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REVIEW

Hematologic Glyco-Signatures: Emerging Blood-Based Sugar Codes Linked to Hyper-Aggressive Breast Cancer

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Abstract: Emerging evidence suggests that aberrant glycosylation patterns in cancer are not confined to tumor tissues but are also reflected systemically in circulating blood components. In hyper-aggressive breast cancer phenotypes, including triple-negative and inflammatory subtypes, distinct alterations in glycoproteins, immunoglobulins, and extracellular vesicle-associated glycans have been reported. These hematologic glyco-signatures represent dynamic "sugar codes" shaped by dysregulated glycosyltransferase activity, inflammatory signaling, and tumor–host interactions. This narrative review synthesizes current knowledge on blood-based glycosylation alterations associated with aggressive breast cancer biology, emphasizing their mechanistic relevance to immune modulation, metastatic dissemination, and tumor progression. Particular attention is given to altered sialylation, fucosylation, and glycan branching patterns observed in circulating proteins, as well as their potential role in immune evasion through lectin–glycan interactions. While hematologic glyco-signatures show promise as minimally invasive biomarkers for diagnosis, prognosis, and disease monitoring, current evidence remains largely exploratory and heterogeneous. Significant challenges persist, including analytical variability, lack of standardized platforms, and limited large-scale clinical validation. Moreover, the causal versus correlative role of circulating glyco-alterations in tumor aggressiveness remains under active investigation. In conclusion, hematologic glyco-signatures represent a promising but still evolving frontier in breast cancer biomarker research. Their integration into clinical oncology will require rigorous validation, harmonization of glycomics methodologies, and comparative studies with established liquid biopsy approaches such as circulating tumor DNA and circulating tumor cells.

Keywords: hematologic glyco-signatures, breast cancer, glycomics, biomarkers, tumor aggressiveness

Introduction

Breast cancer remains a leading cause of cancer-related morbidity and mortality worldwide, with its clinical complexity largely driven by profound molecular and phenotypic heterogeneity. While advances in genomic and transcriptomic profiling have refined disease classification and informed targeted therapies, these approaches provide only a partial representation of tumor biology. Increasingly, attention has shifted toward post-translational modifications—particularly glycosylation—as critical yet underexplored determinants of cancer progression, immune interaction, and therapeutic response.[1,2] Glycosylation, the enzymatic addition of carbohydrate moieties to proteins and lipids, is a highly dynamic and tightly regulated process that influences protein folding, stability, receptor signaling, and cell–cell communication. In cancer, this process becomes dysregulated through altered expression and activity of glycosyltransferases and glycosidases, leading to the generation of aberrant glycan structures. These tumor-associated glycan alterations are not confined to malignant cells but extend into the systemic circulation, where they can be detected on serum glycoproteins, immunoglobulins, and extracellular vesicles. This systemic manifestation has given rise to the concept of hematologic glyco-signatures—circulating patterns of glycosylation that reflect tumor–host interactions.[3,4]

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In breast cancer, particularly in hyper-aggressive subtypes such as triple-negative and inflammatory breast cancer, accumulating evidence suggests that distinct glycosylation changes are associated with enhanced tumor proliferation, immune evasion, and metastatic dissemination. Alterations in sialylation, fucosylation, and glycan branching have been linked to key oncogenic processes, including modulation of growth factor receptor signaling, evasion of immune surveillance via lectin–glycan interactions, and facilitation of tumor cell adhesion within the metastatic cascade. These findings support the biological plausibility of glyco-signatures as both mechanistic contributors to disease progression and as accessible systemic biomarkers.[5,6] Hematologic glyco-signatures offer a potentially complementary approach to established liquid biopsy modalities such as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). Unlike genomic alterations, which are relatively static, glycosylation patterns are dynamic and responsive to microenvironmental and metabolic changes, potentially providing real-time insights into tumor behavior and host response. This dynamic nature positions glyco-signatures as attractive candidates for monitoring disease progression, treatment response, and minimal residual disease.[6,7]

Much of the current evidence is derived from preclinical studies or small, heterogeneous clinical cohorts, and there is considerable variability in analytical methodologies used for glycan characterization. Furthermore, the specificity of circulating glyco-signatures is challenged by confounding systemic factors such as inflammation, metabolic disorders, and liver function, all of which can independently influence glycosylation patterns. As a result, distinguishing cancer-specific glyco-alterations from broader physiological changes remains a significant challenge.[8] In this context, the present narrative review aims to provide a comprehensive and critically balanced synthesis of current knowledge on hematologic glyco-signatures in hyper-aggressive breast cancer. The review explores the biological basis of glycosylation alterations, examines their mechanistic links to tumor aggressiveness, and evaluates their potential clinical applications as diagnostic and prognostic biomarkers. Particular emphasis is placed on distinguishing established evidence from emerging hypotheses, highlighting methodological limitations, and outlining key priorities for future research and clinical translation.

