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Spatial and Molecular Glycoproteomics of Prostate Cancer via MALDI-MSI and HILIC-Enriched LC-MS/MS: Leveraging Cross-MS-Technology-Platform Synergies to Generate Novel Biological Insights

Hongxia Bai[1] , Grace Grimsle[1], Richard Drake[2], Klaus Lindpaintner[1]

[1]Bruker-Daltonics, Life-Science Mass Spectrometry, Billerica, MA, USA; [2] Department of Pharmacology, Medical University of South Carolina

Introduction

We integrate high-resolution mass spectrometry imaging (MSI) of released glycans with intact glycopeptide analysis to uncover spatial and molecular differences in N-glycosylation between tumor and normal prostate tissue. MALDI-MSI revealed prominent changes in glycan spatial distribution, including enrichment of high-mannose and bisected glycans in tumor tissue, while complex-type fucosylated and sialylated glycans predominated in normal regions. LC-MS/MS analysis of glycopeptides validated these trends and highlighted specific glycoproteins involved. This dual-modality approach provides mechanistic insights into glycosylation remodeling during malignant transformation and strongly indicates the potential relevance of glycosylation-specific biomarkers

Methods

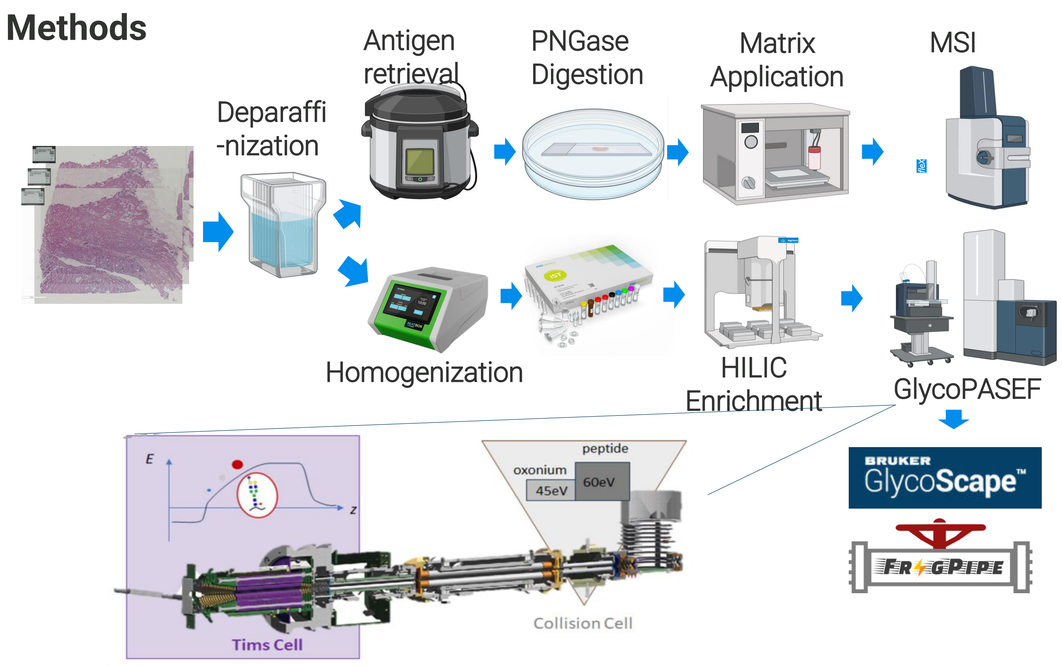

Figure 1. Adjacent normal and Pca tissue sections were processed by MSI for glycomics and by LC-MS/MS for glycoproteomics.

