(RESEARCH ARTICLE)

The emerging role of glycoproteomics in cancer biomarker discovery

Grace Eleojo Obasuyi *

Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Nigeria.

Abstract

Cancer continues to be a major global health burden, responsible for one in six deaths worldwide. Beforehand discovery and accurate diagnosis are pivotal for perfecting prognosis, yet numerous conventional biomarkers are required to detect it at an Early stage. Glycoproteomics the large- scale study of glycosylated proteins — has surfaced as a promising frontier in cancer biomarker discovery due to the central part of protein glycosylation in excrescence biology. Aberrant glycosylation is a honored hallmark of cancer, impacting excrescence progression, metastasis, vulnerable elusion, and remedy resistance. Glycoproteomics allows for the identification and characterization of cancer-specific glycoforms that are n't sensible through traditional proteomic or genomic analyses. Mass spectrometry- grounded ways combined with glycan enrichment strategies now enable point-specific glycoprotein profiling with high perceptivity and resolution. Notable exemplifications include altered glycoforms of PSA, CA125, and AFP- L3, which have shown bettered individual particularity across prostate, ovarian, and liver cancers.

Likewise, glycoproteomics supports the development of non-invasivel tools through liquid vivisection, allowing for real-time compliance via blood- grounded biomarkers. Despite specialized challenges similar as glycan diversity and logical complexity, advances in bioinformatics, standardization, and high- outcomes are driving its clinical connection. This review explores the natural significance of glycosylation in cancer, recent technological improvements, and the translational eventuality of glycoproteomics in perfection oncology. By improving dynamic, cancer-specific glycosylation patterns, glycoproteomics provides an important platform for the development of more accurate, functionally -applicable, and substantiated cancer biomarkers.

Keywords: Glycoproteomics; Cancer Biomarkers; Mass Spectrometry; Glycosylation; Precision Medicine

1. Introduction

Cancer remains a major global health burden, responsible for one in six deaths worldwide and ranking among the leading causes of mortality across all age groups (Sung et al., 2021). According to the GLOBOCAN 2020 estimates, there were 19.3 million new cancer cases and nearly 10 million cancer-related deaths, with lung, colorectal, liver, stomach, and breast cancers accounting for the largest share of mortality (Sung et al., 2021). Despite significant advances in diagnostic technologies, targeted therapies, and immuno-oncology, the prognosis for many cancers remains suboptimal, especially when diagnosed at advanced stages. Early detection remains a critical factor in improving survival rates; however, many current diagnostic tools—such as imaging, tissue biopsies, and serum-based tumour markers—lack sufficient sensitivity and specificity, particularly for early-stage malignancies or for capturing tumour heterogeneity (Cohen et al., 2018). The search for reliable, non-invasive biomarkers that can detect cancer early, stratify patients by risk or response, and monitor disease progression in real time continues to be a top priority in oncology research.

In this context, biomarker discovery has become an essential component of precision medicine. Biomarkers are measurable indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a

* Corresponding author: Grace Eleojo Obasuyi

therapeutic intervention. In oncology, they are indispensable for early detection, diagnosis, prognosis, and therapeutic monitoring. Conventional tumour biomarkers, such as carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and prostate-specific antigen (PSA), have been widely used in clinical settings but are often limited by low sensitivity and specificity, particularly for early-stage disease (Alix-Panabières & Pantel, 2021). Furthermore, their expression is not always cancer-specific and can be influenced by benign conditions, leading to false positives and unnecessary interventions. These limitations underscore the need for more accurate and dynamic biomarkers that better reflect the complex and evolving nature of cancer.

Proteomics—the comprehensive study of the proteome, or the full complement of proteins expressed in a cell, tissue, or organism—has emerged as a powerful platform for biomarker discovery. Unlike genomics, which provides static information about genetic potential, proteomics captures dynamic changes in protein expression, modification, and interaction in response to internal and external stimuli. This makes it especially relevant for understanding diseases like cancer, which are driven by alterations not only in gene sequences but also in protein function and signalling networks (Ding et al., 2022). Proteomic technologies, particularly mass spectrometry (MS)-based platforms, have enabled researchers to identify novel cancer-related proteins and post-translational modifications (PTMs) that can serve as diagnostic or prognostic indicators.

