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Acute Leukemias

PU1 AS MASTER REGULATOR OF AML VENETOCLAX RESISTANCE

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Introduction: Venetoclax-based therapies have improved outcomes in acute myeloid leukemia (AML), especially in elderly or unfit patients. However, resistance remains a major limitation. Recent studies suggest that monocytic differentiation (FAB M4/M5) is associated with reduced venetoclax sensitivity due to lower BCL-2 dependence and increased reliance on alternative anti-apoptotic proteins. This study investigates the link between monocytic differentiation and venetoclax resistance in AML.

Methods: AML cell lines were used to assess the relationship between monocytic differentiation and venetoclax resistance. Differentiation was induced with PMA, followed by Resazurin-based viability assays. FACS analysis confirmed differentiation status, and RT-PCR was used to examine genes linked to venetoclax resistance. Transcriptomic re-analysis of venetoclax-resistant monocytic AML patients identified PU.1 as a transcription factor strongly upregulated in resistant cases. PU.1 nuclear translocation was evaluated by immunofluorescence, and ERK activation (a PU.1 regulator) was confirmed by western blot. *In vitro* results were validated via re-analysis of the BeatAML dataset.

Results: A revised PCR-based MacScore (rMacScore) correlated with venetoclax resistance in AML cell lines. PMA-induced monocytic differentiation of THP-1, HL-60, and NB4 cells led to increased venetoclax resistance and decreased rMacScore, supporting a link between monocytic phenotype and resistance. Pre-treatment with sublethal venetoclax similarly reduced rMacScore, modestly increased resistance, and upregulated monocytic markers, suggesting venetoclax can promote monocytic differentiation and self-resistance.

Transcriptomic re-analysis of venetoclax-resistant monocytic AML patients identified PU.1 as a top upregulated transcription factor. Both PMA-induced differentiation and venetoclax treatment activated PU.1 via ERK phosphorylation, leading to nuclear translocation. MEK inhibition with trametinib blocked PU.1 activation, confirming the role of ERK signaling. BeatAML data validated these findings, with rMacScore correlating with venetoclax resistance, FAB M4/M5 subtypes, and PU.1 expression.

Conclusions: Our study confirms the MacScore as a surrogate marker of venetoclax resistance and supports its application in RT-PCR–based monitoring. We identify monocytic differentiation as a key driver of resistance and PU.1 as a central regulator. Venetoclax itself promotes mild monocytic differentiation and PU.1 activation, contributing to self-resistance. ERK inhibition with trametinib prevents PU.1 activation, offering a potential therapeutic strategy. BeatAML data corroborated our *in vitro* findings.