Platelet-driven remodeling of cancer cell glycoproteins fuels inflammation and metastasis

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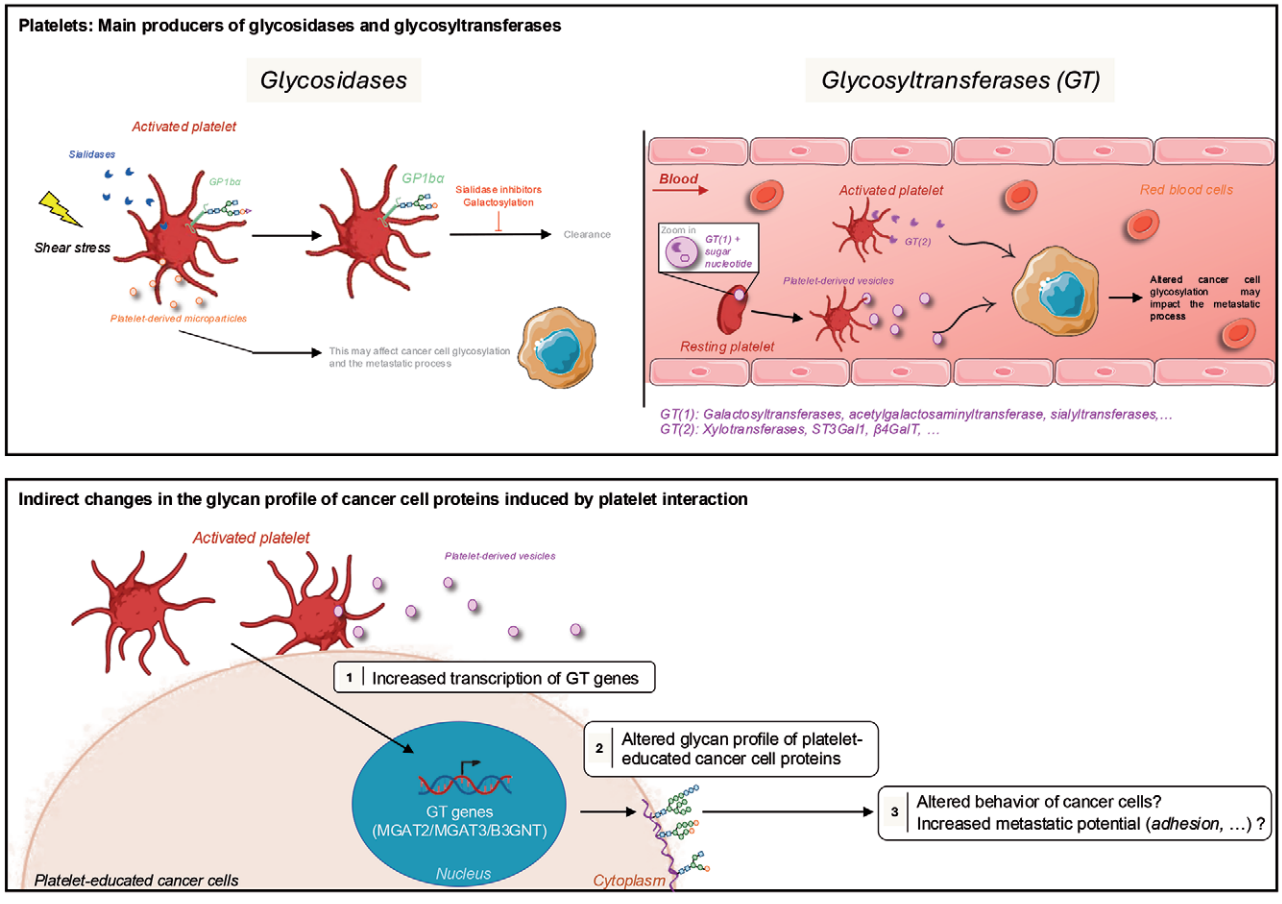
ABSTRACT

This study explores the crucial role of abnormal O- and N-glycosylation (modification of sugar molecules attached to proteins) in cancer progression and metastatic spread. It examines the effect of this deregulation at several stages of tumor development: primary tumor, microenvironment, blood circulation, and extravasation. During most of these stages, cancer cells can interact with platelets. Platelets are no longer simply coagulation agents, but entities capable of educating cancer cells by modifying their enzymatic and transcriptional landscape. The possible use of a specific glycoprotein as a biomarker and a glycan common to several cancers as a therapeutic target has also been described.

GRAPHICAL ABSTRACT



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Key words: O- and N-glycosylation; cancer; inflammation; platelets.

Introduction

The term "metastasis" was first introduced in 1829 by Jean Claude Récamier to describe the spread of cancer cells from a primary tumor to distant organs. Metastasis represents the most lethal stage of cancer, accounting for nearly 90% of cancer-related deaths rather than the primary tumor itself.[1,2] Understanding the mechanisms underlying metastatic spread is therefore central to cancer research. Among these mechanisms, the tumor microenvironment (TME) has emerged as a key factor in tumor progression. Tumors are no longer considered simple masses of malignant cells, but rather complex ecosystems composed of cancer cells and a diverse stromal compartment which, together, determine the outcome of the disease.

