(PB2553) TARGETING GPR183 REVERSES CHEMORESISTANCE AND SUPPRESSES LEUKEMIC PROGRESSION IN ACUTE MYELOID LEUKEMIA BY MODULATING GLYCOSPHINGOLIPID METABOLISM

Topic: 01. Acute lymphoblastic leukemia - Biology & translational research

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Background

Treatment failure in acute myeloid leukemia (AML) is primarily attributed to chemoresistance and disease progression. Through constructing homoharringtonine (HHT)-resistant AML cell lines coupled with transcriptomic analysis, we previously identified GPR183 as significantly upregulated in resistant cells. GPR183 expression negatively correlated with HHT sensitivity in both cell lines and primary patient samples, and served as an independent prognostic factor for overall survival in AML patients. However, the underlying mechanisms and therapeutic targeting of GPR183 remain unexplored.

Aims

To elucidate the mechanism by which GPR183 drives chemoresistance and malignant progression in AML, and to identify and characterize small-molecule inhibitors targeting GPR183 with anti-leukemic efficacy.

Methods

GPR183 was knocked down in MV4-11 cells via lentiviral-mediated shRNA transfection. The effects on malignant phenotypes were assessed by MTS assay for proliferation, flow cytometry for apoptosis, and Transwell assay for migration. Gain-of-function studies were performed by overexpressing GPR183 in AML cells, and chemosensitivity to idarubicin (IDA) and daunorubicin (DNR) was evaluated. To explore downstream mechanisms, proteomic profiling was performed on GPR183-knockdown MV4-11 cells, followed by KEGG pathway enrichment analysis and correlation validation using TCGA database. For inhibitor screening, structure-based virtual screening of the ChemDiv database (~1.5 million compounds) was conducted to identify potential GPR183 binders. Compound N6 was selected based on molecular docking and drug sensitivity assays, and direct interaction with GPR183 was confirmed by drug affinity responsive target stability (DARTS) assay. Anti-leukemic activity was evaluated in 7 AML cell lines (including HHT-resistant sublines) and 13 primary patient samples using MTS and apoptosis assays. In vivo efficacy and safety were further assessed in an MV4-11-derived CDX mouse model.

Results

GPR183 knockdown significantly inhibited proliferation, induced apoptosis, and impaired migration in MV4-11 cells. Conversely, GPR183 overexpression promoted cell proliferation and induced resistance to idarubicin and daunorubicin. In vivo, GPR183 knockdown reduced bone marrow infiltration and prolonged survival in CDX mice ($p<0.01$). Proteomic analysis revealed significant enrichment of the glycosphingolipid biosynthesis pathway upon GPR183 knockdown, with downregulation of key enzymes including ST3GAL5 and UGCG. TCGA data confirmed positive correlations between GPR183 and UGCG ($R=0.42$) as well as ST3GAL5 ($R=0.38$). Virtual screening identified compound N6, and DARTS assay confirmed its direct binding to GPR183. N6 exhibited potent cytotoxic effects across 7 AML cell lines and 13 primary AML samples, and induced substantial apoptosis in AML cells. In the CDX model, N6 administration (20mg/kg, i.p., thrice weekly) significantly reduced bone marrow leukemic burden and extended median survival compared to control ($p<0.01$), with no observable toxicity.

Summary/Conclusion

This study uncovers a novel mechanism by which GPR183 drives AML progression through modulating glycosphingolipid metabolism. We identify N6 as a GPR183-targeting inhibitor with potent and selective anti-leukemic activity in vitro and in vivo. Targeting GPR183 represents a promising therapeutic strategy to overcome chemoresistance and improve outcomes in AML.