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Cancer-specific sialylation of insulin-like growth factor 1 receptor impairs therapeutic antibody binding and efficacy

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Abstract

Despite extensive efforts to develop insulin-like growth factor (IGF1R)-targeted therapies for various malignancies, none has received clinical approval in the past two decades. Here, we reveal that N-glycan sialylation significantly decreases recognition by the humanized monoclonal anti-IGF1R antibody ganitumab across various cancer types, reducing its efficacy both in vitro and in vivo. Sialoforms of IGF1R are virtually absent in normal cells, indicating that the modification is tumor-specific. Pharmacological inhibition of sialyltransferases significantly sensitizes metastatic tumors to ganitumab in a ganitumab-resistant ovarian cancer model. Enzymatic removal of sialic acids from tissue sections resulted in marked enhancement in antibody binding to ovarian cancer patient tumors, but not normal tissues. Upregulation of α2-6 sialyltransferase ST6GAL1 in tumor tissues was found to be responsible for sialylation of IGF1R. Consequently, ST6GAL1-high tumors were more likely to benefit from desialylation-mediated enhancement of ganitumab binding. Furthermore, through comprehensive glycoproteomics analysis, structural prediction, and molecular dynamics simulation, we identify Asn-607 (N607) as a crucial site harboring sialylated glycans. Mechanistically, N607 glycosylation destabilizes the IGF1R-ganitumab complex. Overexpression of IGF1R Asn-607-Gln (N607Q) mutant in IGF1R-knockout cancer cells increases ganitumab efficacy compared to wild-type IGF1R in vivo. Taken together, these findings highlight sialylation as a common barrier in IGF1R-targeted therapies and provide crucial insights for therapy enhancement in cancer and patient stratification for future clinical trials.

Keywords: Insulin-like growth factor receptor (IGF1R); Ganitumab; Monoclonal antibody resistance; N-glycan sialylation; Glycosylation; Sialoforms; ST6GAL1 (α2-6 sialyltransferase); Asn-607 (N607) glycosylation site

1. Introduction

The insulin-like growth factor 1 receptor (IGF1R) is a key receptor tyrosine kinase involved in essential processes such as growth, survival, and metastasis in cancer. Dysregulated IGF1R signaling has been observed in at least 15 different types of cancers, including breast, lung, colorectal, prostate, and ovarian cancers1 . Over the past two decades, extensive efforts have been dedicated to developing therapeutic agents against this receptor, making it one of the most well-studied molecular targets in cancer research. Despite promising initial results of IGF1R inhibition in certain cancers, the translation to sustained success has been challenging1-3 . From 2000 to 2021, over 16 IGF1R inhibitors/monoclonal antibodies (mAbs) were assessed in 183 clinical trials involving more than 12,000 cancer patients, with total costs exceeding $1.6 billion2 . While anti-IGF1R mAbs, such as ganitumab and dalotuzumab, have reached Phase III clinical trials, all of them yielded sub-optimal outcomes1 . Currently, ganitumab remains the only one still in Phase III trials1 . Treatment insensitivity have commonly been attributed to compensatory pathways, such as PI3K, MAPK, and insulin receptor activation, but cotargeting these pathways have proven ineffective in enhancing therapeutic response1-3 . These indicate additional layers of regulation not adequately targeted by current therapies, in particular the role of post-translational modifications. It is worth noting that no trials for ovarian cancer have advanced beyond Phase II, suggesting that this cancer type could be a valuable model for studying such intrinsic resistance to IGF1R-targeting

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therapies4-6 . Ovarian cancer is particularly challenging to treat due to late-stage detection and high recurrence rates following standard therapies7 . While FDA approved PARP inhibitors have shown promise in benefiting a subset of patients with homologous recombination deficienciesin recent years, ovarian cancer still remains the most lethal gynecological malignancy8 . Therefore, there is an urgent need to explore alternative approaches to effectively address this disease. Our previous study has highlighted a significant role of glyco-modifications in the peritoneal dissemination of ovarian cancer9 , a phenomenon that is commonly linked with therapy resistance10.

Aberrant glycosylation, an important hallmark of cancer, plays a crucial role in shaping protein dynamics and functions11,12. This post-translational modification involves addition of glycan moieties to proteins, which alters their chemical and biological properties by impacting flexibility, movement, and charges. Protein glycosylation was also recently shown to influence its interaction with antibodies. For example, N-glycans on the immune checkpoint PD-L1 can impede antibody binding, and their removal could enhance the accuracy of PD-LI histologic quantification, thereby improving predictive value for clinical outcomes13. Previous research has indicated that specific glycan modifications such as sialylation of receptor tyrosine kinases can affect the efficacy of targeted therapies, for example, gefitinib (targeting EGFR) in lung

2. Methods

Cancer cell lines including SKOV3, MDA-MB-231, HCT116, H1299, and normal human ovarian surface epithelial cells were maintained under appropriate culture conditions with fetal bovine serum and antibiotics. Ovarian cancer patient samples were collected with informed consent and processed as formalin-fixed, paraffin-embedded sections for analysis. Western blot and lectin blot were performed to examine IGF1R expression and glycosylation using specific antibodies and biotinylated Sambucus Nigra lectin to detect α2-6-linked sialic acids. For glycosidase treatments, protein lysates were digested with various sialidases and PNGase F to characterize the linkage and type of glycans present on IGF1R. Immunoprecipitation and lectin pulldown assays were used to isolate IGF1R and determine its glycosylation status.