Revised Methods

This work was conducted as a narrative review aimed at synthesizing and critically appraising the current body of literature on hematologic glyco-signatures in hyper-aggressive breast cancer. Given the emerging and interdisciplinary nature of this topic, a flexible and iterative approach to literature identification, selection, and interpretation was adopted to capture both foundational and recent developments across glycomics, oncology, and translational biomarker research. Relevant studies were identified through a structured search of major scientific databases, including PubMed/MEDLINE, Scopus, and Web of Science. The search strategy combined controlled vocabulary and free-text terms related to glycosylation and breast cancer, including but not limited to "glycosylation," "glycomics," "glycoproteins," "sialylation," "fucosylation," "immunoglobulin glycosylation," "extracellular vesicles," "breast cancer," "triple-negative breast cancer," "inflammatory breast cancer," and "liquid biopsy." Additional articles were identified through manual screening of reference lists from relevant publications to ensure comprehensive coverage of key studies.

The review prioritized peer-reviewed original research articles, systematic reviews, and high-quality experimental studies that examined circulating or blood-based glycosylation patterns in the context of breast cancer. Where direct breast cancer evidence was limited, selected studies from related cancer types or mechanistic models were included to provide biological context, with careful distinction made between direct and extrapolated findings. Emphasis was placed on studies investigating serum glycoproteins, immunoglobulin glycosylation, and extracellular vesicle-associated glycans as components of hematologic glyco-signatures. Study selection was guided by relevance to the central themes of the review, including mechanistic insights, biomarker potential, and translational applicability. No strict temporal restriction was imposed; however, priority was given to recent literature to reflect current advances in analytical glycomics technologies and cancer biology. Given the narrative nature of the review, formal meta-analysis and quantitative synthesis were not performed. Instead, findings were qualitatively integrated to highlight recurring patterns, areas of consensus, and points of divergence within the literature.

To enhance scientific rigor and transparency, particular attention was paid to distinguishing levels of evidence, including established clinical observations, emerging experimental findings, and hypothesis-driven interpretations. Methodological variability across studies—such as differences in analytical platforms (eg., mass spectrometry, lectin-

based assays), sample preparation, and cohort characteristics—was critically evaluated and explicitly acknowledged as a limitation affecting comparability and reproducibility. This narrative approach was chosen to provide a comprehensive yet critically balanced synthesis of a rapidly evolving field, while identifying key knowledge gaps and priorities for future investigation.

Physiological Basis of Hematologic Glyco-Signatures

Glycosylation, the enzymatic attachment of carbohydrate moieties (glycans) to proteins and lipids, is one of the most ubiquitous and functionally diverse post-translational modifications in human biology. Glycans serve structural, signaling, and immunomodulatory roles and are integral to maintaining cellular homeostasis. In the hematologic context, glycosylation modulates immune cell recognition, receptor signaling, coagulation, and intercellular communication, making it particularly relevant for systemic responses to cancer.[9] Hematologic glyco-signatures refer to reproducible patterns of glycosylation observed in circulating proteins, plasma glycoproteins, immunoglobulins, and hematopoietic cells. These signatures are not random; they reflect tightly regulated enzymatic processes governed by glycosyltransferases, glycosidases, nucleotide sugar availability, and the cellular microenvironment. Disruption of these regulatory pathways—whether due to oncogenic signaling, inflammatory mediators, or metabolic reprogramming—results in characteristic alterations in circulating glycan patterns that can serve as systemic indicators of disease.[7,10]

In hyper-aggressive breast cancer, tumor cells actively remodel systemic glycosylation through multiple mechanisms. First, the tumor microenvironment secretes cytokines and growth factors, such as interleukin-6 (IL-6) and transforming growth factor-β (TGF-β), which modulate glycosyltransferase expression in hepatocytes, immune cells, and endothelial cells, thereby altering the glycosylation of circulating proteins.[11] Second, metabolic rewiring in cancer cells—including enhanced glycolysis and flux through the hexosamine biosynthetic pathway—increases substrate availability for glycan synthesis, promoting aberrant sialylation, fucosylation, and branching. Third, the interplay between tumor-secreted glycoproteins and immune effectors reshapes the glycan landscape of immunoglobulins and leukocytes, influencing immune recognition, activation, and evasion.[12]

Elevated α2,3- and α2,6-linked sialic acids on circulating glycoproteins and immunoglobulins enhance negative charge and steric hindrance, reducing immune-mediated clearance and facilitating metastatic dissemination.[13] Increased tetra- and tri-antennary N-glycans are associated with hyper-aggressive tumor phenotypes, promoting receptor clustering, signal amplification, and cellular adhesion.[14] Core and terminal fucosylation on plasma proteins and immune cells modulate selectin-mediated adhesion and immune cell trafficking, creating a permissive environment for tumor spread.[15] Accumulation of Tn and sTn antigens on glycoproteins reflects incomplete mucin-type O-glycosylation, correlating with poor prognosis and enhanced tumor invasiveness.[16] These glycan alterations are functionally significant. For example, desialylation of IgG Fc regions enhances antibody-dependent cellular cytotoxicity, whereas hypersialylation suppresses immune effector function, allowing tumors to evade immune surveillance. Similarly, altered fucosylation and branching patterns modulate endothelial adhesion and platelet-tumor interactions, facilitating intravascular survival and metastatic colonization.[17]

Importantly, hematologic glyco-signatures integrate signals from multiple physiological axes—tumor biology, immune response, and systemic metabolism—making them highly sensitive indicators of tumor aggressiveness. Unlike tissue-based biomarkers, which provide a localized snapshot, these blood-based sugar codes offer a dynamic, systemic readout of the interplay between host and tumor. Their reproducibility and accessibility through minimally invasive blood sampling make them particularly attractive for longitudinal monitoring, early detection, and prognostic assessment (Table 1).[18]

