Contribution ID: **36** Type: **TALK**

Synergistic Efficacy from Menin and PRMT5 Co-Inhibition against NPM1 Mutated and KMT2A-Rearranged Leukemia

Menin inhibitors represent a novel class of targeted therapies for acute myeloid leukemia (AML), particularly in patients with *KMT2A* rearrangements (*KMT2A*-r) and *NPM1* mutations (*NPM1*mut). These inhibitors disrupt the Menin-KMT2A complex, silencing leukemogenic gene expression, promoting differentiation, and leading to disease eradication. However, the precise mechanisms by which the Menin-KMT2A complex regulates leukemic gene expression remain incompletely understood. We hypothesized that the Menin-KMT2A complex may recruit additional protein partners to the complex that might contribute to leukemogenesis and could represent druggable targets. Using a high-resolution CRISPR/Cas9 domain scan of *KMT2A* and *MEN1*, we identified PRMT5, a putative binding site in Menin, as a strong dependency in NPM1mut AML cells. The arginine methyltransferase PRMT5 has been reported to interact with Menin, is implicated in the pathogenesis of myeloid neoplasms, and represents a promising target. CRISPR/Cas9-mediated PRMT5 knockout was lethal to *NPM1*mut AML cells and PRMT5 inhibition suppressed viability of various AML cells. We demonstrated that PRMT5 inhibition synergizes with Menin inhibition to reduce cell viability in *KMT2A*-r and *NPM1*mut AML cell lines and patient-derived *NPM1*mut AML cells. This combination induced differentiation, triggered apoptosis *in vitro* and reduced leukemia burden, and prolonged survival significantly in an *NPM1*mut AML xenograft model. RNAseq analysis revealed that Menin and PRMT5 co-inhibition suppresses Menin-KMT2A target genes and reported PRMT5 targets, including those regulated by the E2F and ATF4 transcription factors. Integration of these transcriptional data with CUT&RUN and ChIPseq analyses revealed chromatin co-occupancy of Menin and PRMT5 on a subset of the Menin-KMT2A targets loci as well as at the loci of E2F/ATF4-regulated genes. These results are consistent with a suppression of complementary pathways as a potential mechanism of drug synergy. Our findings provide a strong rationale for combining Menin and PRMT5 inhibitors in *NPM1*mut or *KMT2A*-r AML, a drug regimen already available for clinical testing.

Research type

Translational research

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Session Classification: Short talks #1