Low HOX gene expression in PML-RAR-positive leukemia results from suppressed histone demethylation

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Abstract

Homeobox (HOX) genes are frequently dysregulated in leukemia. Previous studies have shown that aberrant HOX gene expression accompanies leukemogenesis and affects disease progression and leukemia patient survival. Patients with acute myeloid leukemia (AML) bearing PML-RARα fusion gene have distinct HOX gene signature in comparison to other subtypes of AML patients, although the mechanism of transcription regulation is not completely understood. We previously found an association between the mRNA levels of HOX genes and those of the histone demethylases JMJD3 and UTX in PML-RARα-positive leukemia patients. Here, we demonstrate that the release of the PML-RARα-mediated block in PML-RARα-positive myeloid leukemia cells increased both JMJD3 and HOX gene expression, while inhibition of JMJD3 using the specific inhibitor GSK-J4 reversed the effect. This effect was driven specifically through PML-RARα fusion protein since
changes did not occur in cells with mutated RARα and was independent of
differentiation. We confirmed that gene expression levels were inversely
correlated with alterations in H3K27me3 histone marks localized at HOX gene
promoters. Furthermore, data from chromatin immunoprecipitation followed by
sequencing broaden a list of clustered HOX genes regulated by JMJD3 in PML-
RARα-positive leukemic cells. Interestingly, the combination of GSK-J4 and all-
trans retinoic acid (ATRA) significantly increased PML-RARα-positive cell apoptosis
compared with ATRA treatment alone. This effect was also observed in ATRA-
resistant NB4 clones, which may provide a new therapeutic opportunity for
patients with acute promyelocytic leukemia (APL) resistant to current treatment.
The results of our study reveal the mechanism of HOX gene expression regulation
and contribute to our understanding of APL pathogenesis.


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