MS-Based Glycomic Profiling Reveals ST6GalNAc-I–Driven Immunosuppression and Angiogenesis in NSCLC

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Our role: Creative Proteomics provided MS-based glycomic profiling service to support comparative protein analysis in ST6GalNAc-I–KO and MUC5AC-KD LUAD models, enabling identification of key downstream glycoproteins associated with immune suppression and angiogenesis.

Background & Significance

Aberrant tumor sialylation is increasingly linked to immune evasion, angiogenesis, and metastasis. In LUAD, however, the downstream glycoprotein mechanisms remain unclear.

ST6GalNAc-I is a tumor-associated sialyltransferase that generates STn-related glycans. This study shows that ST6GalNAc-I is highly overexpressed in aggressive LUAD and drives immune suppression, vascular remodeling, and metastatic progression.

Study Objective

This study aimed to:

- Define the role of ST6GalNAc-I in tumor cell sialylation during LUAD progression.
- Identify downstream glycoprotein mediators associated with ST6GalNAc-I signaling.
- Determine how these pathways regulate immune evasion, angiogenesis, and metastasis in NSCLC.

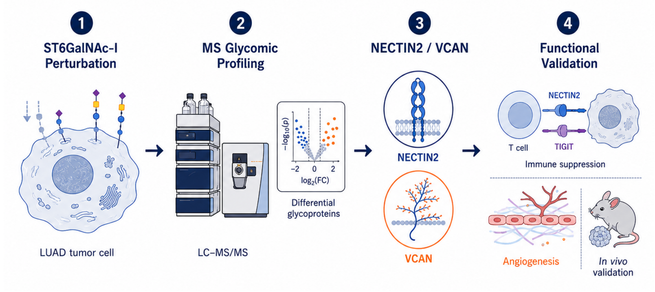
Case Focus

Two mechanistic axes emerged as central to LUAD progression:

- NECTIN2/TIGIT axis for glyco-immune suppression
- MUC5AC/VCAN-V1 axis for glyco-angiogenic remodeling and metastasis

Workflow

ST6GalNAc-I perturbation in LUAD models → MS-based glycomic/proteomic profiling → candidate glycoprotein identification → immune and endothelial functional validation → orthotopic in vivo confirmation



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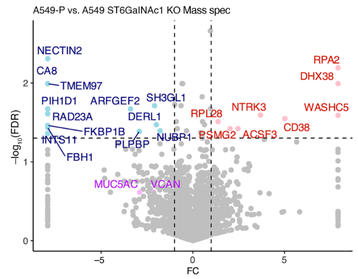
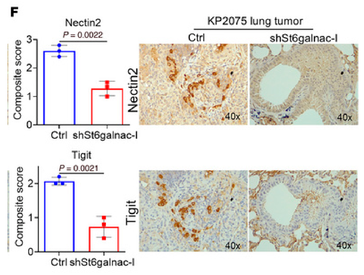
Key Findings

Finding 1 | Glycomic profiling identified NECTIN2 as a key ST6GalNAc-I–associated glycoprotein

MS-based comparative profiling revealed NECTIN2 as one of the top downregulated proteins in ST6GalNAc-I–KO LUAD cells. Pathway annotation linked these changes to immune response, apoptosis, and protein stability, nominating NECTIN2 as a high-priority downstream effector of ST6GalNAc-I signaling.

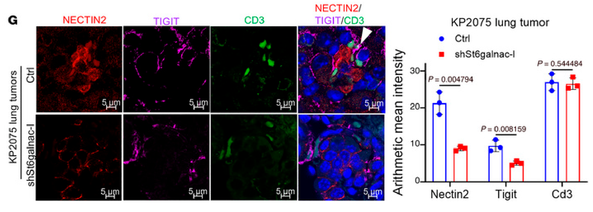


MS-based glycomic/proteomic profiling identified NECTIN2 as a prominent downstream candidate associated with ST6GalNAc-I signaling in LUAD.



Finding 2 | ST6GalNAc-I promotes immune evasion through the NECTIN2/TIGIT axis

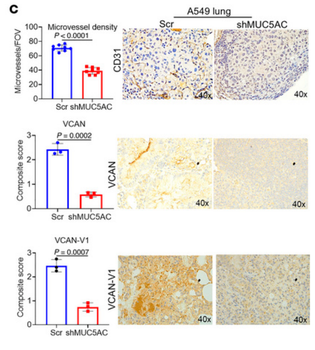
NECTIN2 carried STn-associated sialylation in LUAD cells, and loss of ST6GalNAc-I increased tumor cell susceptibility to T cell–mediated killing. In orthotopic tumors, St6galnac-I knockdown reduced Nectin2/Tigit-associated immunosuppression, supporting a functional glyco-immune checkpoint mechanism in LUAD progression.



ST6GalNAc-I–dependent NECTIN2 signaling contributes to T cell dysfunction and immune suppression in LUAD.

Finding 3 | ST6GalNAc-I/MUC5AC signaling drives VCAN-V1–linked angiogenesis

Comparative omics identified VCAN as a common downstream target of ST6GalNAc-I and MUC5AC. Functional studies showed that depletion of this axis reduced endothelial activation, microvessel density, and angiogenic remodeling. VCAN-V1 emerged as a key matrix-associated effector linking tumor sialylation to vascular development in LUAD.



The ST6GalNAc-I/MUC5AC axis regulates VCAN-V1, endothelial activation, and tumor angiogenesis in LUAD.

Our Contribution (Creative Proteomics)

Creative Proteomics performed **MS-based glycomic profiling** to identify downstream ST6GalNAc-I–associated glycoproteins in LUAD models. This analysis enabled the discovery of key candidates, including NECTIN2 and VCAN, and supported mechanism-focused interpretation of tumor sialylation in immune suppression and angiogenesis.

What This Case Demonstrates

- Comparative glycomic profiling can reveal functional downstream glycoproteins, not just expression changes
- MS-based candidate discovery becomes more actionable when integrated with immune, endothelial, and in vivo validation
- Glycomic profiling is well suited to perturbation-based mechanism studies in cancer progression and metastasis

Why Choose Creative Proteomics

- MS-based glycomic profiling for mechanism studies: supports differential glycoprotein discovery in perturbation-based cancer models
- Data depth demonstrated in this case: profiling was performed in triplicate, using 100 μg total protein per sample, and identified 3,184 proteins for comparative analysis
- Actionable candidate discovery: enabled prioritization of key downstream glycoproteins such as NECTIN2 and VCAN for follow-up immune and angiogenic validation
- Broad glycoproteomics capability: supports glycosylation site identification, glycoprotein/glycan quantification, and glycan structure characterization
- Flexible study design support: suitable for knockout/knockdown, matched-control, and mechanism-focused oncology workflows

Need to uncover glycoprotein mechanisms in your study?

Creative Proteomics provides MS-based glycomic profiling to support mechanism-driven research and help connect glycoprotein changes with biologically relevant phenotypes and validation-ready targets.

Contact us to discuss a customized analytical strategy for your next project.

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