For glycoproteomic profiling, immunoprecipitated IGF1R was separated by SDS-PAGE, and the corresponding bands were digested with trypsin or chymotrypsin before analysis by liquid chromatography, mass spectrometry. The resulting glycopeptides were identified using Byonic software and verified manually. Structural modeling of the IGF1R–ganitumab complex was carried out using AlphaFold3, and molecular dynamics simulations were performed to evaluate the structural stability of the complex with or without sialylated glycans at residue N607. CRISPR/Cas9 editing was used to generate knockout and mutant cell lines for IGF1R, ST6GAL1, and ST6GAL2 to assess the role of specific enzymes and glycosylation sites. The N607Q mutant of IGF1R was produced by overlap PCR and introduced into IGF1R knockout cells for subsequent assays.

Functional analyses were performed using clonogenic survival assays to measure the effect of sialylation on ganitumab sensitivity. In vivo xenograft experiments were conducted by intraperitoneally injecting luciferase-labeled SKOV3 cells into nude mice followed by ganitumab and sialyltransferase inhibitor treatment to evaluate tumor growth and metastatic burden. Tumors were harvested, fixed, and processed for immunohistochemistry and lectin histochemistry to examine changes in antibody binding and sialylation levels. Images were acquired and quantified using automated analysis software. Statistical significance was determined by Student t test, Mann Whitney U test, or one-way ANOVA, with p values less than 0.05 considered significant.

3. Results

Desialylation markedly increased the sensitivity of ovarian cancer cells to the anti-IGF1R antibody ganitumab. In a xenograft model, treatment with ganitumab alone did not reduce tumor burden, whereas co-treatment with a sialyltransferase inhibitor significantly decreased metastatic growth and luminescence signal intensity. In vitro, enzymatic removal of sialic acids enhanced ganitumab binding to IGF1R without affecting receptor localization or activation. Clonogenic assays confirmed that inhibition of sialylation, but not fucosylation, reduced colony formation under ganitumab treatment. These findings were consistent across multiple cancer types including breast, colon, and lung, but not in normal epithelial cells. In patient-derived ovarian tumor sections, desialylation led to stronger ganitumab staining, indicating that tumor-specific sialylation of IGF1R impairs antibody recognition.

Biochemical analysis revealed that IGF1R is modified with α2-6-linked sialylated N-glycans. Treatment with selective sialidases showed a shift in the IGF1R alpha subunit consistent with α2-6 sialylation, while PNGase F digestion confirmed that these sialic acids are attached to N-linked glycans. Lectin pulldown and mass spectrometry identified

Asn-607 as the specific site carrying sialylated glycans, with two major glycoforms detected. This α2-6 sialylation pattern was present in cancer cell lines from several tissues but absent in normal ovarian epithelial cells, demonstrating its tumor-specific nature.

Further experiments showed that the enzyme ST6GAL1 mediates IGF1R sialylation, while ST6GAL2 has no detectable role. Knockout of ST6GAL1 increased ganitumab binding and inhibition of IGF1R phosphorylation, confirming its functional importance. Analysis of patient tumors revealed elevated ST6GAL1 expression compared to normal ovary and a negative correlation between ST6GAL1 levels and ganitumab signal intensity. Structural modeling and molecular dynamics simulations indicated that sialylation at Asn-607 destabilizes the IGF1R–ganitumab complex. Mutation of this site (N607Q) reduced sialylation, increased antibody binding, and enhanced therapeutic efficacy both in vitro and in vivo. Mice bearing N607Q tumors exhibited a pronounced response to ganitumab without changes in tumorigenic potential, establishing N607 sialylation as a key mechanism of therapeutic resistance.

4. Discussion

IGF1R continues to be one of the most important therapeutic targets in cancer biology, yet efforts to design effective inhibitors have repeatedly failed. Previous studies have attributed this failure to constitutive signaling and receptor redundancy, but these factors alone cannot explain the widespread therapeutic resistance observed in clinical settings. In this study, we reveal a novel mechanism of resistance driven by tumor-specific post-translational modification. Our findings identify an N-linked sialylation event at residue N607 of IGF1R that directly impairs the binding and efficacy of ganitumab. This modification is enriched in cancer cells and absent in normal tissues, providing a mechanistic explanation for the limited success of IGF1R-targeted therapies and highlighting the overlooked role of glycosylation in drug response.

