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ORAL ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Decoding the Epigenetic Drivers of Menin-MLL Inhibitor Resistance in KMT2A-Rearranged Acute Myeloid Leukemia

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Menin inhibitors that disrupt Menin-MLL interaction are candidate therapeutic agents for several acute myeloid leukemia (AML) subtypes such as KMT2A rearrangement and NPM1 mutation. Several Menin inhibitors are currently being assessed in clinical trials and have demonstrated promising initial results. However, the development of both innate and acquired resistance to Menin inhibitors could limit their therapeutic potential. While studies have found that around 40% of these resistance cases can be traced back to mutations in the Menin gene, the Menin gene remains unaltered in other majorities, suggesting the presence of other mechanisms driving resistance.

Here, we developed a unique chromatin-focused CRISPR knockout library, named Advanced Catalogue of Epigenetic Regulators (ACER). The ACER library contains approximately 800 traditional and newly-predicted epigenetic regulators using epigenetic network analyses that integrated publicly available gene codependency (DepMap) and protein-protein interaction data (BioPlex) (Figure A). To understand the chromatin mechanisms responsible for Menin-MLL inhibition resistance, we employed the ACER library for CRISPR screen in the context of Menin inhibition. Notably, our screen identified non-canonical polycomb repressive complex PRC1.1 (PCGF1, BCOR, and RYBP) and PRC2.2 (EZH2, SUZ12, and EED) among the top hits that conferred resistance to MLL-Menin inhibition upon gene depletion (Figure B). Consistent with our screen results, the depletion of PRC1.1 components led to a markedly increase in IC50 values when treated with the Menin inhibitor VTP50469 in both human and murine KMT2A-rearranged cell models. While treatment with Menin inhibitors typically induces cellular differentiation in leukemia cells, depletion of PRC1.1 genes resulted in an almost complete blockage in this differentiation process.

Menin inhibitors evict Menin from chromatin and repress the expression levels of Menin-MLL target genes like MEIS1, PBX3, and MEF2C. Strikingly, our ChIP-seq and RNA-seq data indicatethat the loss of PRC1.1 components doesn't impact Menin's displacement from chromatin or the repression of KMT2A target genes by the Menin inhibitor. This is consistent with recent data from phase I clinical trial of revumenib (SNDX-5613) and preclinical patient derived xenograft models, wherein the Menin inhibitor persistently inhibitedkey KMT2A targets, even in resistant samples. These findings highlightthe possibility that resistance to Menin inhibition arising from mechanisms independent of canonical KMT2A target genes. Importantly, our unbiased transcriptomic analysis revealed that MYC signatures as the most affected pathway in PRC1.1-depleted cells following Menin inhibition. Furthermore, we show that both the transcriptionally active Menin-MLL and the repressive PRC1.1 complexes coexist at the MYC promoter, and the interplay between these two complexes determines MYC transcription output in AML. Moreover, enforced expression of MYC leads to resistance against Menin inhibition, while genetic and pharmacologic targeting MYC in PRC1.1 deficient cells rescued the resistance to Menin inhibition.

Finally, in our RNA-seq datasets, we observed a diminished monocyte differentiation signature after PRC1.1 depletion. Considering AML cells with monocytic signatures, typically seen in KMT2A-rearranged AML, often exhibit resistance to BCL-2 inhibitor venetoclax, we hypothesized that AML cells lacking PRC1.1 could be more susceptible to BCL2 inhibition. This was confirmed in our ACER library screen with venetoclax treatment, where the PRC1.1 components PCGF1 and BCOR stood out

as top epigenetic factors rendering drug sensitivity. Our subsequent studies using murine AML models and human primary samples further validated that PRC1.1-deficient AML cells are markedly sensitive to venetoclax. Furthermore, we show that venetoclax can be employed to overcome the resistance to Menin-MLL inhibition.
In summary, our study identifiesthe non-canonical PRC1.1 as a key epigenetic driver of Menin-MLL resistance through a KMT2A target gene-independent mechanism which involves aberrant activation of MYC. We have further provided evidence that AML cells with loss of PRC1.1 are hypersensitive to BCL-2 inhibitor Venetoclax, opening a new therapeutic avenue for tackling Menin-resistant AMLs driven by polycomb inactivation.