Results

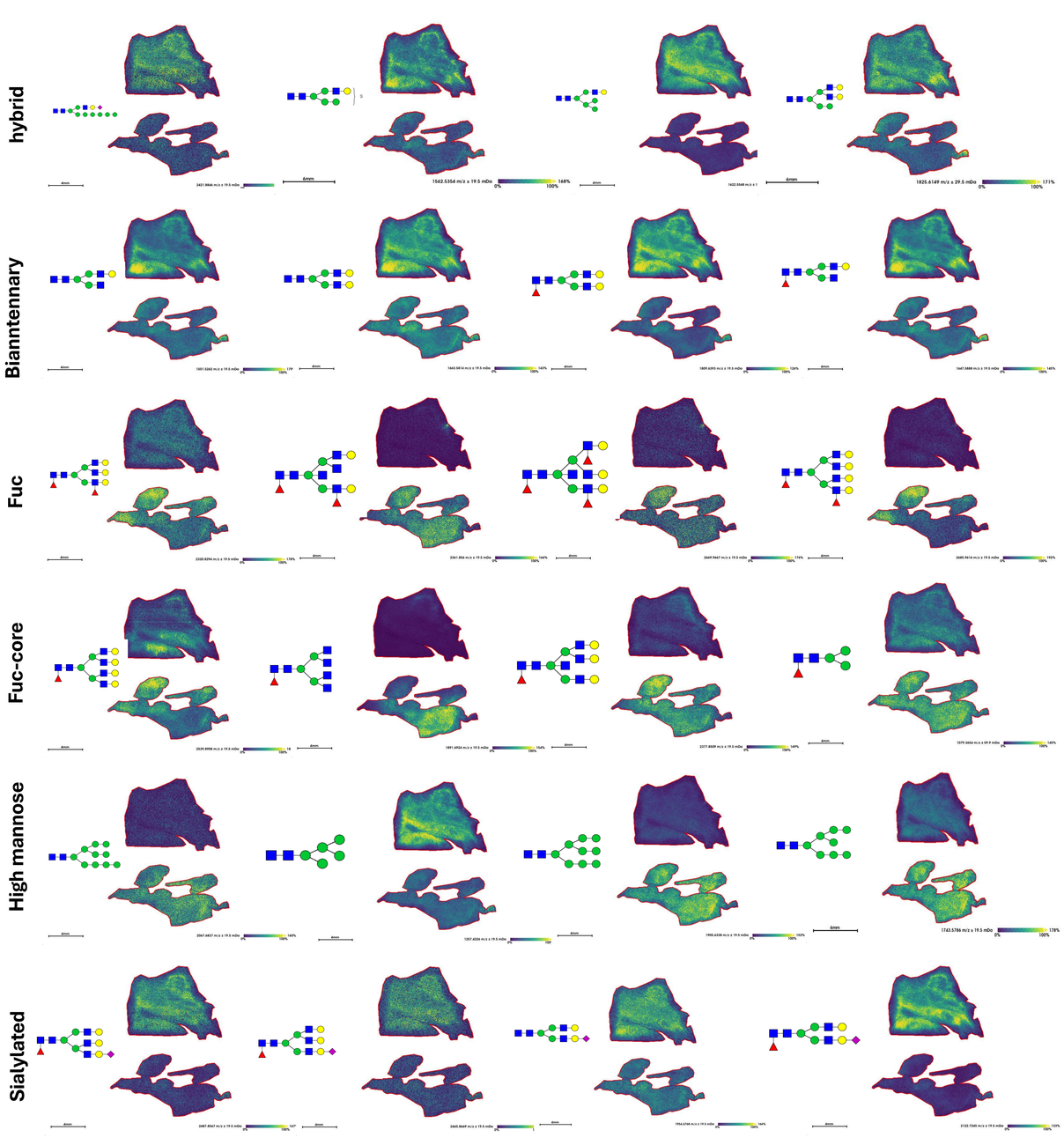

Figure 2. Spatial distribution of representative N-glycan classes across normal and PCa prostate tissues.

