Evaluation of Glycosylation Patterns and Inhibition in Acute Lymphoid Leukemia

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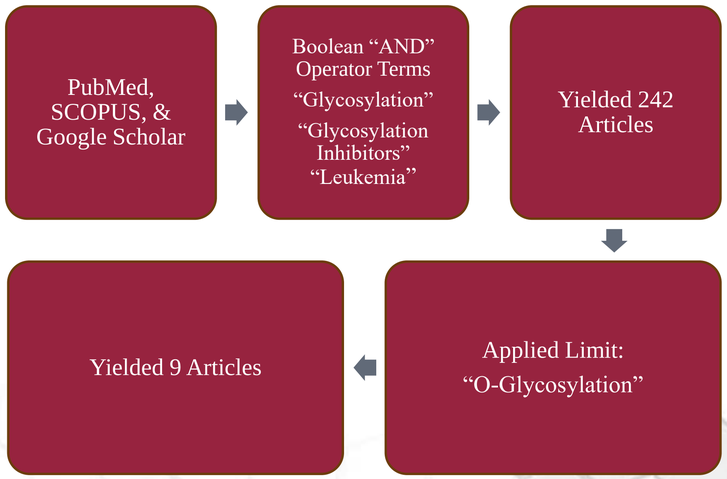
BACKGROUND

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. There are an estimated 5,000 newly diagnosed cases per year, as well as 1500 deaths. Among those diagnosed, 75-80%, are children. Additionally, 80% of diagnosed ALL are of B-Cell origin.[1] Genetic mutations have stunted the growth and development pathways for lymphoid cells of both B cell and T cell origin. Aberrant expression of O-glycans resulting from their incomplete synthesis have been associated with leukemic malignancies.[2] Recent studies have also demonstrated a decrease rate of cellular uptake and effectiveness due to aberrant overexpression of glycosylated proteins.[3]

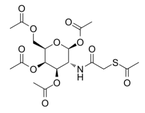
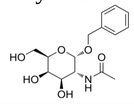
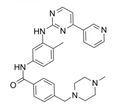
OBJECTIVE

The main objective of this study was to determine the aberrant glycosylation patterns commonly found in Acute Lymphoid Leukemia (ALL) cells and to investigate the various types of glycosylation inhibitors employed in the study and/or treatment of ALL. We hypothesize that the results of our investigation will support the existence and various influences of glycosylation patterns in ALL malignancies.

METHODS



O-Linked Glycosylation Inhibitors

Cell Line(s)	Inhibitor	Inhibitor Concentration	Exposure Time	Cost ($USD/mg)
HL-60[4,6] K562[5,6] U937[5] Jurkat[5] THP-1[6]	Ac5GalNTGc[4,5,6] 	10-100 μM[4,5,6]	24-48 Hours[4.5.6]	Synthesized from D-Galactosamine HCl[6] (1.68)
K562, RPMI 1788, CEM[7]	Benzyl-GalNAc[7] 	5mM[7]	120 hours (5 days)[7]	8.40
K562[8]	Imatinib[8] 	0-0.3μM[8]	24 hours[8]	0.76

CURRENT RESEARCH

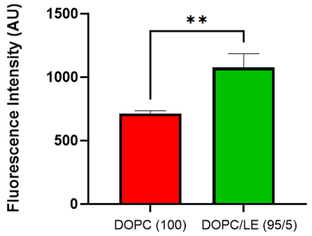


Figure 1. Lipid extracts (LE) were derived from ALL cells (CCRF-CEM) and subsequently used in the preparation of ALL lipid-modified nanoliposomes compared to control. **Above**: **DOPC** (conventional nanoliposomes) and **DOPC/LE** (experimental nanoliposomes). **Result**: The inclusion of LE enhanced cellular uptake by CCRF-CEM cells.

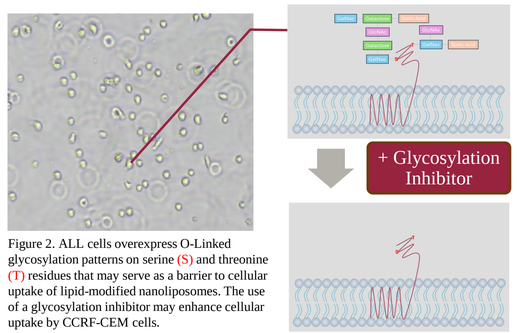


Figure 2. ALL cells overexpress O-Linked glycosylation patterns on serine (S) and threonine (T) residues that may serve as a barrier to cellular uptake of lipid-modified nanoliposomes. The use of a glycosylation inhibitor may enhance cellular uptake by CCRF-CEM cells.

IMPLICATION/CLINICAL RELEVANCE

The knowledge gained from this research will assist with understanding the potential role of O-linked glycosylation patterns in hematological cancers and disease management. This research suggests that O-linked glycosylation patterns expressed on acute lymphoid leukemia cells may serve as a potential barrier to drug therapy. In this general context, our future studies will utilize relevant cellular models of acute lymphoid leukemia and glycosylation inhibitors *in vitro*.

DISCUSSION & CONCLUSION

- Glycosylation is the process of attaching sugar molecules to proteins or lipids. Anomalies in O-linked glycosylation patterns are associated with leukemic malignancies, presenting an attractive target for intervention.
- Limited studies have focused on aberrant glycosylation inhibition to increase intracellular uptake of therapeutic agents. Our research adopted an evidence-driven strategy, combing through reputable databases to compile a roster of effective O-linked glycosylation inhibitors for ALL.
- Recent studies have highlighted the efficacy of Ac5GalNTGc, Benzyl-GalNac, and Imatinib as O-linked glycosylation inhibitors in various lymphoid leukemic cell lines. Specifically, these inhibitors demonstrated the inhibition of mucin-type O-glycosylation in CEM and Jurkat cell lines, both derived from ALL, shedding light on disrupting abnormal glycosylation processes in lymphoblastic leukemia cells.
- Furthermore, our study shows promising results regarding the use of these inhibitors in understanding glycosylation mechanism in ALL. Our future research will employ glycosylation inhibitors to delve deeper into the functional significance of glycosylation in cytotoxic drug therapy and nano drug delivery.

REFERENCES

ACKNOWLEDGEMENT AND DISCLOSURE

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