Analytical Platforms for Detection of Hematologic Glyco-Signatures

The detection and characterization of hematologic glyco-signatures require analytical platforms capable of resolving the structural complexity and heterogeneity inherent to glycans. Unlike nucleic acids or proteins, glycans exhibit extensive branching, variable monosaccharide composition, and diverse linkages, making their analysis technically challenging. Over the past decade, advancements in glycomics technologies have enabled high-resolution profiling of blood-based sugar codes, facilitating their exploration as biomarkers in hyper-aggressive breast cancer (Table 2).[19]

Table 1 Physiological Basis of Hematologic Glyco-Signatures

Physiological Component	Glycosylation Features	Underlying Biological Drivers	Relevance to Blood-Based Glyco-Signatures
Hepatic Glycoprotein Synthesis	Complex N-glycans; controlled fucosylation and sialylation	Steady-state hepatic glycosyltransferase activity; balanced acute-phase protein turnover	Baseline circulating glycan architecture originates from liver-derived glycoproteins (eg., transferrin, haptoglobin, alpha-1-acid glycoprotein).
Immunoglobulin Production (B Cells, Plasma Cells)	Fc N-glycans with regulated galactosylation, sialylation, fucosylation	Physiological humoral immunity; homeostatic cytokine levels (IL-6, BAFF)	IgG glycoforms shape innate immune tone and contribute to inter-individual glycome variability.
Platelet Glycosylation Dynamics	O-glycans and terminal sialic acids on membrane glycoproteins (GPIbα, GPVI)	Normal megakaryocyte maturation; regulated platelet turnover	Platelet glyco-patterns influence hemostasis and thrombosis, contributing to the circulating glycome.
Red Blood Cell Glycocalyx	Sialic-acid–rich O- and N-glycans	Erythropoiesis and erythrocyte aging; homeostatic desialylation	RBC-derived glycans maintain serum sialic acid balance and influence immune interactions.
Lipoprotein-Associated Glycans (HDL, LDL, Apo Proteins)	N- and O-glycans modulating lipid transport	Lipid metabolic pathways; apolipoprotein biosynthesis	Lipoprotein glycosylation contributes to systemic glycome pools and reflects metabolic state.
Extracellular Vesicles (EVs) in Circulation	High-mannose, sialylated, and fucosylated glycans on EV surfaces	Constitutive cell turnover; intercellular communication	EV glycomes reflect tissue-of-origin signals and normalize the background against which tumor-derived EVs are detected.
Acute-Phase Response (Baseline)	Moderate increases in branched N-glycans and sialylation	Low-grade homeostatic inflammation; mild cytokine activation	Establishes the physiological reference point from which pathological glyco-shifts are quantified.
Endothelial Glycocalyx Shedding	GlcNAc- and heparan-rich glycan fragments	Normal vascular turnover; shear stress physiology	Endothelial contributions define circulating glycan fragments and influence systemic glycome composition.
Glycan Salvage Pathways & Metabolic Inputs	Balanced flux through the hexosamine biosynthetic pathway (HBP)	Normal glucose, glutamine, and UDP-sugar pools	Systemic metabolic status modulates foundational glycan structures detectable in blood.

Mass Spectrometry (MS)

Mass spectrometry remains the cornerstone for glycan analysis due to its sensitivity, specificity, and structural resolution. Both matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) and liquid chromatography–mass spectrometry (LC-MS) platforms allow detailed characterization of N- and O-glycans on serum proteins, immunoglobulins, and circulating glycoproteins. Coupled with enzymatic digestion and permethylation strategies, MS can identify specific glycan compositions, branching patterns, and sialylation or fucosylation states that are associated with hyper-aggressive tumor phenotypes. High-resolution MS further enables detection of minor glycan variants, which may be critical for differentiating aggressive versus indolent breast cancers.[20]

Lectin Microarrays

Lectin-based approaches exploit the carbohydrate-binding specificity of lectins to capture and profile glycan motifs. Lectin microarrays provide semi-quantitative assessment of glycan abundance and diversity in plasma or serum samples. By comparing lectin-binding patterns between patient cohorts, researchers can identify characteristic glycosylation signatures associated with tumor aggressiveness. These arrays are particularly useful for high-throughput screening and have been successfully applied to distinguish triple-negative breast cancer from hormone receptor-positive subtypes based on plasma glyco-profiles.[21]