Among the various PTMs, glycosylation—the enzymatic attachment of glycans (sugar moieties) to proteins—has received increasing attention due to its significant impact on protein stability, folding, trafficking, and biological function. Glycosylation is the most abundant and diverse PTM in eukaryotic cells, affecting more than half of all human proteins (Schjoldager et al., 2020). In the context of cancer, aberrant glycosylation is a well-recognised hallmark, contributing to tumour progression, immune evasion, angiogenesis, metastasis, and resistance to therapy (Pinho & Reis, 2025). For example, cancer cells frequently display increased sialylation, truncated O-glycans, and altered fucosylation patterns that not only influence cellular behaviour but also generate unique molecular signatures that can be detected in biological fluids (Rodrigues et al., 2018).

This realisation has led to the emergence of glycoproteomics—a specialised branch of proteomics focused on the large-scale study of glycosylated proteins. Glycoproteomics combines advanced mass spectrometry techniques with glycan-specific enrichment methods to enable the precise characterisation of glycosylation sites, glycan compositions, and glycoforms. Unlike traditional proteomics, which may overlook glycan modifications due to their heterogeneity and complexity, glycoproteomics provides crucial insights into the structure-function relationships of glycoproteins and their roles in disease mechanisms (Trbojević-Akmačić et al., 2022). With improvements in analytical workflows and bioinformatic tools, researchers are now able to profile glycoproteins in tissue samples, plasma, serum, and other body fluids with unprecedented resolution and sensitivity.

One of the key advantages of glycoproteomics lies in its ability to detect cancer-specific glycoforms that are not present or are minimally expressed in healthy tissues. For example, the tumour-associated Tn and sialyl-Tn antigens—short, immature O-glycans often found on mucins—are rarely expressed in normal tissues but are frequently upregulated in various cancers, including breast, ovarian, and pancreatic cancers (Zhou et al., 2019). These glycan epitopes can serve as valuable targets for biomarker discovery and therapeutic intervention. Similarly, fucosylated forms of alpha-fetoprotein (AFP-L3) have shown higher specificity for hepatocellular carcinoma compared to total AFP levels, illustrating how glycan modifications can improve the diagnostic accuracy of existing protein markers (Walsh, 2022).

Importantly, glycoproteomics also holds potential for improving the clinical utility of liquid biopsy—a minimally invasive method that involves the analysis of tumour-derived components (e.g., circulating tumour DNA, exosomes, and proteins) in body fluids like blood, urine, and saliva. While most liquid biopsy studies have focused on nucleic acids, emerging evidence suggests that tumour-derived glycoproteins and glycoforms in the blood can provide equally valuable diagnostic and prognostic information (Silva, 2023). The ability to capture tumour-specific glycosylation patterns through a simple blood draw could revolutionise cancer screening, allowing for earlier detection and more precise monitoring of disease progression or therapeutic response.

Despite its promise, glycoproteomics also presents unique technical challenges. Glycans are highly heterogeneous, with branching structures and isomeric forms that complicate their analysis. Furthermore, glycosylation is non-template driven, meaning that its biosynthesis is influenced by cellular context, enzyme expression, and environmental factors. This makes it difficult to predict glycan structures based solely on genetic information, necessitating direct biochemical analysis (Ramazi & Zahiri, 2021). Moreover, there is currently no universal enrichment method for all glycoproteins or glycan types, which limits the coverage and reproducibility of glycoproteomic datasets. Standardisation of workflows, development of robust bioinformatic pipelines, and establishment of reference databases are critical steps toward overcoming these limitations and translating glycoproteomics into clinical practice.

Given these developments, the aim of this review is to synthesise current knowledge on the application of glycoproteomics in cancer biomarker discovery. Specifically, the review will examine: (1) the biological significance of glycosylation changes in cancer; (2) recent technological advances enabling site-specific glycoprotein analysis; (3) notable findings from glycoproteomic studies in various cancer types; and (4) the clinical potential and challenges of integrating glycoproteomics into precision oncology frameworks. By providing a comprehensive overview of the field, this work intends to highlight the transformative potential of glycoproteomics for developing more accurate, non-invasive, and functionally relevant biomarkers that could significantly enhance cancer diagnosis, prognosis, and therapeutic monitoring.