Disclosures No relevant conflicts of interest to declare.

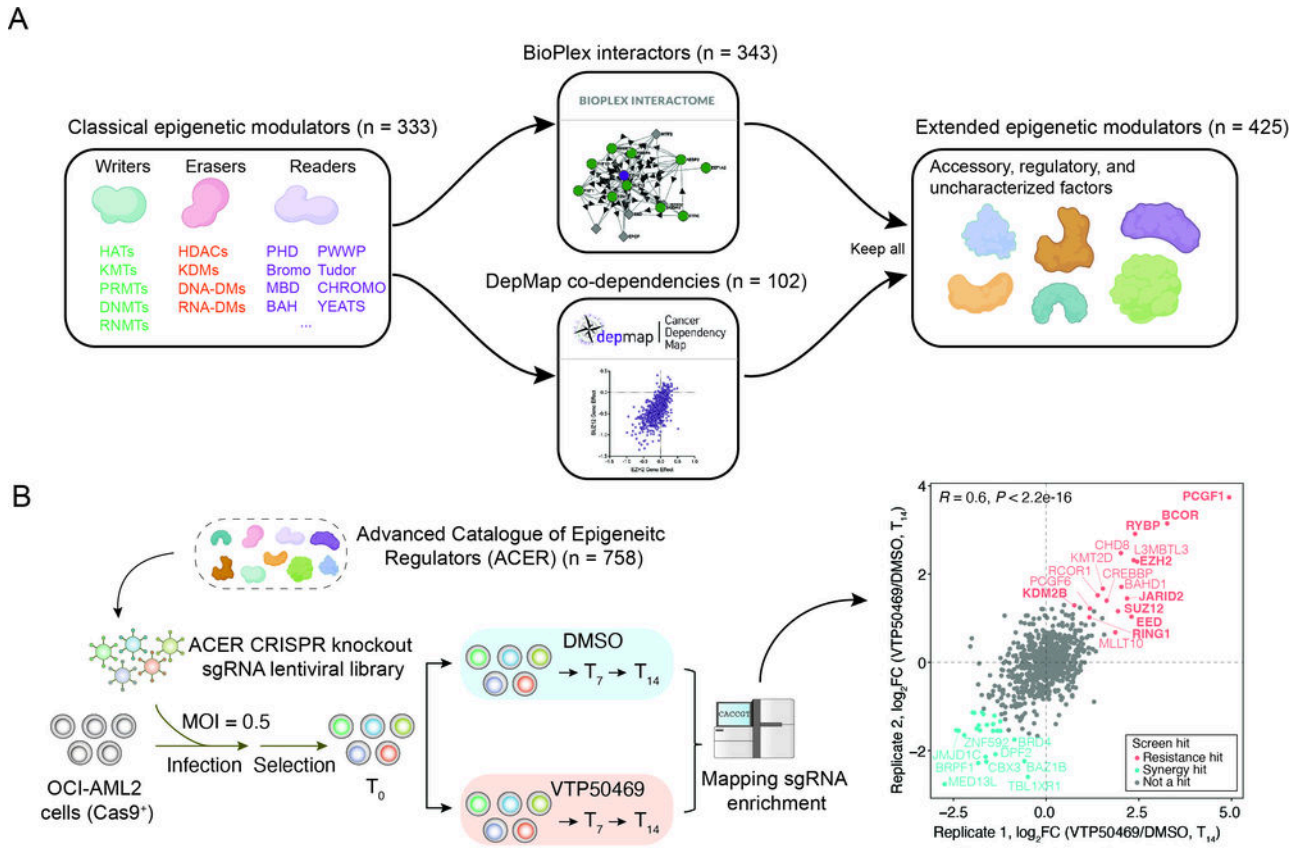

Figure 1

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