The tumor stroma includes cancer stem cells and non-malignant cell types such as cancer-associated fibroblasts (CAFs), endothelial cells, pericytes, and immune cells including tumor-associated macrophages (TAMs) and neutrophils (TANs). Although not malignant, these cells actively remodel the TME and promote metastatic progression. CAFs contribute to invasion and metastasis by restructuring the extracellular matrix (ECM) through secretion of TGF-β, matrix metalloproteinases (MMP), and collagen, and by releasing cytokines such as IL-32 that activate pro-metastatic signaling pathways.[3] They also promote tumor growth and angiogenesis through factors such as VEGF, FGF, and IL-8.[4-6] Endothelial cells further support tumor progression by driving angiogenesis and lymphangiogenesis via VEGF, PDGF, and HGF secretion,[7-10] providing routes for tumor cell dissemination to distant organs.[11] Immune cells within the TME also play dual and context-dependent roles. TAMs promote metastasis by sustaining chronic inflammation through cytokines such as IL-6 and IL-23, while enhancing angiogenesis via VEGF, IL-8, and MMP9.[12-14] Neutrophils, once considered short-lived innate immune responders, are now recognized as highly plastic cells. TANs can adopt either anti-tumoral or pro-tumoral phenotypes depending on TME signals such as cytokines, hypoxia, and metabolic stress. Pro-tumoral TANs promote angiogenesis, immunosuppression, ECM remodeling, and metastatic spread, further contributing to a permissive microenvironment for cancer dissemination.[15-20] More recently, platelets have been identified as additional components of the TME. Extravasated platelets were first observed in ovarian cancer and later in breast cancer and melanoma.[21,22] Their presence, particularly at the tumor periphery, correlates with advanced disease stages.[23] Platelets may access the extravascular space through intratumoral hemorrhage, transmigration, or extramedullary hematopoiesis.[24] Within tumors, platelets induce transcriptional and phenotypic changes in cancer cells. Beyond the primary tumor, circulating platelets interact with cancer cells in the bloodstream, protecting them from immune surveillance, facilitating extravasation, and releasing growth-promoting factors. A particularly novel aspect of platelet biology is their ability to influence glycosylation. Activated platelets can express or secrete functional glycosyltransferases (GTs), enabling them to glycosylate extracellular molecules.[25] This is especially relevant given that aberrant glycosylation is now recognized as a hallmark of cancer, often driven by dysregulated GT and glycosidase expression.[26] These alterations generate abnormal glycan patterns on cell surface and secreted glycoproteins that promote malignancy. Among the most prominent cancer-associated glycans are sialyl Lewis X (SLe^X) and sialyl Lewis A (SLe^A) antigens.[27,28] Normally involved in immune cell trafficking during inflammation, their aberrant expression in cancer facilitates interactions with E- and P-selectins on endothelial cells, enabling circulating tumor cells to arrest on inflamed endothelium and initiate metastatic colonization.[29-33] The ability of platelets to modulate extracellular glycosylation therefore represents a potentially significant, yet underexplored, contributor to metastatic dissemination.

This review was conceived as a narrative synthesis of literature. Relevant publications were identified through searches of major scientific databases, including PubMed, using combinations of keywords related to platelet biology, cancer glycosylation, metastasis, and inflammation. We first outline the fundamental principles of N- and O-glycosylation and summarize current knowledge on how glycosylation alterations contribute to cancer progression, with particular emphasis on metastasis and inflammation. We then examine the interplay between cancer cells and platelets, highlighting emerging evidence that platelets may influence the glycosylation landscape of tumor cells. Finally, we discuss the potential therapeutic implications of this platelet–glycosylation axis and consider how targeting these mechanisms may inform future anticancer strategies.

Generalities on glycosylation

Glycosylation is one of the most important co- and post-translational modifications of proteins, as it can act as a key regulatory mechanism controlling several pathophysiological processes, including cancer.[29-33] This is achieved by the combined action of specific enzymes: GTs and glycosidases. GTs catalyze the transfer

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of osidic residues from a donor (usually a nucleotide-ose) to an acceptor, i.e. the target molecule to be glycosylated (protein or lipid), whereas glycosidases hydrolyze the glycosidic linkage between a sugar and its substituent. There are two main glycosylation types: N-glycosylation and O-glycosylation, which differ in the way a polypeptide is linked to a carbohydrate.

