic cell fate. We also show enrichment of retinoic acid receptor A (RARA) at the *TET2* locus and at several RAR elements in response to ATRA in AML cells. Using very low dose ascorbate and ATRA, we show that the combination treatment can enhance the efficacy of Olaparib and Venetoclax to alter the cell cycle, promote differentiation, and induce apoptosis of AML cells. These data demonstrate the potential for ATRA and ascorbate to increase TET activity and drive myeloid differentiation and death of AML cells that can be exploited as an adjuvant therapy for the treatment leukemia.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-189774