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Acute Leukemias

AUTOPHAGY INHIBITION POTENTIATES MIDOSTAURIN EFFICACY IN FLT3-MUTATED ACUTE MYELOID LEUKEMIA UNDER HYPOXIC CONDITIONS

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Mutations in FMS-like tyrosine kinase 3 (FLT3) are found in about 30% of newly diagnosed acute myeloid leukemia (AML) patients and confer poor prognosis. Despite the multikinase inhibitor midostaurin (mido) has improved outcomes for FLT3-mutated (FLT3m) AML, relapses occur in over 40% of cases. The hypoxic bone marrow niche provides a protective environment for leukemic stem cells (LSCs), playing a crucial role in the development of resistance mechanisms. We investigated in vitro how hypoxia impacts on the efficacy of mido on FLT3m AML cells and how therapeutic efficacy of mido can be enhanced.

Mido and/or chloroquine (Cq) were administered as single agents and in combination to FLT3-ITD AML cell lines MV-4-11 and MOLM-13 under normoxic (20% O2) and hypoxic (1% O2) conditions. Apoptosis induction, cell proliferation, metabolic activity, gene expression changes and protein expression were evaluated after 24 and 48 hours of exposure to the drugs.

In FLT3-mutated AML cell lines, the main metabolic alteration due to mido treatment was a reduction in glutamate levels. Gene expression analysis revealed lower transcriptional levels of genes encoding enzymes involved in non-essential amino acid synthesis and m-TORC1 signalling suppression. These results suggests that autophagy was promoted as a potential survival mechanism to evade the antileukemic effects of mido. Co-treatment with the autophagy inhibitor Cq enhanced apoptosis and reduced expression of phosphorylated FLT3 and autophagy-related proteins (BECLIN, ATG3, LC3I-I-I) under both normoxic and hypoxic conditions. According to autophagy inhibition, the combination reversed Mido-induced mTORC1 suppression and ultimately activated DNA repair pathways, including ATM and p53 signalling.

Our data suggest that Cq might contribute to eradicate FLT3m cells in hypoxia. The association of mido with autophagy inhibitors could be evaluated as a therapeutic strategy to overcome LSC resistance in the hypoxic niche.

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