N-glycosylation

N-glycosylation is characterized by an amide bond between an N-acetylglucosamine (GlcNAc) and an asparagine (Asn) residue located in the polypeptide's Asn-X-Ser/Thr consensus sequence; X can be any amino acid other than proline[34]. This co-translational modification involves several steps. First, GTs catalyze the addition of 2 N-acetylglucosamines (GlcNAc) and 5 mannoses (Man) to dolichol phosphate, a lipid expressed at the endoplasmic reticulum (ER) membrane.[34] The dolichol phosphate bearing the "$GlcNAc_2Man_5$" carbohydrate structure is then transferred into the ER lumen by a flippase.[34] Once in the ER, the successive action of dolichol-phosphomannose and dolichol-phosphoglucose transforms this "$GlcNAc_2Man_5$" carbohydrate composition into "$Glc_3Man_9GcNAc_2$".[34] It is then transferred in bulk to the polypeptide chain during synthesis, when the Asn-X-Ser/Thr consensus sequence is recognized by the oligosaccharyltransferase (OST) complex.[34] The three glucoses present in the carbohydrate composition are then used for correct protein folding.[34] The first glucose and the second glucose are removed by α-glucosidase I and α-glucosidase II respectively.[34] The last remaining glucose acts as a quality control signal, promoting the interaction of the glycoprotein with the chaperone proteins calnexin and calreticulin, which allow the protein to fold correctly.[34] The remaining glucose is then degraded by α-glucosidase II.[3]. Following the intervention of α-mannosidases I and II, all N-glycans share a common pentasaccharide core region: $GlcNAc_2Man_3$.[34] The protein continues to mature towards the Golgi apparatus, where diversification occurs.[34] N-glycans can be divided into three categories according to the composition of their side chain: high-mannose or oligomannose (addition of only mannose in addition to the three in the core), hybrid (addition of mannose and other oses in addition to the three in the pentasaccharide core) or complex (addition of a type of ose other than mannose in addition to the three in the core).[34] The generic term for 'mature' N-glycans is 'branched N-glycans'. Hybrid or complex structures may include the addition of galactose (Gal) by galactosyltransferases (β4GalT, ...), fucose (Fuc) by fucosyltransferases (FUT) or N-acetylglucosamine (GlcNAc) by N-acetylglucosaminyltransferases (GnT or MGAT, …).[34] Special N-glycans exist, known as 'bisected N-glycans', which are characterized by the addition of a β1,4 N-acetylglucosaminyl transferase by MGAT3 to the central mannose of the common pentasaccharide core.[35] This prevents the addition of further sugar residues to this branch and plays a role in cancer by modulating galectin-mediated signaling pathways and cancer cells proliferation.[36]

O-glycosylation

O-glycosylation, the most common being mucin-type O-glycosylation, is a post-translational modification defined by the initial addition of an N-acetylgalactosamine (GalNAc) to the hydroxyl group of a serine (Ser) or threonine (Thr) residue to form the Tn antigen (GalNAc-Ser/Thr).[37] This reaction takes place in the *Cis* compartment of the Golgi apparatus and is catalyzed by GTs of the N-acetylgalactosaminyltransferase (GALNT) family.[37] The Tn antigen can evolve through several elongation steps to form eight cores with different structures (core 1 to core 8).[37] For example, C1GALT1 catalyzes the addition of a β1,3 galactose to the Tn antigen to form the T antigen corresponding to core 1 or B3GNT6 (core 3 synthase) catalyzes the addition of a GlcNAc to the Tn antigen to form core 3. These backbones can then be extended by the action of various GTs such as sialyltransferases (ST3Gal, ST6Gal, etc.) or fucosyltransferases (FUT) into more complex carbohydrate motifs that confer different functions to proteins[37].

Glycosylation alterations in cancer: causes and consequences for inflammation and metastasis

Potential causes of glycosylation deregulation in cancer

Unlike oncogenes which drive the initiation of malignant transformation, glycosylation is not a primary trigger of cancerization. However, the dysregulation of GT — whether through overexpression or silencing — generates aberrant glycan structures on proteins[38] and lipids that collectively reshape the cell surface and thereby contribute to tumor progression and expansion.

Hypoxia is known to be one of the main characteristics of solid tumors.[39] Because the cancer cells grow quickly, but the blood vessels grow slowly, the cancer cells cannot get enough oxygen.[39] This leads to the activation of a key transcription factor, hypoxia-inducible factor (HIF1α).[39] This transcription factor regulates the expression of many genes, including those encoding GT.[39] A study realized by Belo *et al.* has shown that down-regulation of HIFα in human pancreatic adenocarcinoma cells leads to an increase in the levels of FUT1 and FUT2 mRNAs.[40] It has also been observed that transient knockout of GATA2 and GATA3, two transcription factors that stabilize HIFα, reduces the expression of ST3GAL4 and MGAT5.[41,42] Moreover, Koike *et al.* demonstrated that hypoxia directly increases FUT7 and ST3GAL1 transcription in human colorectal cancer cells.[43,44] These two GTs are involved in the synthesis of SLe antigens.[43] Finally, in 2020, Greville *et al.* showed that exposure of human ovarian and breast cancer cells to hypoxic conditions (0.5 to 2% O_2) resulted in significant changes in the composition of N-glycans secreted by the two types of cell lines compared to normoxic conditions (21% O_2).[41] These changes included alterations to the bisected oligomannosylated glycans, truncated and branched glycans with poly-L-lactosamine (alternating Gal and GlcNAc), galactosylated and sialylated structures.[41]

