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Editorial: Glycobiology in hematology: a promising avenue for cancer diagnostics and therapeutics

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Editorial on the Research Topic
Glycobiology in hematology: a promising avenue for cancer diagnostics and therapeutics

The 'sugar decoration' of proteins and lipids, also known as glycosylation, adds an additional dimension to their functioning and signaling in both health and disease (1). It is estimated that 50%–70% of mammalian proteins are glycosylated, which impacts on protein stability and subcellular localization. Furthermore, glycans attached to proteins or lipids expressed at the plasma membrane regulate processes like cell adhesion and immune responses. In cancer, glycosylation is commonly altered, providing potential novel therapeutic targets or diagnostic biomarkers. Such changes in glycosylation have also been described in hematological malignancies.

Sanmartin-Martinez et al. reviewed the role of N-glycans in myeloid malignancies. For instance, N-glycan expression patterns differ between acute myeloid leukemia (AML) cell lines depending on their French–American–British (FAB) classification, including increased paucimannoses and alpha-L fucoses. Aberrant glycosylation profiles promote oncogenic signaling, chemoresistance, and niche hijacking. Prominent examples hereof are the glycosylation-dependent subcellular localization of fms-like tyrosine kinase 3 (FLT3) and tyrosine-protein kinase KIT in AML, and glycosylation-dependent overstimulation of MPL signaling in calreticulin mutated myeloproliferative neoplasms. Moreover, increased mannosylation and sialylation have been associated with chemoresistance in AML, by respectively stabilizing drug efflux pumps or promoting glycan-dependent binding to E-selectin, leading to niche hijacking. These findings may have clinical implications, whereby (aberrant) glycans on myeloid malignancies are promising targets for novel therapeutics, or can be used as biomarkers.

Indeed, the research by Zhang et al. describes that high expression levels of genes that regulate mannosylation are associated with worse survival in patients with AML. In line with these data, mass spectrometry-based glycomics demonstrated that cytarabine (AraC)-resistant AML cells express elevated levels of high mannose N-glycans, which can be

detected by the high mannose-binding lectin Concanavalin A (ConA). Indeed, the extent of ConA-binding correlated with cytarabine sensitivity in a panel of AML cell lines, whereby high ConA-binding cell lines were less sensitive compared to cell lines that weakly bound ConA. A preliminary staining on two patient-derived AML samples taken at diagnosis was also capable of predicting AraC sensitivity. Thus, ConA staining may be a potential novel diagnostic tool to predict AraC sensitivity in AML.

Also, in multiple myeloma (MM), differences in glycosylation have been reported, among which is the increased decoration with sialic acids, called hypersialylation. O'Dwyer et al. comprehensively reviewed the role of hypersialylation in MM, which, in general, has a negative effect on survival. Specifically, high expression levels of the enzymes that add sialic acids to glycans, among which are ST3GAL1 and ST3GAL6, associated with poor progression free and overall survival of patients with MM. Mechanistically, sialic acid expression on MM cells stimulates the generation of E-selectin ligands, which interact with their receptor in a sialic acid-dependent manner, impacting on cell trafficking and drug resistance. Furthermore, ligand sialylation is required for interactions with Siglec receptors expressed on immune cells, which activate immune inhibitory signaling. Indeed, desialylation of MM cells improved natural killer (NK) cell-mediated killing.

The review by Heisterkamp further extends on the impact of glycosylation on B-cell malignancies in the bone marrow. For instance, hypersialylation of N-glycans and a higher complexity of O-glycans have been described in B-cell precursor acute lymphoblastic leukemia. Also in MM, differences in glycosylation have been found, for instance in glycosaminoglycans and proteoglycans. Of note, the impact of the previously mentioned sialylation was also prominent in this review. For instance, (1) sialylation of the B-cell maturation antigen (BCMA) receptor promoted its internalization, (2) sialylation interfered between CD44 and hyaluronic acid binding, and (3) sialylation of CD38 prevented NK cell activity as induced by the anti-CD38 antibody daratumumab.

