(PS1962) COMBINED TARGETING OF KDM4 HISTONE DEMETHYLASES REDUCES JAK2V617F-DRIVEN MYELOPROLIFERATION

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background

Expression of the histone demethylase KDM4C is increased in patients with myeloproliferative neoplasms (MPN) and acute myeloid leukemia (AML). KDM4C belongs to the large KDM4 protein family and catalyzes the demethylation of mono-, di-, and trimethylated histones H3 at lysine 9 and 36 (H3K9 and H3K36). Although KDM4C has been shown to mediate a functional dependency in JAK2-mutant neoplasms, redundancy among KDM4 family members limits the therapeutic potential of targeting KDM4C alone.

Aims

In this study we tested the hypothesis that combined targeting of two KDM4 histone demethylases attenuates JAK2^{V617F}-driven myeloproliferation.

Methods

We lentivirally depleted KDM4A and KDM4C, individually and in combination, in three JAK2^{V617F}-mutant cell lines UKE1, SET2, and HEL, and assessed cell proliferation and apoptosis. In addition, we knocked down KDM4A and KDM4C in JAK2^{V617F} knock-in mice and evaluated disease progression by peripheral blood counts, spleen weight, and flow-cytometric analysis. Finally, we tested pharmacological KDM4 inhibition, both *in vitro* and *in vivo*. To gain mechanistic insight into KDM4A and KDM4C function, we performed ChIP-seq, RNA-seq, and ATAC-seq in KDM4A- and KDM4C-depleted HEL cells, enabling integrated multi-omics analyses.

Results

Combined knockdown of KDM4A and KDM4C effectively reduced proliferation of JAK2^{V617F}-mutant UKE1, SET2, and HEL cells compared to control cells by increasing apoptosis. Similar results were observed in the JAK2^{V617F} knock-in mouse model, in which combined knockdown of KDM4A and KDM4C significantly reduced leukocytosis, thrombocytosis, and splenomegaly. Pharmacological inhibition with the KDM4C-specific inhibitor SD70 was less effective than treatment with the KDM4 pan-inhibitor TACH101. The latter both effectively attenuated JAK2^{V617F}-driven myeloproliferation *in vitro*, and reduced leukemic burden in a HEL Rag2$^{-/-}$ γc$^{-/-}$ xenograft mouse model. RNA-seq and ATAC-seq analyses in HEL cells revealed that combined knockdown of KDM4A and KDM4C synergistically reduced gene expression of proliferation-associated genes, including those involved in STAT, BCL6 and PAX3 transcription factor signaling. Moreover, integration of the RNA- and ATAC-seq data with our ChIP-seq analyses showed that KDM4A and KDM4C synergistically mediate their pro-leukemic effects through regulation of PIM1, NQO2, and PTP4A3.

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Summary/Conclusion

Combined targeting of KDM4 histone demethylases effectively reduced JAK2^{V617F}-driven myeloproliferation *in vitro* and *in vivo*. Therefore, pharmacological inhibition with the KDM4 pan-inhibitor TACH101, which is currently being tested in a phase II clinical trial for advanced solid tumors, represents a promising therapeutic approach for JAK2^{V617F}-mutated myeloid malignancies.

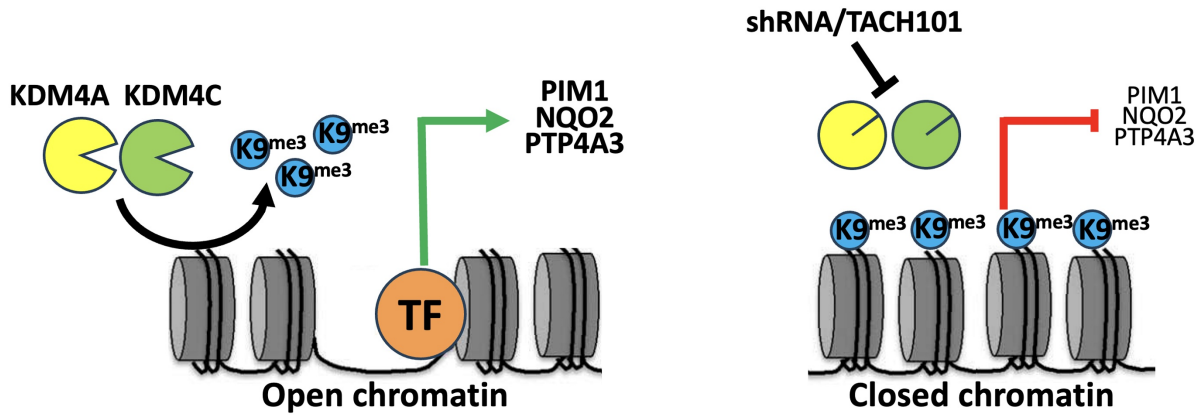


Figure 1. Targeting KDM4 histone demethylases reduces leukemic signaling in the JAK2^{V617F} context. KDM4 histone demethylases promote chromatin opening at the PIM1, NQO2, and PTP4A3 loci thereby contributing to pro-leukemic signaling. In contrast, knockdown or pharmacologic inhibition of KDM4 demethylases lead to chromatin closure and reduced expression of these pro-leukemic genes, ultimately resulting in increased apoptosis of malignant cells.

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