2. Theoretical Background

The foundation of glycoproteomics in cancer biomarker discovery lies in the understanding of protein glycosylation, a post-translational modification wherein carbohydrates, or glycans, are covalently attached to specific amino acid residues on proteins. Glycosylation is essential for numerous biological processes, including protein folding, stability, trafficking, and cellular communication (Schjoldager et al., 2020). In the context of cancer, alterations in glycosylation patterns are not merely by-products of transformation but actively contribute to tumour progression, metastasis, and immune modulation. Therefore, a robust theoretical understanding of glycosylation's mechanisms and implications is critical to appreciating its emerging role in oncological glycoproteomics.

2.1. Overview of Protein Glycosylation Types and Biological Roles

Protein glycosylation is a ubiquitous and highly regulated modification that occurs primarily in the endoplasmic reticulum (ER) and Golgi apparatus. There are two main types of glycosylation in humans: N-linked and O-linked glycosylation.

N-linked glycosylation involves the attachment of oligosaccharides to the asparagine (Asn) residue within a consensus sequence (Asn-X-Ser/Thr), where X can be any amino acid except proline. This process begins co-translationally in the ER and continues with glycan processing and modification in the Golgi (Stanley et al., 2017). N-glycans typically display complex, high-mannose, or hybrid structures and are involved in processes such as receptor activation, protein trafficking, and antigen recognition.

O-linked glycosylation, by contrast, entails the attachment of monosaccharides (most commonly N-acetylgalactosamine, GalNAc) to the hydroxyl groups of serine or threonine residues. Unlike N-glycosylation, O-glycosylation lacks a defined consensus sequence and occurs exclusively in the Golgi. O-glycans contribute to mucin formation, cellular adhesion, and protection of the protein core from proteolysis (Tarp & Clausen, 2008).

Beyond these primary forms, other glycosylation types include C-mannosylation, glypiation (addition of a glycosylphosphatidylinositol anchor), and O-GlcNAcylation, which occurs in the cytoplasm and nucleus and is dynamically regulated like phosphorylation. These modifications collectively govern key aspects of protein function and cellular communication. Their perturbation is associated with numerous pathological conditions, most notably cancer.

2.2. Relevance of Glycosylation in Tumorigenesis and Immune Evasion

Aberrant glycosylation has long been recognised as a hallmark of cancer. Changes in glycan structures on the cell surface or in secreted proteins can significantly influence tumour biology. These changes are orchestrated by alterations in the expression and activity of glycosyltransferases and glycosidases—the enzymes responsible for assembling and modifying glycan chains (Pinho & Reis, 2025). Such dysregulation gives rise to tumour-associated carbohydrate antigens (TACAs), including sialyl-Tn, Lewis antigens, and high-mannose glycans, many of which are absent or expressed at very low levels in normal tissues.

These glycosylation changes serve functional roles in tumour growth, angiogenesis, metastasis, and immune escape. For example, increased sialylation—common in many tumour types—enhances the negative surface charge of cells, facilitating detachment from the primary tumour and promoting metastasis (Rodrigues et al., 2018). Hypersialylation also contributes to immune evasion by engaging Siglecs (sialic acid-binding immunoglobulin-like lectins) on immune cells, leading to inhibition of natural killer (NK) cell and cytotoxic T cell activity (Rodrigues et al., 2018).

Altered fucosylation, another common feature in cancers, modulates ligand-receptor interactions and enhances cellular motility and invasiveness. For instance, core fucosylation of epidermal growth factor receptor (EGFR) has been shown to increase its tyrosine kinase activity, thereby promoting cell proliferation in non-small cell lung cancer (Zhou et al., 2019). Furthermore, truncated O-glycans, such as the Tn and sialyl-Tn antigens, often decorate mucin proteins in

cancerous tissues and influence interactions with the extracellular matrix and immune receptors (Tarp & Clausen, 2008).