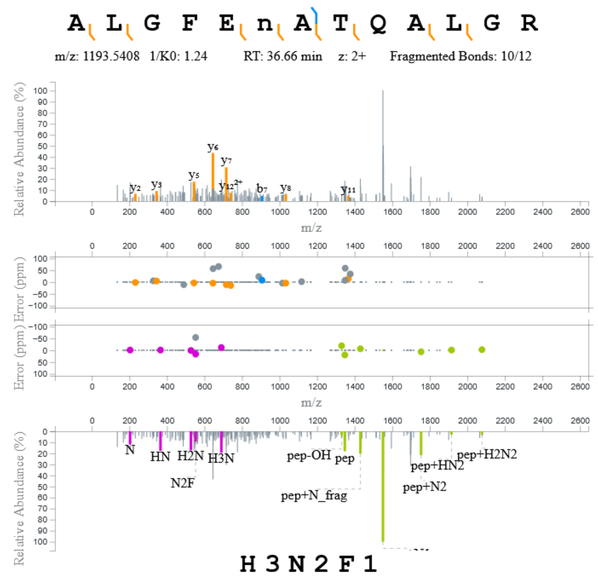

Figure 3. A representative glycopeptide spectrum match with peptide backbone ALGFENATQALGR and the glycan composition H3N2F1. This peptide is from Galectin-3-binding protein (LG3BP), which is known to play roles in cancer progression, immune modulation, and metastasis, and has been reported as a potential biomarker in prostate and other cancers.

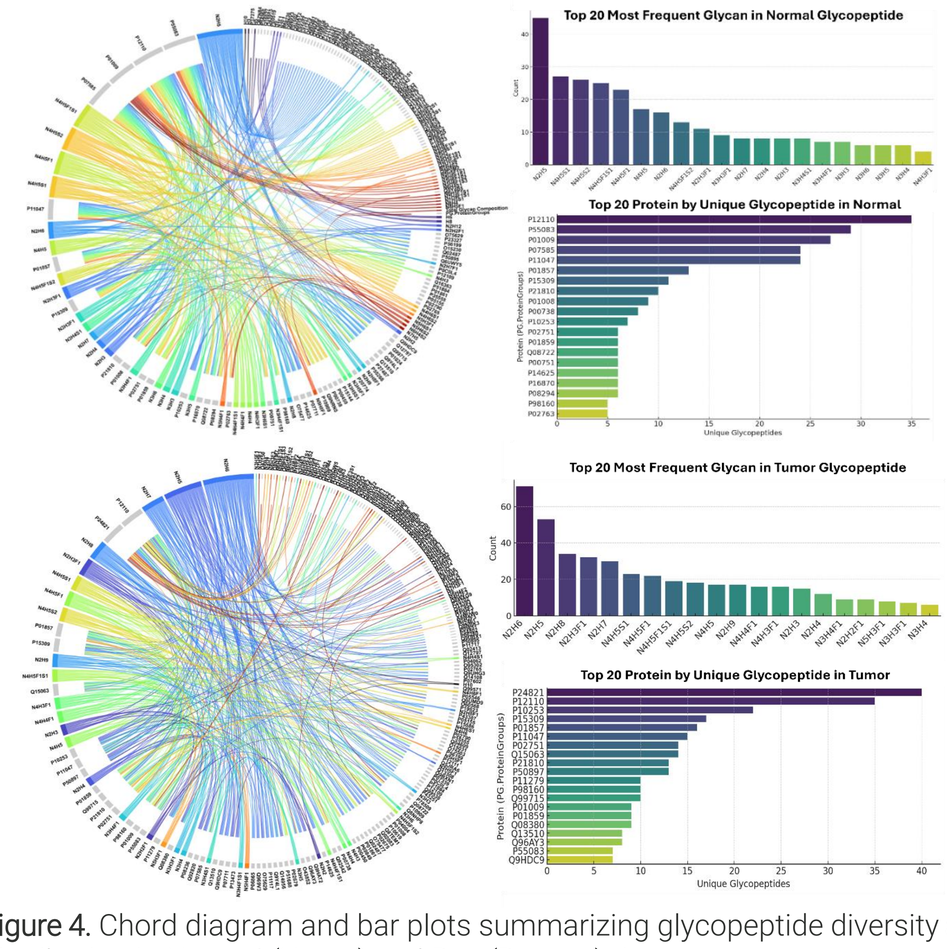

Figure 4. Chord diagram and bar plots summarizing glycopeptide diversity and distribution in Normal (Upper) and Pca (Bottom) tissue.