Table 2 Analytical Platforms for Detection of Hematologic Glyco-Signatures

Analytical Platform	Core Principle/Technology	Key Strengths	Limitations	Typical Applications in Glyco-Signature Research
LC–MS/MS Glycoproteomics	Separation of glycopeptides by liquid chromatography followed by mass spectrometric fragmentation	High structural resolution; site-specific glycan profiling; quantitative accuracy	Requires complex sample prep; higher cost; expert analysis	Mapping site-specific glycan changes on serum proteins and EV glycoproteins.
MALDI–TOF MS Glycomics	Matrix-assisted laser desorption/ ionization and time-of-flight mass detection of released glycans	High throughput; rapid spectra acquisition; suitable for large cohorts	Limited isomer discrimination; moderate structural detail	Global N- and O-glycome profiling, biomarker discovery, disease stratification.
HILIC-UPLC Glycan Profiling	Hydrophilic interaction liquid chromatography for released glycan separation	Robust reproducibility; separation of glycan isomers; scalable for clinical studies	Requires fluorescent labeling; moderate sensitivity	Diagnostic glycan signature quantification; longitudinal patient monitoring.
Capillary Electrophoresis (CE-LIF)	Charge-based separation of labeled glycans with laser-induced fluorescence detection	Excellent resolution of charged and sialylated species; low sample volume	Limited detection of neutral glycans; requires derivatization	Detailed sialylation pattern analysis, rapid profiling of serum N-glycans.
Lectin Microarrays	Glycan-binding lectins immobilized on arrays to capture glycan motifs	High-throughput motif-level mapping; low cost; minimal sample processing	Does not provide full structural detail; semi-quantitative	Screening for sialylation, fucosylation, mannosylation patterns in serum and EVs.
Glycan-Specific ELISA (Lectin-ELISA/Antibody-ELISA)	Lectins or glycan-specific antibodies quantify glycoforms on target proteins	Clinically scalable; high sensitivity; low sample complexity	Requires predefined glycan targets; limited discovery potential	Validation of known glyco-biomarkers (eg., sLeX, sTn, core-fucosylation).
Ion Mobility Mass Spectrometry (IM-MS)	Gas-phase separation of glycan isomers prior to MS detection	Superior isomer resolution; enhances structural confidence	Requires specialized MS instrumentation; analytical complexity	Distinguishing glycan isomers in aggressive cancer signatures.
NMR-Based Glycomics	Nuclear magnetic resonance analysis of glycan structures	Non-destructive; absolute structural verification	Low sensitivity; large sample amounts needed	Confirmatory structural validation of complex glycans.
Raman Spectroscopy/SERS Glyco-Analytics	Vibrational fingerprinting enhanced by metal nanoparticles (SERS)	Extremely rapid; minimal sample processing; potential point-of-care use	Limited structural specificity; requires calibration	Screening changes in global glyco-patterns in real time.
Single-EV Glycomics (Nano-IR, Nanopore, Flow-Glycomics)	High-resolution glycan detection on individual extracellular vesicles	Captures heterogeneity; detects rare tumor-derived EV signatures	Technically demanding; not yet standardized; high cost	Detection of tumor-specific EV glyco-signatures in aggressive breast cancer.
Computational Glyco-Bioinformatics Platforms	AI-assisted glycan annotation, spectral deconvolution, and machine-learning modeling	Enables multi-omics integration; predictive analytics; pattern recognition	Dependent on data quality and training sets	Building predictive models of hyper-aggressive breast cancer glyco-signatures.

Capillary Electrophoresis (CE)

Capillary electrophoresis, often coupled with laser-induced fluorescence, offers precise separation of glycan isomers and quantification with high sensitivity. CE provides advantages in resolving structural variants that may not be

distinguishable by mass alone, such as linkage-specific sialylation and positional fucosylation. This level of resolution is critical when subtle glycosylation changes correlate with aggressive tumor behavior.[22]

Chromatography-Based Approaches

High-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) are widely used for glycan separation prior to detection. Fluorescent labeling of released glycans allows quantitative profiling of specific glycoforms, facilitating comparative analysis between patient groups. When combined with MS or CE, chromatographic separation enhances structural elucidation and improves biomarker discovery.[23]

Integration with Bioinformatics and Machine Learning

Glycomics datasets are often high-dimensional and complex, necessitating computational approaches for meaningful interpretation. Machine learning algorithms, including supervised classification and unsupervised clustering, have been employed to identify glycan patterns predictive of hyper-aggressive breast cancer. Integrative pipelines that combine glycan profiling with clinical and proteomic data can enhance predictive accuracy and support the development of multi-marker diagnostic panels.[24–26]

Emerging Technologies

Recent innovations, such as single-cell glycomics, microfluidic lectin chips, and imaging mass spectrometry, provide unprecedented resolution in detecting glycan signatures in specific blood cell populations and spatial contexts. These approaches hold promise for real-time monitoring of glycosylation dynamics during disease progression and therapeutic intervention.[27]

Mechanistic Links of Hematologic Glyco-Signatures to Tumor Aggressiveness

The association between hematologic glyco-signatures and tumor aggressiveness in breast cancer is increasingly understood as a reflection of interconnected molecular and systemic processes that govern tumor progression, immune modulation, and metastatic dissemination. Rather than representing isolated biomarkers, circulating glycosylation patterns appear to emerge from coordinated alterations in tumor cell metabolism, glycosyltransferase activity, and host inflammatory responses, collectively shaping a dynamic "glyco-environment" detectable in peripheral blood (Figure 1).[28] A central mechanistic feature underpinning these signatures is the reprogramming of glycosyltransferase expression in malignant breast epithelial cells. Enzymes such as sialyltransferases and fucosyltransferases are frequently upregulated in aggressive tumor phenotypes, resulting in increased terminal sialylation and altered fucosylation of cell surface and secreted glycoproteins. These modifications enhance tumor cell survival and dissemination by reducing susceptibility to immune-mediated clearance and promoting detachment from the primary tumor microenvironment.[29]

