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Acute Leukemias

TARGETING THE B3-ADRENERGIC–FERROPTOTIC AXIS UNCOVERS A METABOLIC VULNERABILITY IN T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Introduction: Beta-adrenergic receptors (β-ARs) contribute to the pathogenesis of various malignancies. Emerging evidence highlights the therapeutic potential of the selective β3-AR antagonist SR59230A (SR), which induces apoptosis, particularly under hypoxic conditions, and modulates lipid metabolism and glucose homeostasis in cancer cells. Elevated β3-AR expression in T-ALL suggests a promising therapeutic target for resistant leukemia subsets. Methods. β3-AR expression was assessed in normal peripheral blood mononuclear cells (PBMCs) and T-ALL cell models via flow cytometry. Metabolic profiling was performed using the Seahorse XFe Analyzer, and cytotoxicity was evaluated with MTS assay. RNA sequencing (RNA-seq) was conducted to investigate transcriptomic changes. Ferroptosis and metabolic markers were analyzed by Western blot and immunofluorescence. Ferritin and iron levels were quantified in cell models and patient hematopoietic populations using the Cobas8000 system. The selectivity of SR was evaluated in PBMCs from healthy donors. In one T-ALL patient, metabolic and transcriptomic changes were assessed following SR administration. Additionally, the combinatorial effect of SR with hyaluronan (via CD44 receptor) was tested.

Results: T-ALL cell lines showed high β3-AR expression (Molt-3: 40%; Molt-4: 63%; CCRF-CEM: 75%) versus PBMCs (4–7%). SR reduced T-ALL cell viability in a dose-dependent manner, while PBMCs showed no significant cytotoxicity or metabolic alterations, indicating leukemia-specific effects. Seahorse analysis revealed pronounced reductions in mitochondrial and glycolytic metabolism after 24 h of 15 µM SR. In a treated patient, mitochondrial metabolism decreased and RNA-seq showed increased expression of ferroptosis-related genes, consistent with reduced fatty acid oxidation and enhanced ferroptotic susceptibility. Ferritin and iron measurements highlighted a ferro-metabolic signature correlating with therapeutic response. Combining SR with hyaluronan potentiated anti-leukemic activity at lower doses, suggesting CD44-mediated enhancement of SR efficacy.

Conclusions: T-ALL cells exhibit selective sensitivity to β3-AR antagonism, leading to metabolic reprogramming and increased ferroptotic susceptibility. PBMC data confirm the leukemia-specific action of SR. Metabolic and ferroptosis signatures in both cell models and patients provide potential biomarkers of therapeutic response. Hyaluronan co-treatment may further enhance SR efficacy, supporting β3-AR as a promising target in T-ALL therapy.