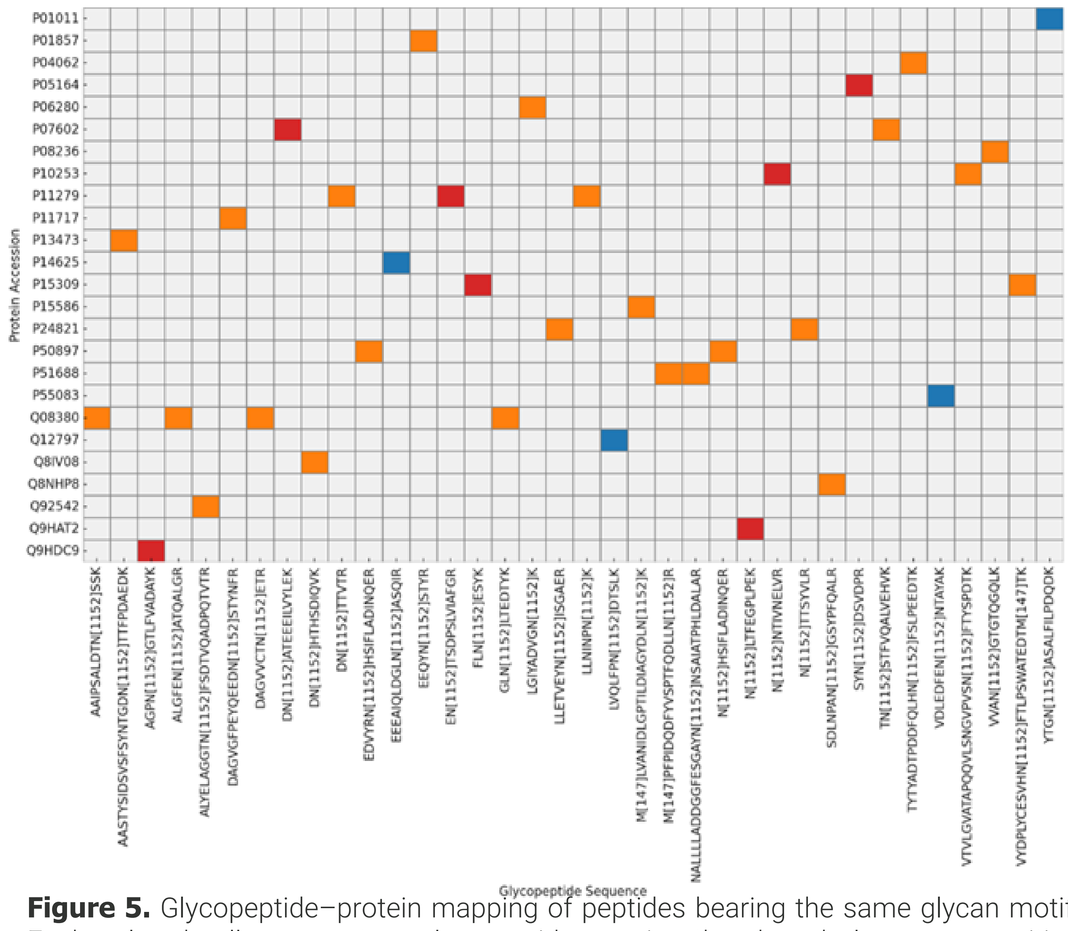

Figure 5. Glycopeptide–protein mapping of peptides bearing the same glycan motif. Each colored cell represents a glycopeptide carrying the shared glycan composition H3N2F1, identified on a corresponding protein (y-axis).Orange indicates detection in tumor tissue, blue indicates normal tissue, and red marks shared by both. This map highlights the diversity of peptide backbones and proteins carrying the same glycan.

Summary

- Dual approach: MALDI-MSI + LC-MS/MS glycoproteomics
- PCa: ↑ High-mannose, biantennary glycansNormal: ↑ Fucosylated, sialylated glycans
- Normal and PCa showed different glycoproteins profiles
- Shared glycan (H3N2F1) found on diverse proteins/peptides
- These results underscore the value of combining imaging and glycoproteomics to uncover biologically meaningful glycosylation changes in cancer.

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