One of the most consistently implicated mechanisms linking glycosylation to tumor aggressiveness involves immune evasion. Hypersialylated glycans expressed on tumor-derived proteins and extracellular vesicles can engage inhibitory Siglec receptors on natural killer cells and macrophages, leading to suppression of cytotoxic immune responses. This glyco-mediated immune checkpoint axis is increasingly recognized as a parallel pathway to classical immune checkpoints, contributing to immune escape in highly aggressive breast cancer subtypes.[30] In parallel, alterations in glycan branching and fucosylation have been associated with enhanced receptor signaling and cellular proliferation. Increased N-glycan branching, often driven by elevated MGAT5 activity, promotes clustering and stabilization of growth factor receptors on the tumor cell surface. This amplifies downstream oncogenic signaling pathways, including PI3K/AKT and MAPK cascades, thereby supporting sustained proliferative signaling and resistance to apoptosis.[31]

Hematologic glyco-signatures also reflect the systemic dissemination of tumor-derived components, particularly through circulating glycoproteins and extracellular vesicles. These vesicles carry tumor-specific glycan patterns that can influence distant microenvironments, potentially contributing to pre-metastatic niche formation. While direct causal evidence remains limited, experimental data suggest that glycan-mediated interactions with endothelial and stromal cells may facilitate tumor cell adhesion, extravasation, and organ tropism during metastasis.[32] These glycosylation changes are not solely tumor-autonomous phenomena but are also shaped by host systemic responses, including chronic inflammation

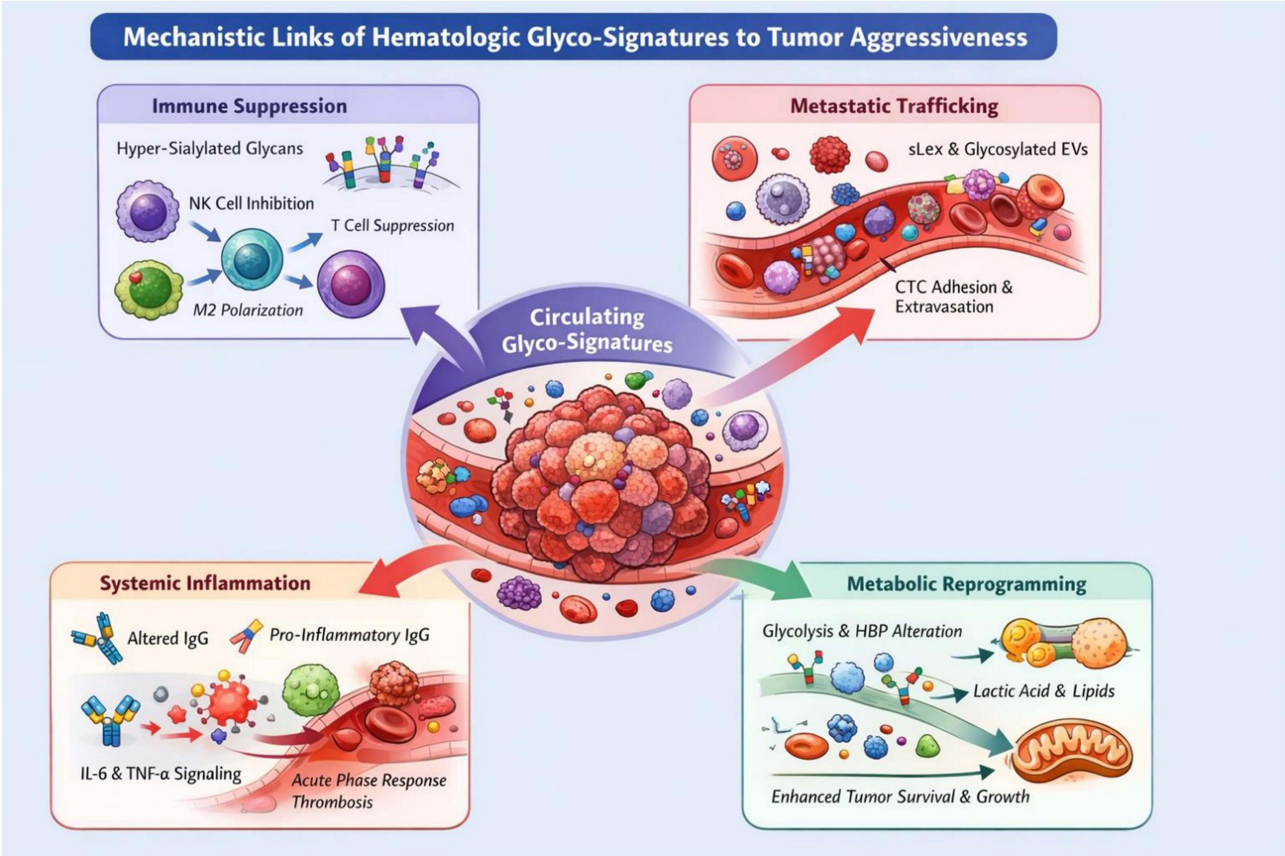

Figure 1 Mechanistic Links of Hematologic Glyco-Signatures to Tumor Aggressiveness.