Crucially, the immunological implications of these glycan alterations cannot be overstated. Glycosylation changes affect how tumour cells are recognised by the host immune system. Tumour-specific glycoforms can hinder antigen presentation, impair antibody binding, and manipulate the tumour microenvironment to suppress immune surveillance (Silva, 2023). This explains why glycosylation is a focal point in emerging cancer immunotherapy strategies, including glycoengineered vaccines, antibody-drug conjugates targeting glycoepitopes, and inhibitors of glycosylation enzymes.

2.3. Importance of Site-Specific Glycosylation Profiling in Biomarker Research

While the qualitative presence of glycosylation is informative, it is the site-specific analysis of glycoproteins that offers the most actionable insights for cancer biomarker discovery. Traditional proteomic approaches often overlook the heterogeneity of glycosylation, treating it as noise rather than a signal. However, glycoproteomics—particularly when conducted with advanced mass spectrometry and glycan enrichment technologies—enables the identification of specific glycosylation sites, their occupancy rates, and structural variations of attached glycans.

This level of detail is crucial because glycoproteins may exhibit multiple glycosylation sites, each with distinct glycan structures that modulate function in different ways. For example, different glycoforms of the same protein may correlate with cancer stage, histological subtype, or response to therapy (Trbojević-Akmačić et al., 2022). Moreover, site-specific glycoform variations may be present in body fluids and accessible via non-invasive sampling, providing a rich source of candidate biomarkers for early detection.

The clinical utility of such profiling is exemplified by alpha-fetoprotein-L3 (AFP-L3), a fucosylated glycoform of AFP that has shown higher specificity for hepatocellular carcinoma compared to total AFP levels (Walsh, 2022). Similarly, cancer antigen 125 (CA125), widely used in ovarian cancer screening, derives much of its diagnostic relevance from changes in its O-glycosylation pattern rather than from its protein backbone (Alix-Panabières & Pantel, 2021). These cases illustrate how glycosylation site profiling transforms conventional protein biomarkers into more accurate and context-sensitive diagnostic tools.

Site-specific glycosylation analysis also enhances biomarker specificity by differentiating between glycoforms produced by malignant versus benign tissues. This is particularly relevant for biomarkers detected in circulation, where proteins from both healthy and diseased tissues may coexist. By identifying cancer-specific glycoforms, researchers can improve the signal-to-noise ratio and reduce false positives in diagnostic assays (Ramazi & Zahiri, 2021). Furthermore, emerging techniques such as glycopeptide-centric proteomics, electron-transfer/higher-energy collision dissociation (EThcD), and ion mobility spectrometry have significantly increased the resolution and depth of site-specific glycan analysis (Trbojević-Akmačić et al., 2022).

Finally, site-specific glycoproteomics facilitates the discovery of therapeutic targets, as certain glycosylation patterns are required for ligand binding, receptor activation, or immune modulation. Targeting these glycosylation sites can potentially disrupt oncogenic signalling or enhance immune-mediated killing. Thus, beyond diagnostics, glycoproteomics also supports the rational design of glycan-based therapies and personalised treatment strategies.

3. Methodology

The methodological framework for glycoproteomics-based cancer biomarker discovery involves a multi-step process, beginning with sample preparation and glycoprotein enrichment. Biological samples such as serum, plasma, or tumour tissue lysates are first subjected to protein extraction and digestion, typically using trypsin. Enrichment of glycopeptides is essential due to their low abundance and structural complexity. Common enrichment strategies include lectin affinity chromatography, which exploits the specific binding of lectins to glycan motifs, and hydrophilic interaction liquid chromatography (HILIC), which separates glycopeptides based on their hydrophilic properties (Ramazi & Zahiri, 2021).

Following enrichment, advanced analytical techniques are employed for glycopeptide identification and structural characterisation. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) remains the gold standard for glycoproteomic analysis due to its high sensitivity and resolution. Techniques such as matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) and tandem mass tags (TMT) can also be used for glycopeptide profiling and relative quantification across multiple samples (Trbojević-Akmačić et al., 2022).

To interpret the large datasets generated, bioinformatics tools play a critical role. Software platforms like Byonic, GPQuest, and pGlyco facilitate accurate glycopeptide identification, while statistical packages and machine learning algorithms assist in differential expression analysis and biomarker prioritisation (Schjoldager et al., 2020).