The importance of proper glycosylation in NK cell responses is further underscored by the research paper by Chen et al. In this study, B7-H6, a prominent checkpoint inhibitor molecule, was found to be N-glycosylated in different cell lines, having six functional N-glycosylation sites. Among these six, the N43 and N208 glycosylation sites in B7-H6 were found to be essential for activating NK responses. Specifically, N-glycosylation at N43 was required for the interaction of B7-H6 with its ligand NKp30 that is expressed by NK cells. Further, N-glycosylation at N208 was required to stabilize B7-H6 expression, as lack of N208 glycosylation led to membrane B7-H6 shedding.

Taken together, glycosylation plays an important role in the survival of hematological malignancies. Hence, targeting glycosylation may be of interest to improve current treatment protocols and to develop novel therapeutic strategies. In this respect, glycosylation may be directly targeted or the interaction between glycosylated proteins and their ligands may be modulated. The latter already made clinical progress, for instance, by using E-selectin inhibitors like GMI-1271/uproleselan in hematological malignancies. However, although uproleselan increased chemosensitivity of AML cells and MM *in vitro* (2, 3), it failed to do so in clinical trials [NCT03616470]. Direct glycan modulation may also improve treatment responses. However, currently available glycosylation modulators, in general, are not suitable for clinical applications. Furthermore, specificity is an issue, as healthy cells also require proper glycosylation for their functioning. Therefore, more efforts should be made to develop novel inhibitors and to design drug-delivery approaches to specifically target glycosylation pathways in cancer cells.

As mentioned in three out of the five papers in this Research Topic, glycosylation is important to steer NK cell functioning. Hence, glycosylation modulation is also a promising method to improve anti-cancer immune responses. In this respect, chimeric antigen receptor (CAR) T-cell therapy that is FDA-approved for the treatment of MM and diffuse large B-cell lymphoma, among others (4), may benefit from glycan modifications. As CAR T cells are produced outside the patient, this also circumvents the problem of unavailability of (selective) inhibitors for systemic administration. In addition, genetic modifications may be introduced to alter cellular glycosylation. Indeed, recent studies demonstrated that glycan modification, i.e. reducing sialic acid levels or complex N-glycans, increased CAR T-cell responses (5, 6).

In conclusion, glycosylation holds promise for the development of novel therapeutics and diagnostic tools for hematological cancers. Therefore, we anticipate that in the coming years, the glycan profiles of hematological (cancer) cell types will be further characterized to steer innovative glycan-targeted treatments.

Author contributions

TZ: Writing – review & editing. VW: Conceptualization, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Reily C, Stewart TJ, Renfrow MB, Novak J. Glycosylation in health and disease. *Nat Rev Nephrol*. (2019) 15:346–66. doi: 10.1038/s41581-019-0129-4

2. Barbier V, Erbani J, Fiveash C, Davies JM, Tay J, Tallack MR, et al. Endothelial E-selectin inhibition improves acute myeloid leukaemia therapy by disrupting vascular niche-mediated chemoresistance. *Nat Commun*. (2020) 11:2042. doi: 10.1038/s41467-020-15817-5

3. Muz B, Azab F, Fiala M, King J, Kohnen D, Fogler WE, et al. Inhibition of E-Selectin (GMI-1271) or E-selectin together with CXCR4 (GMI-1359) re-sensitizes multiple myeloma to therapy. *Blood Cancer J*. (2019) 9:68. doi: 10.1038/s41408-019-0227-3

4. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. (2023) 20:359–71. doi: 10.1038/s41571-023-00754-1

5. Durgin JS, Thokala R, Johnson L, Song E, Leferovich J, Bhoj V, et al. Enhancing CAR T function with the engineered secretion of C. perfringens neuraminidase. *Mol Ther*. (2022) 30:1201–14. doi: 10.1016/j.ymthe.2021.11.014

6. De Bousser E, Festjens N, Meuris L, Plets E, Van Hecke A, Wyseure E, et al. N-glycosylation engineering in chimeric antigen receptor T cells enhances anti-tumor activity. *bioRxiv*. (2023). doi: 10.1101/2023.01.23.525164. 01.23.525164.