DNA methylation is an epigenetic modification characterized by the addition of methyl groups to DNA by *DNA methyltransferases*. This makes it possible to regulate gene expression, in particular by inhibiting it in a stable but potentially reversible way.[45] This process plays a crucial role in embryonic development and is often deregulated in cancer. Cancer cells often display aberrant methylation profiles that directly or indirectly modulate gene expression.[46-49] In 2011, Chachadi *et al.* showed that treatment of colorectal cancer cells with a DNA methyl-

transferase inhibitor, 5-aza-2'-deoxycytidine (5-Aza-dC), induced an increase in the expression of ST3GAL6 and FUT3, both of which are involved in the formation of SLe antigens.[48] These results highlight that these two GTs are inhibited in cancer cells by hypermethylation of their gene promoters, which tends to reduce their metastatic potential.[48] In contrast, Kawamura *et al.* showed that the B4GALNT2 gene, which is involved in the production of the Sd^a antigen, is also hypermethylated in gastric cancer.[49] As a result, the expression of the Sd^a antigen is reduced in favor of the SLe antigens, which share the same acceptor.[49] This ultimately leads to an increase in cancer cell migration.[49]

Other teams, such as Ide *et al.* have focused on N-glycans and the MGAT4 enzyme.[47,50] In the case of pancreatic cancer, the authors demonstrated that the MGAT4a isoenzyme is under-expressed in pancreatic cancer lines, while the MGAT4b isoenzyme is over-expressed compared with normal tissues.[47] They also demonstrated that treatment with 5-Aza-dC in combination with butyrate, which also affects DNA methylation, induced an increase in MGAT4a.[47] Thus, the downregulation of MGAT4a in pancreatic cancer cells is directly due to hypermethylation of its gene.[47] DNA methylation can also indirectly regulate the expression of GT genes. Chakraborty *et al.* showed that treating cells with 5-Aza-dC prevents methylation of NM23, a tumor suppressor gene.[46] Reactivated NM23 can then inhibit MGAT5 mRNA expression and so the formation of β1,6-branched N-glycans involved in chemotaxis and cancer cell motility.[46] This indicates that the gene encoding MGAT5 is over-expressed in cancer due to hypermethylation of NM23, which confers invasive properties on cancer cells.[46]

Taken together, these data demonstrate that both hypoxia and aberrant gene methylation deregulate GT expression in cancer cells. This leads to an aberrant glycosylation with the overexpression, deletion or a loss of specific carbohydrate structures, which can alter the behavior of cancer cells.[5]. It is also likely that, both within the bloodstream and the TME, cancer cells and interacting cells engage in extensive communication, exchanging RNAs, proteins, and other molecules that can influence their glycosylation and, consequently, modulate their behavior.

Glycosylation deregulation in cancer: implications for inflammation and metastasis

Glycosylation alterations and metastasis

Metastasis is a multistep process in which cancer cells disseminate from the primary tumor to distant organs, involving tumor cell detachment and invasion, survival during circulation, extravasation into distant tissues, and proliferation to form secondary tumors. Numerous studies have demonstrated that glycosylation plays a critical role throughout all stages of this process (*Supplementary Table 1*).

Cancer cell adhesion within the primary tumor

Within the primary tumor, cancer cells adhere to each other through adhesion junctions mediated by cadherins, calcium-dependent transmembrane proteins involved in cell-cell adhesion, cell motility, and growth differentiation.[52] During metastasis, the expression of these molecules decreases, and altered glycosylation contributes to this process. In hepatocellular carcinoma, hyperglycosylation of E-cadherin has been associated with reduced E-cadherin levels, potentially through altered stability or increased degradation, thereby weakening cell–cell adhesion and promoting cancer cell dissemination and invasion. Luo *et al.* demonstrated that ST6GALNAC1 overexpression in breast cancer cells significantly reduces E-cadherin expression while upregulating mesenchymal markers such as N-cadherin, Snail, and ZEB1.[53] Similarly, addition of the SLe^X antigen to E-cadherin reduces cancer cell adhesion and facilitates tumor invasion.[54] MGAT5 overexpression alters N-cadherin and E-cadherin function in fibrosarcoma and gastric cancer, reducing homotypic adhesion.[55] Carvalho *et al.* further showed that aberrant N-glycosylation by MGAT5 on the Asn-554 residue of E-cadherin disrupts its localization, cis-dimer formation, and junction stability, and that blocking this glycosylation decreases tumor invasion.[56] FUT8 inhibition in MCF-7 breast cancer cells similarly improves E-cadherin function and reduces migration and invasion.[5]. Conversely, reducing N-glycosylation of E-cadherin promotes stabilization of adherent junctions,[58] potentially through interaction with protein phosphatase A, reducing cancer cell invasion.[59]