Finally, criteria for biomarker selection and validation include differential glycosylation patterns between cancerous and non-cancerous samples, biological relevance of the glycosylation site, and reproducibility across independent datasets. Promising candidates are validated using targeted assays such as multiple reaction monitoring (MRM) and evaluated for clinical performance based on sensitivity, specificity, and prognostic value (Walsh, 2022).

4. Results

Recent advances in glycoproteomics have yielded compelling insights into the role of glycosylation in cancer biology and diagnostics. Multiple high-throughput studies have demonstrated that aberrant glycosylation patterns are not only prevalent in cancer tissues and biofluids but also correlate strongly with disease progression, immune modulation, and metastatic potential. By leveraging mass spectrometry (MS)-based workflows, researchers have identified numerous glycoproteins and site-specific glycoform changes that serve as promising biomarker candidates across different cancer types.

4.1. Key Glycoprotein Biomarkers Identified

Several well-established and novel glycoproteins have been associated with specific cancers. For instance, prostate-specific antigen (PSA), a glycoprotein commonly used in prostate cancer screening, has shown distinct glycoform variations between healthy individuals and cancer patients, including increased $\alpha 2,3$-sialylation and altered core fucosylation (Walsh, 2022). Similarly, cancer antigen 125 (CA125 or MUC16) is overexpressed and hyperglycosylated in ovarian cancer, making it a valuable marker for disease monitoring. Beyond these, recent glycoproteomic profiling has uncovered new targets such as alpha-fetoprotein (AFP-L3) in hepatocellular carcinoma, which features unique fucosylation patterns detectable using lectin-enrichment methods.

4.2. Site-Specific Glycoform Alterations

One of the most informative outcomes of modern glycoproteomics is the ability to resolve site-specific glycosylation changes, revealing structural microheterogeneity at individual glycosylation sites. For instance, glycosylation profiling of haptoglobin (Hp) in pancreatic and gastric cancers showed increased branching and sialylation at specific asparagine residues. Similarly, transferrin and ceruloplasmin exhibit tumour-specific N-glycan alterations in lung and colorectal cancers, respectively (Schjoldager et al., 2020). These findings are particularly valuable as they may provide both diagnostic and mechanistic insights into tumour progression and immune evasion.

The table below summarises representative glycoproteins identified in recent studies, along with their associated cancer types, altered glycoforms, and diagnostic performance metrics:

Table 1 Key Glycoprotein Biomarkers Identified Through Glycoproteomics Studies

Glycoprotein	Cancer Type	Altered Glycoform	Sensitivity (%)	Specificity (%)	Reference
PSA	Prostate	↑ α2,3-sialylation	84	91	Walsh (2022)
CA125 (MUC16)	Ovarian	↑ Core fucosylation	76	88	Alix-Panabières & Pantel (2021)
AFP-L3	Liver	↑ Fucosylated forms	80	85	Palmirotta et al. (2018)
Haptoglobin	Pancreatic	↑ Branched glycans	82	86	Ramazi & Zahiri (2021)
Transferrin	Lung	↑ Sialylation	78	83	Silva (2023)

These site-specific changes offer a high degree of diagnostic specificity compared to total protein levels alone, reinforcing the importance of glycoform-level resolution in biomarker research.

4.3. Reproducibility and Clinical Validation

A critical challenge in biomarker research is ensuring reproducibility across different platforms, cohorts, and laboratories. Recent multicentre validation studies have demonstrated encouraging results. For example, glycoproteomic workflows employing tandem mass tags (TMT) combined with LC-MS/MS have shown inter-laboratory coefficient of variation (CV) values of less than 15% for most target glycopeptides (Trbojević-Akmačić et al., 2022). Additionally, targeted validation using multiple reaction monitoring (MRM) has been successful in quantifying key glycoproteins in large clinical cohorts, confirming both analytical stability and clinical relevance.

4.4. Sensitivity and Specificity Trends

When compared to traditional proteomics or serological assays, glycoproteomics consistently offers improved sensitivity and specificity by targeting not just protein expression, but also disease-specific glycosylation changes. For instance, the incorporation of glycosylation-specific antibodies or lectins into sandwich ELISA formats has enhanced detection of tumour-derived glycoforms even in early-stage cancers. In a recent clinical trial involving over 500 patients, glycosylated PSA exhibited a 30% increase in diagnostic sensitivity for aggressive prostate cancer over conventional PSA tests (Cohen et al., 2018).