The addition of a single sialic acid residue can alter the structural dynamics of receptor-antibody interactions. We demonstrate that α2-6-linked sialylation at N607 weakens the stability of the IGF1R–ganitumab complex, reducing antibody affinity even though the modification site lies outside the known binding interface. Removal of this sialic acid through enzymatic digestion or inhibition of the responsible enzyme ST6GAL1 restored both antibody binding and therapeutic efficacy in vitro and in vivo. Molecular dynamics simulations supported these observations by showing that sialylation introduces conformational flexibility that interferes with antibody access. Together, these results establish glycan remodeling as a major determinant of antibody performance in cancer therapy.

Our study also reveals ST6GAL1 as the key enzyme responsible for the pathological sialylation of IGF1R. Elevated ST6GAL1 expression in tumor samples correlated with reduced antibody binding and poorer response, while genetic disruption of this enzyme sensitized tumors to ganitumab treatment. These results suggest that co-targeting ST6GAL1 or blocking specific sialylation events may enhance the efficacy of IGF1R-directed therapies. More broadly, they emphasize that post-translational glycosylation patterns are not passive modifications but active regulators of therapeutic resistance. By identifying N607 sialylation as a modifiable barrier to antibody engagement, this work introduces a new conceptual framework for overcoming treatment resistance through the intersection of structural biology, glycobiology, and precision oncology.

5. Conclusion

In conclusion, this study identified a critical post-translational modification on IGF1R that alters its therapeutic targeting in cancer. The findings revealed that sialylation at residue N607, catalyzed by ST6GAL1, directly reduces the binding and antitumor efficacy of the monoclonal antibody ganitumab. Removal of this sialylated glycan restored antibody recognition and improved therapeutic outcomes across several cancer models, demonstrating that selective modulation of glycosylation can overcome inherent drug resistance.

The results have broader implications for precision oncology, as the presence of sialylated IGF1R was observed in multiple cancer types but not in normal tissues. This suggests that tumor-specific glycosylation may explain the limited success of IGF1R-targeted therapies in clinical trials. Because the loss of this glycan did not alter receptor function or protein maturation, targeting it offers a specific and safe approach to enhance therapeutic sensitivity. The study also establishes ST6GAL1 expression and IGF1R N607 sialylation status as potential biomarkers for identifying patients most likely to respond to anti-IGF1R therapy.

Future work should explore strategies that exploit this discovery, including the development of glycoform-specific antibodies or antibody–sialidase conjugates that selectively remove sialic acids from IGF1R. By combining biochemical,

structural, and translational evidence, this study provides a foundation for the rational design of next-generation therapeutics that integrate glycosylation profiling with targeted receptor inhibition.

Compliance with ethical standards

Disclosure of conflict of interest

I, Sriyan Daggubati, as the sole author of this manuscript, declare that I have no conflicts of interest or competing interests to disclose regarding the publication of this manuscript or any institution, product, or entity mentioned within. Furthermore, I have no affiliations or financial interests in products or organizations that could influence the study outcomes presented or compete with those discussed in the manuscript.

References

[1] Wang P, Mak V C, and Cheung L W T. *Drugging IGF-1R in cancer: New insights and emerging opportunities.* Genes & Diseases 10, 199–211 (2023).

[2] Jentzsch V, Osipenko L, Scannell J W, and Hickman J A. *Costs and Causes of Oncology Drug Attrition With the Example of Insulin-Like Growth Factor-1 Receptor Inhibitors.* JAMA Network Open 6, e2324977 (2023).

[3] Beckwith H and Yee D. *Minireview: Were the IGF Signaling Inhibitors All Bad?* Molecular Endocrinology 29, 1549–1557 (2015).

[4] Liefers-Visser J A L, Meijering R A M, Reyners A K L, van der Zee A G J, and de Jong S. *IGF system targeted therapy: Therapeutic opportunities for ovarian cancer.* Cancer Treatment Reviews 60, 90–99 (2017).

[5] Konecny G E et al. *Results of TRIO-14, a phase II, multicenter, randomized, placebo-controlled trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-ganitumab in newly diagnosed epithelial ovarian cancer.* Gynecologic Oncology 163, 465–472 (2021).

[6] Davidson T M et al. *Results of TRIO-15, a multicenter, open-label, phase II study of the efficacy and safety of ganitumab in patients with recurrent platinum-resistant ovarian cancer.*

[7] Abraham M J et al. *GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers.* SoftwareX 1–2, 19–25 (2015).

[8] Ran F A et al. *Genome engineering using the CRISPR-Cas9 system.* Nature Protocols 8, 2281–2308 (2013).

[9] Brinkman E K, Chen T, Amendola M, and van Steensel B. *Easy quantitative assessment of genome editing by sequence trace decomposition.* Nucleic Acids Research 42, e168 (2014).

[10] Bankhead P et al. *QuPath: Open source software for digital pathology image analysis.* Scientific Reports 7, 16878 (2017).

[11] Ma J et al. *P-cadherin mechanoactivates tumor-mesothelium metabolic coupling to promote ovarian cancer metastasis.* Cell Reports 44, 115096 (2024).