Activation of signaling pathways driving cancer metastasis

Glycosylation changes in cancer cells can activate several pro-metastatic signaling pathways, including Wnt/β-catenin, EGFR, TGF-β, and NOTCH. Regarding the Wnt/β-catenin pathway, MUC13 overexpression increases β-catenin nuclear translocation and promotes tumor growth in hepatocellular carcinoma.[60] while O-glycosylated MUC5AC overexpression in gastric cancer enhances proliferation, invasion, and metastasis.[61] DGAGT1 deletion reduces N-glycosylation of Wnt and its receptors, limiting tumor development,[62,63] and GALNT1 overexpression increases O-glycosylation of CD44, activating this pathway and promoting cancer cell proliferation and invasion.[64]

For EGFR signaling, B4GALNT3 overexpression increases colon cancer stemness and invasion through EGFR O-glycosylation modification.[65] C1GALT1-mediated increase in EGFR O-glycosylation promotes tumor progression, while inhibition of C1GALT1 reduces malignancy.[66] FUT6 regulates proliferation, migration, and epithelial-mesenchymal transition (EMT) through EGFR/ERK/STAT signaling in head and neck cancers.[67] Concerning TGF-β signaling, a key inducer of EMT,[68] inhibition of N-glycosylation disrupts TGF-β receptor interaction and reduces EMT in lung and gastric cancer cells.[69,70] Altered glycosylation also modulates cancer cell–ECM interactions. Fucosylation of TGF-β receptors by FUT3, FUT6 and FUT8 enhances Smad activation, receptor signaling, and metastatic potential, while their inhibition reduces invasion and migration.[68,71] ST6GAL1 inactivation partially reverses the mesenchymal phenotype.[72] MGAT5 inhibition suppresses TGF-β-induced EMT by blocking branched N-glycan formation while MGAT3 overexpression counteracts TGF-β-driven EMT.[73,74] For the NOTCH pathway, POFUT1 and POGLUT1 overexpression, reported in multiple cancers, enhances NOTCH surface expression and activation of target genes.[75-77] Conversely, inhibition of POGLUT1 reduces NOTCH signaling.[75] Conversely, ST6GAL1 inhibition decreases NOTCH1 expression, reducing proliferation, invasion, and metastasis in non-small cell lung cancer.[78]

Immune evasion and survival of cancer cells in the bloodstream

Once in the bloodstream, cancer cells develop strategies to evade the immune system. Poly-LacNAc (repeated [-Galβ(1,4)-GlcNAcβ(1,3)-]$_n$ glycan extensions) structures mask underlying carbohydrate epitopes and reduce immune recognition[79] and can bind galectin-3 to further shielding tumor cells.[80] In metastatic PC3 prostate cancer cells, poly-LacNAc-modified MUC1 reduces NK cell cytotoxicity by decreasing granzyme B secretion and limiting TRAIL access.[81] Sialylated glycans contribute to immune evasion through interactions with SIGLECs on immune cells: binding to SIGLEC-7 inhibits NK cell activation, while desialylation of SIGLEC-C enhances anti-tumor responses.[82,83] Loss of SIGLEC expression on tumor-associated macrophages promotes their repolarization from immunosuppressive M2 to anti-tumor M1 macrophages.[83]

Glycosylation deregulation additionally affects immune checkpoint signaling.[84] Altered glycosylation of PD-L1 enhances its interaction with PD-1 on T cells, leading to stronger immune suppression,[85,86] while targeting fucosylation with 2F-Fuc has been shown to improve responses to immune checkpoint inhibitors.[87] Increased fucosylation is a hallmark of malignant transformation and contributes to immune evasion.[88]

Finally, aberrant glycosylation can inhibit complement activation and promote regulatory T cell recruitment by inducing CCL22, creating an immunosuppressive TME.[89]

Intravasation and extravasation of cancer cells: Key steps in metastasis

The interaction of cancer cells with the ECM is a key step in the metastatic process, enabling both intravasation and extravasation. Glycosylation dysregulation can alter the functions of anchoring proteins and extracellular basement membrane proteins such as integrins, laminin, fibronectin (FN1), vitronectin and collagen, as well as ECM remodeling and degradation, thereby facilitating tumor invasion and spread.