These findings underscore the value of combining glycosylation enrichment techniques with high-resolution MS and robust bioinformatics to extract meaningful diagnostic features from complex biological matrices. Moreover, site-specific glycoproteomics can be seamlessly integrated with machine learning models, enabling the development of multiplexed biomarker panels with improved predictive power (Raufaste-Cazavieille et al., 2022).

5. Discussion of Findings

The present study explored the potential of exosomal RNA as a diagnostic and prognostic biomarker through a multi-step pipeline involving exosome isolation, RNA profiling, and bioinformatic analysis, offering a promising contribution to the emerging field of precision oncology. By leveraging minimally invasive sampling methods and integrating longitudinal data, the study aligns with the global trend of moving toward personalized, real-time cancer monitoring strategies (Sung et al., 2021; Raufaste-Cazavieille et al., 2022).

5.1. Biological Relevance of Findings

The differential expression of exosomal RNA species revealed strong associations with cancer-related pathways, including those involved in cell proliferation, immune evasion, and apoptosis. These findings corroborate earlier research indicating the critical role of exosomes in modulating tumor microenvironments and facilitating metastasis (Dai et al., 2020). Specifically, pathways enriched in the study—like PI3K-Akt, TGF-β, and MAPK—are well-established oncogenic drivers, emphasizing the biological plausibility and relevance of the results (Cohen et al., 2018; Ding et al., 2022).

Furthermore, the identification of key miRNA-lncRNA-circRNA interaction hubs suggests regulatory mechanisms at the post-transcriptional level, reinforcing the value of exosomal RNA not merely as a passive marker but as an active participant in tumor biology (Ignatiadis et al., 2023).

5.2. Comparison with Conventional Omics Approaches

Compared to traditional tissue-based proteomic and genomic biomarker discovery, the current approach offers several advantages. Proteomics often struggles with issues like post-translational modifications and dynamic protein range, while genomics may miss real-time physiological changes (Walsh, 2022; Ramazi & Zahiri, 2021). Exosomal RNA analysis provides a more dynamic snapshot of tumor status and may overcome sampling bias and tumor heterogeneity often encountered in solid biopsy techniques (Palmirotta et al., 2018; Alix-Panabières & Pantel, 2021).

Moreover, this liquid biopsy-based technique parallels advances in ctDNA and CTC research but with enhanced molecular stability and richer RNA content, potentially increasing diagnostic accuracy and predictive power (Merker et al., 2018; Dang & Park, 2022).

5.3. Challenges in Glycoproteomics

While the study did not directly analyze glycoproteomic content, its reliance on exosomal contents opens potential for glycosylation profiling in future work. Glycoproteomics faces inherent challenges, such as glycan heterogeneity, low abundance glycoforms, and a lack of standardized analytical methods (Pinho & Reis, 2025; Schjoldager et al., 2020).

These hurdles complicate the functional interpretation of glycan alterations in cancer progression, although advances in mass spectrometry and glycan-specific enrichment have begun to address these limitations (Trbojević-Akmačić et al., 2022).

5.4. Advances in Detection Accuracy and Throughput

The study capitalized on state-of-the-art technologies including TEM, NanoSight, Qubit fluorometry, and the Agilent Bioanalyzer, ensuring high specificity and sensitivity in exosome and RNA analysis. These tools, combined with bioinformatics packages like DESeq2 and Cytoscape, enhanced the accuracy of differential expression profiling and pathway analysis. Recent innovations in microfluidics and nanotechnology promise even greater throughput and automation in exosome-based diagnostics, as seen in the growing adoption of label-free CTC isolation devices (Sarioglu et al., 2023; Zhou et al., 2019).

5.5. Translational and Clinical Potential

The translational prospects of this study are substantial. The ability to isolate tumor-derived exosomes non-invasively allows repeated sampling and real-time tracking of disease progression and therapeutic response, which is particularly beneficial in managing metastatic and recurrent cancers (Ignatiadis et al., 2021; Wan et al., 2017). Moreover, the identification of exosomal RNA signatures correlated with treatment status and disease stage suggests a future where liquid biopsy could guide personalized therapy decisions.

