(PF431) METABOLIC REWIRING VIA METFORMIN RESTORES VENETOCLAX SENSITIVITY IN AML

Topic: 03. Acute myeloid leukemia - Biology & translational research

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Background

Venetoclax (VEN)–based therapy has significantly improved outcomes in acute myeloid leukemia (AML). However, resistance frequently emerges and limits long-term efficacy. Increasing evidence suggests that metabolic and epigenetic reprogramming contributes to drug resistance, yet the mechanistic interplay between these processes in VEN-resistant (VEN-R) AML remains poorly understood.

Aims

To elucidate the metabolic–epigenetic mechanisms underlying VEN resistance in AML and to identify therapeutic strategies capable of restoring antileukemia efficacy.

Methods

VEN-R AML cell lines (MOLM13, MOLM14, HL-60, KG-1) were established through continuous VEN exposure. Metabolomic and transcriptomic profiling was performed in parental and VEN-R lines. VEN-R MOLM14 cells were treated with metformin (MET) to assess metabolic restoration. Protein expression was assessed by Western blot and flow cytometry. The DNMT1-targeting hypomethylating agent OR-2100 (decitabine prodrug; jRCT2071220035) was evaluated alone or in combination with MET. Public RNA-sequencing datasets (GSE270621, GSE183329, GSE97346) were analyzed for clinical and transcriptional/epigenetic validations.

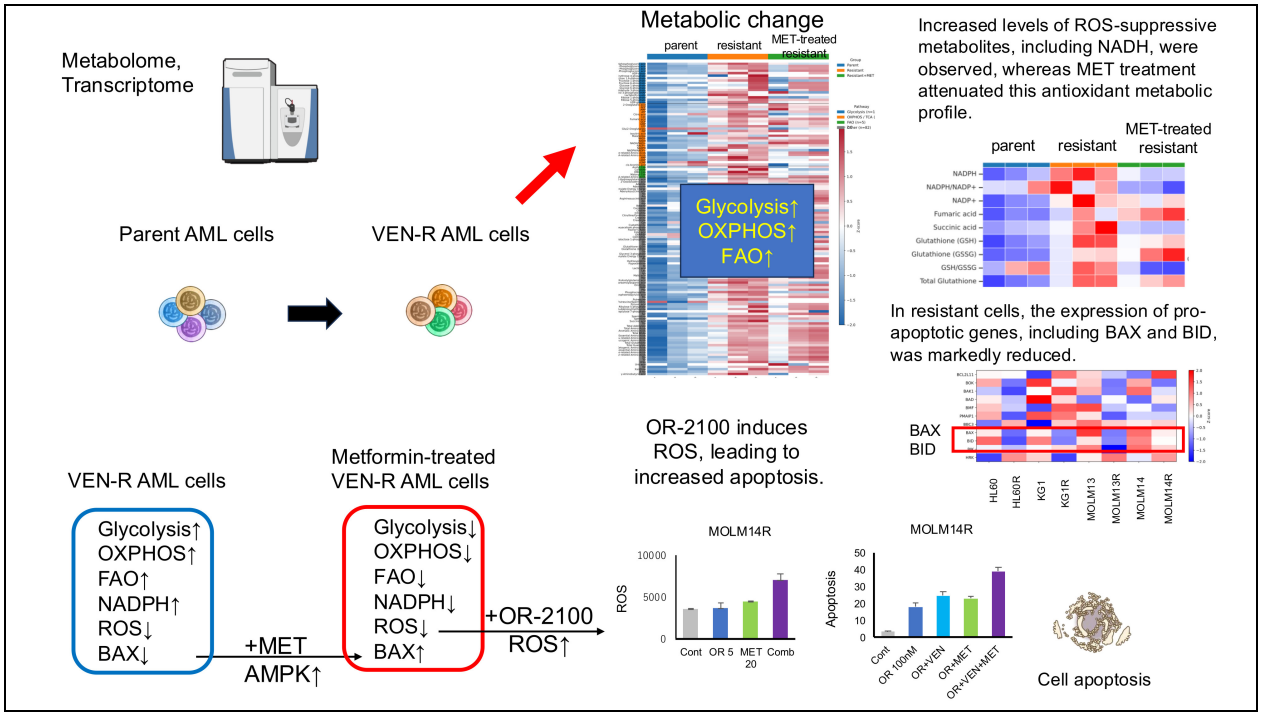
Results

VEN-R cells exhibited high basal MCL1 expression, which decreased under glucose-free conditions, indicating that glucose-dependent metabolic reprogramming supports MCL1 overexpression in VEN-R AML cells. Metabolome showed that VEN-R cells demonstrated coordinated activation of glycolysis, fatty acid oxidation (FAO), and oxidative phosphorylation (OXPHOS), generating a reductive intracellular state conducive to resistance. Consistent with these observations, two independent patient-derived RNA-seq datasets confirmed similar upregulation of these metabolic pathways in clinically VEN-R AML samples. Furthermore, metabolites involved in ROS scavenging, including NADPH, fumarate, and glutathione, were increased in the resistant cells. Consistent with these metabolic alterations, flow cytometric analysis demonstrated a reduction in intracellular ROS levels in the resistant cells. Comparative RNA sequencing analyses between parental and resistant cells in MOLM13, MOLM14, HL60, and KG1a consistently showed lower BAX expression in the resistant cells. These findings suggest that resistant cells evade VEN-induced cell death by suppressing BAX expression, at least in part through attenuation of intracellular ROS levels. Based on RNA sequencing data (GSE97346), MET treatment in MOLM14 and HL60 cells downregulated glycolysis, OXPHOS, and FAO, indicating MET can reprogram aberrant cellular metabolism in VEN-R AML cells. Furthermore, MET induced up-regulation of the AMPK pathway. Western blot showed MET induced a BAX upregulation via pAMPK up-regulation. Combined MET and VEN treatment markedly enhanced apoptosis, indicating that MET overcame VEN resistance. Moreover, triple therapy with the DNA hypomethylating agent OR-2100, MET and VEN substantially promoted cell apoptosis through increased ROS induction.

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Summary/Conclusion

VEN resistance in AML is primarily driven by upregulation of glycolysis, FAO, and OXPHOS that maintain MCL1 and suppress BAX through ROS attenuation. MET reprograms metabolic rewiring leading to downregulation of MCL1 and upregulation of BAX. The combination treatment of VEN, MET, and OR-2100 may constitute a clinically feasible metabolic-priming approach.



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