Janik *et al.* treated WM9 and WM239 metastatic melanoma cells with swainsonine (SW), an inhibitor of N-glycosylation and found that chemically altering the N-glycosylation of α3β1 and αvβ3 integrins affects their binding to ECM proteins such as vitronectin.[90] Pocheć *et al.* then compared two melanoma cell lines: WM793 (primary) and WM1205Lu (highly metastatic)[91] and revealed that the acquisition of a metastatic profile is associated with an increase in sialylated β1-6-branched structures on N-glycans carried by the αvβ3 integrin promoting cancer cell adhesion to vitronectin.[91] This increase in β1-6-branched structures, common across cancer types, results from MGAT5 overexpression.[92] To counterbalance this, Yoshimura et al. induced overexpression of MGAT3 — which competes with MGAT5 for substrate — in highly metastatic B16-hm murine melanoma cells, and demonstrated that this inhibits cell attachment to collagen and laminin during extravasation.[92] However, Kariya *et al.* showed that reducing MGAT3 expression in MDA-MB-435S melanoma cells decreases their invasiveness and motility by reducing the cross-linking of integrin β4 with with gelatin-3,[93] indicating that the role of glycosylation is not uniform across all integrins. Further studies have highlighted the involvement of other glycosyltransferases (GTs) in integrin function. Indeed, Yuan *et al.* reported that desialylation of α2,6-sialylated integrins such as α2, α5 and β1 increased adhesion, but not migration or invasion, of MDA-MB-231 breast cancer cells to the ECM.[94] ST6GAL1 overexpression in colon cancer cells induces increased sialylation of β1 integrin and talin, which in turn promotes collagen IV expression tumor invasion and cell motility.[95] Lastly, Radhakrishnan *et al.* have shown that overexpression of B3GNT6 (or core 3 synthase) indirectly modifies α2β1 integrin expression by altering MUC1 glycosylation, thereby reducing tumor growth and metastasis in pancreatic cancer.[96]

Beyond integrins, aberrant glycosylation also affects the enzymatic activity of metalloproteinases MMP2 and MMP9, impairing the ability of cancer cells to degrade ECM components and invade surrounding tissues. TIMPs, which modulate MMP activity, are also impacted, potentially influencing the balance between ECM degradation and remodeling.

Glycosylation alterations and inflammation

Chronic inflammation is a well-established driver of cancer progression and metastasis promoting genomic instability, tumor growth through cytokine and growth-factor signaling, angiogenesis, and creation of a microenvironment that favors invasion and dissemination. This inflammatory state arises from the interplay between innate and adaptive immunity. When regulatory mechanisms fail, inflammation becomes chronic, contributing to cancer progression. Importantly, pro-inflammatory cytokines such as TNF-α, IL-2, IFN-α, and IFN-γ remodel cell-surface glycosylation by regulating the expression and activity of GTs and sulfotransferases, and these inflammation-induced glycan alterations ultimately contribute to the metastatic process.

In innate immunity, neutrophils are notably characterized by surface expression of MAC-1 (CD11b/CD18). In response to inflammatory signals such as TNF-α or IL-8, MAC-1 surface expression increases and undergoes conformational changes enabling high-affinity binding to ligands such as ICAM-1, fibrinogen, iC3b, and extra cellular matrix proteins. Kelm *et al.* demonstrated that during chronic inflammation, unusual glycan epitopes appear on MAC-1, including high-mannose oligosaccharides and biantennary galactosylated N-glycans and that selective targeting of CD11b glycans reprograms downstream signaling pathways, resulting in impaired transepithelial migration and differential regulation of effector functions, including phagocytosis, superoxide release, and apoptosis.[97] Furthermore, SLeX structures on MAC-1 are critical for its interaction with E-selectin, and targeting CD11b glycosylation effectively blocks neutrophil transepithelial migration.[98]

Dendritic cells and macrophages also undergo inflammation-induced glycosylation changes. A subset of monocyte-derived dendritic cells displays abundant sialylated glycans on their surface.[99,100] but upon maturation under pro-inflammatory stimuli, ST6GAL1 and ST3GAL4 expression and activity are markedly downregulated, driving transition toward an inflammatory dendritic cell phenotype.[101,102] Similarly, α2,6-sialylation in macrophages supports cell survival and restrains excessive inflammatory signaling, whereas decreased sialylation correlates with enhanced inflammatory activation. Together, these findings underscore that inflammation-driven sialylation alterations shape innate immune cell polarization and contribute to a self-sustaining inflammatory loop facilitating tumor progression.

In adaptive immunity, glycosylation of the TCR and BCR is essential for maintaining proper receptor conformation and effective signaling. During chronic inflammation, reduced sialylation or increased truncated N-glycans (e.g., Man□GlcNAc□) can drive excessive or dysregulated activation of inflammatory pathways. Cytokines such as IL-4, IL-6, IL-12, and TGF-β regulate T cell differentiation (Th1, Th17, etc.) and reshape their N-glycome by dysregulating MGAT5, ST6GAL1, and FUT8 expression, thereby altering T cell interactions with regulatory lectins including galectins and SIGLECs, and modifying activation thresholds, cytokine production, and cell survival.[103]

A similar pattern is also observed in B lymphocytes.[103] Additionally, IgG Fc fragment glycosylation is a critical regulator of inflammatory responses: in cancer, the N-glycan composition of IgG is frequently altered, with increased afucosylated or agalactosylated forms promoting a pro-inflammatory sate and sustaining a self-amplifying inflammatory loop.[103] Hypogalactosylation and hyposialylation of IgG produce antibodies with a more pro-inflammatory Fc configuration, enhancing Fcγ receptor binding and complement activation, while higher fucosylation reduces antibody-dependent cellular cytotoxicity activity.[103]

Altogether, these feedback loops between aberrant glycosylation and inflammatory signaling maintain a chronic pro-inflammatory state that reshapes the tumor microenvironment and enhances the metastatic potential of cancer cells, highlighting glycosylation as both a key mediator and amplifier of tumor progression.