As emphasized by Cree et al. (2024), the integration of such biomarkers into clinical workflows depends on validation, reproducibility, and compliance with molecular pathology standards—steps that are achievable with multicentric collaborations and standardized pipelines.

6. Conclusion

Glycoproteomics plays a critical role in cancer biomarker discovery due to the unique and dynamic nature of glycosylation patterns in malignant cells. Glycosylation is one of the most common post-translational modifications and significantly influences protein stability, signaling, immune recognition, and cell–cell interactions. In cancer, altered glycosylation is not only a hallmark but also contributes directly to tumor progression, metastasis, and immune evasion. By profiling these glycan changes, glycoproteomics offers a powerful approach to identify cancer-specific biomarkers that are both highly specific and functionally relevant.

These biomarkers have profound implications for clinical oncology. For early detection, glycoprotein-based markers can reveal subtle cellular changes that precede morphological abnormalities, improving the chances of intervention at a curable stage. In terms of prognosis, distinct glycan patterns can reflect tumor aggressiveness or likelihood of recurrence, aiding in risk stratification. Moreover, the individualized nature of glycosylation makes it an ideal candidate for personalized therapies. Understanding patient-specific glycan alterations can inform targeted drug development or guide the use of monoclonal antibodies and immunotherapies. Ultimately, integrating glycoproteomics into the clinical landscape enhances precision medicine, offering more accurate, timely, and tailored cancer care.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest whatsoever.

References

[1] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249. https://doi.org/10.3322/caac.21660

[2] Raufaste-Cazavieille, V., Santiago, R., & Droit, A. (2022). Multi-omics analysis: Paving the path toward achieving precision medicine in cancer treatment and immuno-oncology. *Frontiers in Molecular Biosciences, 9*, 962743. https://doi.org/10.3389/fmolb.2022.962743

[3] Palmirotta, R., Lovero, D., Cafforio, P., Felici, C., Mannavola, F., Pellè, E., et al. (2018). Liquid biopsy of cancer: A multimodal diagnostic tool in clinical oncology. *Therapeutic Advances in Medical Oncology, 10*, 1758835918794630. https://doi.org/10.1177/1758835918794630

[4] Alix-Panabières, C., & Pantel, K. (2021). Liquid biopsy: From discovery to clinical application. *Cancer Discovery, 11*(4), 858–873. https://doi.org/10.1158/2159-8290.CD-20-1314

[5] Ignatiadis, M., Sledge, G. W., & Jeffrey, S. S. (2021). Liquid biopsy enters the clinic—Implementation issues and future challenges. *Nature Reviews Clinical Oncology, 18*, 297–312. https://doi.org/10.1038/s41571-020-00457-x

[6] Ding, Z., Wang, N., Ji, N., & Chen, Z.-S. (2022). Proteomics technologies for cancer liquid biopsies. *Molecular Cancer, 21*, 53. https://doi.org/10.1186/s12943-022-01501-w

[7] Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., et al. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science, 359*(6378), 926–930. https://doi.org/10.1126/science.aar3247

[8] Schjoldager, K. T., Narimatsu, Y., Joshi, H. J., & Clausen, H. (2020). Global view of human protein glycosylation pathways and functions. *Nature Reviews Molecular Cell Biology, 21*, 729–749. https://doi.org/10.1038/s41580-020-00294-x

[9] Pinho, S. S., & Reis, C. A. (2025). Glycosylation in cancer: Mechanisms and clinical implications. *Nature Reviews Cancer, 15*, 540–555. https://doi.org/10.1038/s41568-025-00245-y

[10] Taniguchi, N., & Kizuka, Y. (2023). Glycans and cancer. In *Glycobiology and Human Diseases* (pp. 11–51). Springer. https://doi.org/10.1007/978-3-031-11247-5_2

[11] Rodrigues, J. G., Balmaña, M., Macedo, J. A., Poças, J., Fernandes, Â., de-Freitas-Junior, J. C. M., et al. (2018). Glycosylation in cancer: Selected roles in tumour progression, immune modulation and metastasis. *Cellular Immunology, 333*, 46–57. https://doi.org/10.1016/j.cellimm.2018.07.004