and metabolic reprogramming. Acute-phase proteins produced by the liver undergo significant glycosylation remodeling in response to inflammatory cytokines, contributing to circulating glyco-alterations that may overlap with tumor-associated signatures. This intersection complicates the interpretation of hematologic glyco-signatures, as they represent composite outputs of both tumor-derived and host-derived processes.[33] Emerging evidence further suggests a potential convergence between altered glycosylation and intracellular stress-adaptation pathways, including those involved in DNA damage response and replication stress signaling. Highly proliferative breast cancer cells exhibit metabolic conditions that favor both aberrant glycan synthesis and activation of checkpoint pathways, such as ATR–CHK1 signaling, indicating a possible coordinated adaptation to oncogenic stress. However, this relationship remains largely exploratory and requires further experimental validation in breast cancer-specific models.[32,33]

Clinical Translation of Hematologic Glyco-Signatures

The mechanistic insights into hematologic glyco-signatures have laid the foundation for their translation into clinical oncology, particularly in the management of hyper-aggressive breast cancer. By providing a minimally invasive, dynamic snapshot of tumor-host interactions, these blood-based sugar codes offer multiple avenues for clinical application, ranging from early detection to prognostication and therapeutic monitoring.[34]

Early Detection and Risk Stratification

One of the most promising applications of hematologic glyco-signatures is in the early identification of aggressive breast tumors. Traditional screening modalities, such as mammography, often fail to detect small, rapidly proliferating lesions, particularly in dense breast tissue. Circulating glyco-signatures can serve as sensitive indicators of underlying oncogenic activity. For example, elevated sialylation and increased branching of N-glycans in serum proteins have been associated

with triple-negative and HER2-enriched breast cancer subtypes, enabling stratification of high-risk individuals prior to clinical manifestation. Integration of glycan profiling with conventional imaging or genetic risk scores could enhance early detection and guide timely intervention.[35,36]

Prognostic Stratification

Beyond detection, hematologic glyco-signatures provide robust prognostic information. Specific patterns of glycosylation, such as hypersialylation of immunoglobulins or aberrant fucosylation of plasma proteins, correlate with metastatic potential, recurrence risk, and overall survival. Unlike static tumor markers, these sugar codes reflect systemic alterations, capturing the interplay between tumor biology, immune modulation, and inflammation. Clinicians can leverage glyco-signature profiling to identify patients who may benefit from more aggressive treatment regimens or closer surveillance, thereby personalizing patient management.[37,38]

Therapeutic Monitoring and Response Prediction

Hematologic glyco-signatures offer a dynamic metric for monitoring treatment response. Changes in circulating glycan patterns can precede radiologic or clinical evidence of response, providing early insights into therapy efficacy. For instance, normalization of aberrant glyco-patterns following chemotherapy or targeted therapy may indicate tumor regression, whereas persistent or emerging glycan alterations could signal resistance or progression. This real-time monitoring has the potential to inform treatment modifications, reducing unnecessary toxicity and optimizing therapeutic outcomes.[7]

Integration with Multi-Omic Platforms

The clinical utility of hematologic glyco-signatures is further enhanced when integrated with other biomarkers, including genomic, proteomic, and metabolomic data. Machine learning algorithms can combine glycan profiles with molecular and clinical variables to develop predictive models with higher accuracy than single-modality biomarkers. Such integrative approaches support precision oncology, allowing for nuanced risk stratification, tailored therapeutic decisions, and improved patient outcomes.[39]

Therapeutic Targeting

Beyond their role as biomarkers, the mechanistic relevance of glyco-signatures opens opportunities for therapeutic intervention. Inhibitors of sialyltransferases, fucosyltransferases, and glycan-binding lectins are under investigation as strategies to disrupt tumor-promoting glycosylation pathways. Targeting these enzymes may enhance immune recognition, reduce metastatic potential, and synergize with conventional therapies, highlighting the dual diagnostic and therapeutic potential of hematologic glyco-signatures.[40]

Challenges to Clinical Implementation

Despite their promise, several challenges remain. Standardization of sample collection, glycan detection, and data analysis is critical for reproducibility across clinical settings. Inter-patient variability and the influence of comorbidities on glycosylation profiles must be accounted for to ensure specificity. Regulatory validation, cost-effectiveness, and integration into existing clinical workflows are also necessary steps before widespread adoption.[41,42]

Emerging Evidence Linking Metabolic Glycosylation Flux with Replication Stress and ATR–CHK1 Signaling in Hyper-Aggressive Breast Cancer

Emerging literature increasingly supports a conceptual convergence between altered cellular metabolism, dysregulated glycosylation pathways, and activation of DNA damage response networks in aggressive breast cancer phenotypes. Although this intersection remains largely hypothesis-driven, it provides a biologically coherent framework for understanding how metabolic stress and proliferative pressure may jointly shape both intracellular tumor behavior and systemic hematologic glyco-signatures. Metabolic glycosylation flux refers to the dynamic redistribution of glucose

and related metabolites into the hexosamine biosynthetic pathway and downstream glycan synthesis processes. In hyper-aggressive breast cancer cells, enhanced glycolytic activity and metabolic reprogramming increase substrate availability for nucleotide sugar production, thereby promoting excessive glycosylation of proteins and lipids. This metabolic shift is often accompanied by upregulation of glycosyltransferases and heightened glycan branching, reflecting an adaptive response to oncogenic signaling and microenvironmental stress.[43]