Platelet-mediated glycoprotein remodeling in cancer cells as a driver of inflammation and metastasis

It is known that platelets can interact with cancer cells in tumors such as breast, lung, pancreatic, and melanoma cancers, while in others, like leukemias, lymphomas, and head and neck squamous cell carcinomas, these interactions are weaker, indirect, or may even be absent.[104] Being highly glycosylated cells, platelets may, in cancers where such interactions occur, potentially influence subtle changes in cancer cell glycosylation patterns. In this section, we explore the mechanisms that could underlie this selective influence (*Supplementary Table 2*).

Interaction cancer cell-platelet

Trousseau syndrome describes a malignancy-associated hypercoagulable state in which patients develop recurrent, migratory, or otherwise unexplained venous or arterial thromboses in the setting of an underlying cancer. One of the manifestations of this syndrome is deep vein thrombosis, which occurs four to seven times more frequently in patients with cancer than in the general population. This substantially increased thrombotic risk is not simply a complication of malignancy but also an independent prognostic factor, as it is associated with significantly reduced overall survival in affected patients.[105,106] Several comprehensive and recent review have been published on this topic concerning clinical[107,108] or basic science aspects.[109-111] Shortly, the procoagulant state observed in cancer patients such as pancreatic, brain and lung cancers arises from these interactions, which could influence both platelets and cancer cells. This has given rise to two complementary concepts: *cancer cell–educated platelets*, the earliest described paradigm, and platelet-educated cancer cells, a concept that has gained attention since a decade.

The paradigm of cancer cell/tumor–educated platelets was described in part by Best *et al*. through mRNA sequencing of blood platelets. Platelet mRNA profiles were shown to differ between cancer patients and healthy individuals, enabling cancer detection with 96% accuracy and identification of the primary tumor location across six tumor types with 71% accuracy. Several types of interaction may be responsible for this modification or exchange of cellular components. Several types of interactions may be responsible for this modification or exchange of cellular components between cancer cells and platelets. These interactions can lead to platelet activation and aggregation — a phenomenon known as tumor cell-induced platelet aggregation (TCIPA) — which significantly contributes to the increased risk of cancer-associated thrombosis (CAT) through both direct and indirect mechanisms.[104] We will focus on interactions including glycoproteins. Direct mechanisms involve physical interactions between cancer cells and platelets, including the binding of cancer cell–expressed PSGL-1 (SLe^x antigen) to P-selectin on platelets. Indirect mechanisms include the ability of cancer cells to secrete soluble platelet agonists, or to produce extracellular vesicles (EVs).[110,112,113] EVs are small procoagulant and proinflammatory membrane vesicles that can be generated by from various cell types.[106] Large EVs (>200 nm-1000 nm<) are generated by direct budding of the plasma membrane and are characterized by high levels of phosphatidylserine exposure.[114] In pancreatic cancer, EVs express tissue factor (TF), the primary initiator of the extrinsic coagulation cascade. In mouse models, several teams demonstrated that these large EVs promote thrombus formation in a TF-dependent manner through interactions between PSGL-1 (SLe^x antigen) on cancer cell–derived EVs and P-selectin on platelets.[113,115,116] Recent publication also demonstrated the implication of cancer cells exosomes in platelets activation.[117] Cancer cells-educated platelets become activated and aggregate around the cancer cells in the bloodstream, increasing the risk of CAT.[104] They also play a critical role in tumor progression and metastasis. Indeed, numerous studies show that a high platelet count correlates with increased metastatic potential.[118,119]

More recently, attention has shifted toward the concept of platelet-educated cancer cells, reflecting the ability of platelets to directly transfer biomolecules such as mRNA and proteins, including fibrinogen, or to generate EVs. The pioneering study demonstrates that direct interactions between platelets and tumor cells — via platelet TGF-β and direct cell contacts — induce EMT in cancer cells, thereby promoting metastasis *in vivo*.[120] Beyond this direct cell-to-cell signaling, platelets can also influence cancer cell behavior through the release of EVs. Notably, Plantureux *et al.* demonstrated that EVs circulating in the bloodstream can display molecular features derived from both platelets and cancer cells (PECAM and CD41).[23] These hybrid vesicles may influence metastatic dissemination and contribute to the establishment of metastases.

Importantly, the concepts of cancer cell–educated platelets and platelet-educated cancer cells are not mutually exclusive and may operate in a coordinated and interconnected manner, further increasing the complexity of platelet–tumor interactions. Such bidirectional crosstalk may also extend to glycosylation processes, as will be discussed in the following section.

