NOVEL COMBINATION OF CLINICAL MENIN INHIBITOR ZIFTOMENIB AND THE NUCLEAR EXPORT INHIBITOR SELINEXOR SYNERGISTICALLY INHIBIT MLL-R AML

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INTRODUCTION

- Menin is a scaffold protein that tethers histone-lysine-N-methyltransferase MLL1 (KMT2A) to chromatin by binding to the menin-binding domain (MBD) of KMT2A.
- The N-terminus of the KMT2A gene recombines with a range of genes to form more than 60 fusion proteins (FPs) in MLL-rearranged (MLL-R) AML.
- In myeloid progenitor cells, the menin-KMT2A complex modulates the expression of the leukemogenic homeobox A9 (HOX A9) gene, as well as its co-factor, MEL1.
- Menin inhibitors evict menin from the chromatin and reduce KMT2A and KMT2A-PP binding to their targets in MLL-R leukemia, breaking the differentiation block and inducing tumor regression.
- Aberrant nuclear export is common in cancer, resulting in anomalous localization of various proteins, including tumor suppressor proteins (TSPs).
- Blocking XPO1-CRIM using a selective inhibitor of nuclear export (SINE) compound selemin has been shown to have robust anti-leukemia activity.
- In the present study, we hypothesized that inhibition of menin and nuclear export would synergistically suppress AML cell proliferation and survival.
- We have used the clinical-stage menin inhibitor ziftomenib and selemin to simultaneously target menin-KMT2A protein-protein interactions and nuclear export.

METHODS

- To assess growth inhibition, an ATP-based cell proliferation assay was used.
- Combination synergy was determined using CalcuSyn Version 2.0 synergy software.
- Stem-like progenitor cells were isolated using the StemSpan CD34+ expansion kit (StemCell Tech).
- Colony formation efficiency was determined using a MethoCult assay (StemCell Tech).
- Gene and protein expression and cell death were detected using quantitative real-time PCR, western blotting, and annexin-V/PI fluorescence-activated cell sorting, respectively.

RESULTS

- The clinical candidate ziftomenib, in combination with selemin, synergistically inhibited the growth of MLL-R AML cells (MV4-11, MOLM13, and SEM; C1 = 1) without inducing toxicity to normal cells.
- Enhanced suppression of menin expression by the combination of ziftomenib and selemin suggests molecular basis for the synergy between these two compounds.
- The topmost upregulated gene TME1355B and downregulated gene CENPK was further investigated for their role in the synergy.
- These preclinical findings demonstrate that simultaneous inhibition of the menin-KMT2A interaction and nuclear export could be a viable strategy for the treatment of MLL-R AML.

CONCLUSIONS

- The clinical candidate ziftomenib, in combination with selemin, synergistically inhibited the growth of MLL-R AML cells (MV4-11, MOLM13, and SEM; C1 < 1) without inducing toxicity to normal cells.
- Enhanced suppression of menin expression by the combination of ziftomenib and selemin suggests molecular basis for the synergy between these two compounds.
- The topmost upregulated gene TME1355B and downregulated gene CENPK was further investigated for their role in the synergy.
- These preclinical findings demonstrate that simultaneous inhibition of the menin-KMT2A interaction and nuclear export could be a viable strategy for the treatment of MLL-R AML.

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