Concurrently, rapidly proliferating tumor cells experience replication stress characterized by stalled replication forks, increased DNA lesions, and genomic instability. This state of intrinsic cellular stress activates the ATR–CHK1 signaling axis, a central checkpoint pathway responsible for maintaining replication fidelity and coordinating DNA repair with cell cycle progression. In aggressive breast cancer subtypes, persistent activation of ATR–CHK1 signaling has been associated with survival under conditions of high proliferative demand and metabolic constraint.[44] Recent experimental insights suggest that metabolic glycosylation flux and replication stress responses may not operate as independent processes but instead exhibit functional interdependence. Enhanced glycan synthesis demands substantial nucleotide sugar pools, which compete with nucleotide availability required for DNA replication and repair. This metabolic competition may exacerbate replication stress, thereby reinforcing activation of ATR–CHK1 signaling as a compensatory survival mechanism. Conversely, checkpoint activation may further reshape metabolic pathways, promoting survival-oriented metabolic rewiring that sustains aberrant glycosylation.[45] Within this integrated framework, hematologic glyco-signatures may represent systemic readouts of these intracellular stress-adaptation processes. Circulating glycosylation patterns, including altered sialylation and fucosylation profiles, may indirectly reflect heightened metabolic flux and checkpoint dependency in tumor cells. This raises the possibility that blood-based glyco-signatures could serve not only as biomarkers of tumor presence but also as surrogate indicators of replication stress burden and ATR–CHK1 pathway engagement in aggressive disease states.[46]

Critical Appraisal of the Current State of Research on Hematologic Glyco-Signatures in Breast Cancer

The study of hematologic glyco-signatures in breast cancer has expanded rapidly in recent years, driven by advances in glycomics technologies and growing recognition of glycosylation as a central regulator of tumor biology. Despite this progress, the field remains at a predominantly exploratory stage, with most findings derived from preclinical models, small clinical cohorts, or indirect systemic analyses. As such, the current evidence base should be interpreted as hypothesis-generating rather than confirmatory in terms of clinical application. A major strength of existing research lies in its consistent demonstration that breast cancer is associated with widespread alterations in glycosylation patterns across circulating biomolecules, including serum glycoproteins, immunoglobulins, and extracellular vesicles. Recurrent observations of increased sialylation, altered fucosylation, and changes in glycan branching provide biological plausibility for the concept of systemic glyco-signatures reflecting tumor activity. These findings are further supported by mechanistic studies linking glycosyltransferase dysregulation to oncogenic signaling pathways, immune modulation, and metastatic behavior.[47–49]

However, the field is constrained by several important limitations. First, there is substantial heterogeneity in study design, patient stratification, and analytical platforms. Techniques such as mass spectrometry, lectin-based assays, and chromatographic profiling often yield non-comparable results due to differences in sensitivity, glycan resolution, and normalization strategies. This lack of methodological standardization significantly impairs reproducibility and cross-study validation.[50] Second, many reported associations between circulating glyco-alterations and breast cancer aggressiveness are correlative rather than causative. While glycosylation changes are frequently linked to advanced disease states, it remains unclear whether these alterations actively contribute to tumor progression or primarily reflect downstream systemic responses to tumor burden and inflammation. This distinction is critical for evaluating their utility as therapeutic targets versus passive biomarkers.[51,52]

Third, confounding biological variables such as age, metabolic status, chronic inflammation, liver function, and comorbid conditions substantially influence circulating glycosylation profiles. These factors complicate the interpretation of glyco-signatures as cancer-specific indicators and raise concerns regarding specificity, particularly in real-world

clinical populations.[53,54] Fourth, evidence supporting the clinical utility of hematologic glyco-signatures remains limited by small sample sizes, retrospective study designs, and a lack of large-scale prospective validation. Direct comparisons with established liquid biopsy modalities—such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and proteomic panels—are still insufficient, making it difficult to position glyco-signatures within the current diagnostic hierarchy (Table 3).[55,56]

Table 3 Key Direct Glycomics Studies in Breast Cancer

First Author, Year	Sample Type(s)	Glycan Class/ Focus	Platform/ Approach	Main Breast-Cancer–Related Glycan Changes	Clinical/Biological Link	Citations
Benesova 2024	Primary breast tumor tissue + normal breast	N-glycans (permethylated)	MALDI-TOF-MS	Subtype-specific N-glycan profiles; mucinous tumors enriched in highly branched sialylated/fucosylated glycans; luminal tumors show lower branching; normal tissue enriched in bisecting GlcNAc; high-mannose linked to vascular invasion and nodal metastasis[46]	Subtyping, association with tumor size, proliferation, LVI, nodal metastasis[46]	46
Ščupáková 2021	Primary tumors, lymph nodes, multiple metastases, normal tissues (rapid autopsy)	N-glycans (spatial)	MALDI imaging MS on single-patient TMAs	Overall N-glycan abundance increases with metastatic progression; high-mannose most frequently elevated in metastases; bone metastases show higher core-fucosylation and reduced high-mannose[47]	Site-specific metastatic glycosylation; supports high-mannose, fucosylated and complex N-glycans as metastatic markers/ targets[47]	47
Li 2019	Breast cancer tissue, para-carcinoma tissue, benign tumor; breast cancer cells	N-glycans	PGC-ESI-MS /MS	Cancer tissues: increased high-mannose and core-fucosylated glycans; decreased bisected and sialylated glycans vs para-carcinoma; three high-mannose glycans show strong diagnostic performance[48]	Discrimination of cancer vs benign/adjacent tissue; potential tissue and cell biomarkers[48]	48
Goetz 2009	Normal mammary epithelial vs invasive/non-invasive breast cancer cell lines	N- and O-glycans	MS-based quantitative glycomics	Distinct neutral, sialylated and fucosylated glycan profiles between normal, non-invasive and invasive cells; profiles cluster by invasiveness[49]	Differentiation of invasive vs non-invasive cell phenotypes[49]	49
Kyselova 2008	Human serum (stages I–IV breast cancer vs disease-free)	N-glycans (permethylated)	MALDI-MS glycomic profiling	Progressive increase in sialylation and fucosylation with advancing stage; 8 N-glycans strongly associated with breast cancer[50]	Staging and prognosis using serum N-glycan patterns[50]	50