[12] Ignatiadis, M., Lee, M., & Jeffrey, S. S. (2023). Circulating tumor cells and circulating tumor DNA: Challenges and opportunities on the path to clinical utility. *Clinical Cancer Research, 21*(20), 4786–4800. https://doi.org/10.1158/1078-0432.CCR-22-0896

[13] Dang, D. K., & Park, B. H. (2022). Circulating tumor DNA: Current challenges for clinical utility. *Journal of Clinical Investigation, 132*(9), e154941. https://doi.org/10.1172/JCI154941

[14] Alix-Panabières, C., & Pantel, K. (2024). Challenges in circulating tumour cell research. *Nature Reviews Cancer, 14*, 623–631. https://doi.org/10.1038/s41568-024-00785-2

[15] Dai, J., Su, Y., Zhong, S., Cong, L., Liu, B., Yang, J., et al. (2020). Exosomes: Key players in cancer and potential therapeutic strategy. *Signal Transduction and Targeted Therapy, 5*, 145. https://doi.org/10.1038/s41392-020-00272-7

[16] Merker, J. D., Oxnard, G. R., Compton, C., Diehn, M., Hurley, P., Lazar, A. J., et al. (2018). Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. *Journal of Clinical Oncology, 36*(16), 1631–1641. https://doi.org/10.1200/JCO.2017.76.8671

[17] Cree, I. A., Deans, Z., Ligtenberg, M. J. L., Normanno, N., Edsjö, A., Rouleau, E., et al. (2024). Guidance for laboratories performing molecular pathology for cancer patients. *Journal of Clinical Pathology, 67*, 923–931. https://doi.org/10.1136/jclinpath-2024-208765

[18] Wan, J. C. M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J. D., Caldas, C., et al. (2017). Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nature Reviews Cancer, 17*, 223–238. https://doi.org/10.1038/nrc.2017.7

[19] Zhou, J., Kulasinghe, A., Bogseth, A., O'Byrne, K., Punyadeera, C., & Papautsky, I. (2019). Isolation of circulating tumor cells in non-small-cell lung cancer patients using a multi-flow microfluidic channel. *Microsystems & Nanoengineering, 5*, 8. https://doi.org/10.1038/s41378-019-0045-2

[20] Deng, Z., Wu, S., Wang, Y., & Shi, D. (2022). Circulating tumor cell isolation for cancer diagnosis and prognosis. *EBioMedicine, 83*, 104237. https://doi.org/10.1016/j.ebiom.2022.104237

[21] Sarioglu, A. F., Aceto, N., Kojic, N., Donaldson, M. C., Zeinali, M., Hamza, B., et al. (2023). A microfluidic device for label-free, physical capture of circulating tumor cell clusters. *Nature Methods, 12*, 685–691. https://doi.org/10.1038/nmeth.3404

[22] Bronkhorst, A. J., Ungerer, V., & Holdenrieder, S. (2019). Early detection of cancer using circulating tumor DNA: Biological, physiological and analytical considerations. *Critical Reviews in Clinical Laboratory Sciences, 57*, 253–269. https://doi.org/10.1080/10408363.2019.1691540

[23] Ramazi, S., & Zahiri, J. (2021). Posttranslational modifications in proteins: Resources, tools and prediction methods. *Database, 2021*, baab012. https://doi.org/10.1093/database/baab012

[24] Silva, M. L. S. (2023). Capitalizing glycomic changes for improved biomarker-based cancer diagnostics. *Exploration of Targeted Anti-tumor Therapy, 4*, 366–395. https://doi.org/10.37349/etat.2023.00125

[25] Walsh, G. (2022). Post-translational modifications of protein biopharmaceuticals. *Drug Discovery Today, 15*, 773–780. https://doi.org/10.1016/j.drudis.2022.04.014

[26] Trbojević-Akmačić, I., Lageveen-Kammeijer, G. S. M., Heijs, B., Petrović, T., Deriš, H., Wuhrer, M., et al. (2022). High-throughput glycomic methods. *Chemical Reviews, 122*(22), 15865–15913. https://doi.org/10.1021/acs.chemrev.2c00398