(*Continued*)

Table 3 (Continued).

First Author, Year	Sample Type(s)	Glycan Class/ Focus	Platform/ Approach	Main Breast-Cancer–Related Glycan Changes	Clinical/Biological Link	Citations
Vreeker 2021	Human serum, various breast cancer subtypes vs controls	N-glycans (linkage-specific sialic acid)	High-resolution MS	Modest case–control differences (few tri-/tetra-antennary glycans); clear differences in N-glycan profiles between breast cancer subtypes; some prior signatures not replicated[51]	Highlights subtype heterogeneity and replication issues in serum N-glycomics[51]	[51]
Gebrehiwot 2019	Whole serum and purified IgG (Ethiopian women, stages I–IV)	N-glycans (total and IgG)	Glycoblotting + MALDI-TOF-MS	35 serum N-glycans up-regulated in breast cancer; 17 complex, core-fucosylated, highly branched/sialylated glycans show high AUC for early stages; IgG contains key core-fucosylated agalactosyl glycans distinguishing stage II[52]	Non-invasive early-stage biomarkers; links to immune effector function and aggressive disease[52]	[52]
Lee 2020	Human serum (invasive ductal carcinoma vs healthy)	N-glycans	MALDI-TOF-MS + NosIDsys pattern recognition	24 glycan biomarkers differentiate cancer vs control; strong performance for stage I (AUC 0.93; sensitivity 84.1%, specificity 82.3%); HR/HER2 and lymph-node subtypes separable by N-glycome[53]	Diagnostic platform for early detection and subtyping[53]	[53]
Feleke 2025	Human serum (Ethiopian patients, early-stage enriched)	Sulfated N-glycans	Glycoblotting, WAX separation + MALDI-TOF-MS	Seven mono-sulfated, Lewis-type, highly fucosylated/ sialylated N-glycans markedly elevated in breast cancer with AUC ≥ 0.8; absent in non-sulfated pool[54]	Candidate early-stage serum biomarkers based on sulfated N-glycans[54]	[54]
Fry 2011	Primary tumors; serum and urine from metastatic breast cancer	Mixed N- and O-glycans (lectin binding)	Lectin microarray (45 lectins) with evanescent-field fluorescence	Distinct lectin-binding patterns between metastatic breast cancer samples and controls across tissue, serum, urine; detects global N/ O-glycan alterations from small sample amounts[55]	High-throughput discovery platform for systemic metastatic glycomic signatures[55]	[55]
Funkhouser et al, 2022 (tissue–serum link)	Same 150 patients: tumors + serum	N-glycans	Permethylation + MALDI-TOF-MS	Tissue N-glycan features (high-mannose, branching, fucosylation) linked to clinical parameters and intended correlation with serum glycomics[56]	Framework for paired tissue–serum glycome subtyping and monitoring[56]	[56]

Conclusion

Hematologic glyco-signatures represent an emerging and biologically plausible dimension of breast cancer heterogeneity, reflecting systemic alterations in glycosylation processes associated with tumor–host interactions. In hyper-aggressive breast cancer phenotypes, circulating changes in glycoproteins, immunoglobulin glycosylation, and extracellular vesicle-associated glycans appear to correlate with key pathological processes, including immune modulation, tumor progression, and metastatic potential. Collectively, current evidence supports the view that these blood-based "sugar codes" may serve as promising candidates for minimally invasive biomarkers in diagnosis, prognostication, and disease monitoring. However, the existing body of literature remains largely exploratory, with substantial variability across analytical platforms, study designs, and patient cohorts. Furthermore, the precise biological role of circulating glyco-alterations—whether as functional mediators of disease progression or as reflective systemic signatures of tumor activity—has not yet been definitively established.

From a translational perspective, significant challenges remain, including the need for methodological standardization in glycomics profiling, validation in large and independent clinical cohorts, and direct comparison with established liquid biopsy modalities such as circulating tumor DNA and circulating tumor cells. Addressing these limitations will be essential before hematologic glyco-signatures can be reliably integrated into routine clinical practice. While hematologic glyco-signatures offer a compelling and rapidly evolving framework for understanding breast cancer biology, their clinical utility remains in an early developmental stage. Continued multidisciplinary research is required to clarify their mechanistic relevance and to determine their eventual role within precision oncology.

Disclosure

The authors report no conflicts of interest in this work.

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