Possible mechanisms by which platelet can influence cancer cell glycosylation

Glycosidases

Sorensen *et al.* showed that platelets sequentially lose sialic acid (Sia) and galactose (Gal), exposing underlying Gal and GlcNAc residues.[121] This desialylation is enhanced during platelet storage (7–10 days at 4°C) prior to transfusion, promoting recognition of GlcNAc motifs by integrin αMβ2 (MAC-1) and accelerating platelet clearance.[122,123] Hoffmeister *et al.* demonstrated that enzymatic galactosylation can partially mask these residues and prolong circulation,[124] but it is insufficient for long-term survival because platelets secrete sialidases that remove terminal sialic acids from GPIbα, exposing Gal and further enhancing clearance.[121,125] Platelet glycosylation is also important in pathology, especially thrombocytopenia. Tribulatti *et al.* showed that Trypanosoma cruzi trans-sialidase removes sialic acids from platelets, halving counts in mice and inducing thrombocytopenia in acute Chagas disease.[126] Shear stress similarly remodels platelet glycosylation, increasing glycosidase activity, platelets EVs release, and clearance. In immune thrombocytopenia, autoantibodies trigger desialylation outside platelets and ultimately platelet clearance, which can be improved with sialidase inhibitors.[127-130]

These findings suggest that platelets, through secretion of glycosidases like sialidases, may influence the glycosylation of neighboring cells, including cancer cells, highlighting a potential regulatory mechanism that warrants further investigation.

Extracellular glycosylation

In vertebrates, protein glycosylation has always been described as taking place in nucleated cells at the level of the Golgi apparatus and the ER.[131] For this reason, platelets have long been thought to be incapable of post-translational modification, because they lack a nucleus, Golgi apparatus and ER.

Xylosyltransferases catalyze the transfer of xylose (Xyl) residues to Ser residues carried by the core protein, initiating the assembly of glycosaminoglycan chains that ultimately form proteoglycans.[132] Proteoglycans are involved in a number of key biological processes, including the formation of the ECM and its mechanical, signaling and water-binding properties, as well as embryonic development, tissue healing, regulation of cell proliferation, cell adhesion and cell migration.[132] Condac *et al.* showed that serum xylosyltransferase levels are very high in patients with a disease associated with significant fibrosis and/or ECM turnover, such as diabetes or systemic sclerosis.[133] They have also shown that this increase in serum xylosyltransferase levels is due to the activation of platelets, which are their main source.[133] The presence of additional GT families in human and murine platelets was also confirmed by Lee-Sundlov *et al.*, who characterized these enzymes and demonstrated that platelets serve as important carriers of GTs, particularly ST3GAL1 and β4GalT.[134] Consequently, their findings demonstrate that platelet activation regulates the release of circulating soluble GTs, which in turn can reshape cell-surface glycan structures and thereby influence cell behavior.[134,135]

Moreover, Wandall *et al.* demonstrated that three different families of GT (sialyltransferases, galactosyltransferases, acetylgalactosaminyltransferases) may be exposed on the surface of inactivated platelets or secreted into the extracellular space with the associated sugar nucleotides during their activation, allowing platelets to initiate and elongate glycans on extracellular acceptor molecules.[25] These GTs are packaged into vesicles during megakaryocyte maturation and then delivered by pro-platelets to nascent platelets where they accumulate[25]. Thus, platelet activation leads to platelet release, allowing glycosylation of extracellular acceptor molecules.[25] When Wandall *et al.* referred to "vesicles," the precise mechanisms involved remained undefined. However, platelets are a major producer of microvesicles and exosomes circulating in the bloodstream, positioning them as key regulators of both local and systemic tumor–host communication. Their prevalence is so high that platelet-derived vesicles are currently being investigated as potential cancer biomarkers.[136] Because these vesicles transport diverse types of RNA, proteins, and enzymes inherited from the cells from which they originate, it is plausible that they serve as a mechanism through which platelets influence the glycosylation machinery of cancer cells.

Last year, we demonstrated that platelets can indirectly educate cancer cells by reshaping the transcriptional landscape of genes involved in glycosylation in cancer cells themselves.[137] Notably, platelet-educated cancer cells exhibit increased expression of three GT families: MGAT2, MGAT3, and B3GNT. Dysregulation of these enzymes is likely to have profound consequences for tumor progression.[137] Moreover, overexpression of MGAT2 (GnT-II) in neuroblastoma has been shown to enhance complex N-glycan branching, thereby promoting cancer cell proliferation and invasion.[138] In contrast, deregulation of MGAT3 (or GnT-III) as reported in breast cancer and melanoma, has been associated with inhibition of EMT and, consequently, suppression of metastatic dissemination.[92,139] In addition, B3GNT3 has been linked to increased immune cell infiltration in lung adenocarcinoma, as well as to pelvic lymph node metastasis in patients with cervical cancer.[140,141] Thus, the education of cancer cells by platelets may amplify glycosylation-driven changes in cancer cells and thereby potentiate metastatic progression.

Platelets can influence cancer cell glycosylation through several complementary mechanisms. Direct contact with cancer cells may remodel surface glycans, while platelet-derived soluble GTs or vesicle-encapsulated enzymes can modify extracellular and cell-surface glycans at a distance. Furthermore, platelet-derived factors can alter the transcriptome of cancer cells, increasing or decreasing the expression of genes encoding GT and further reshaping the glycosylation landscape. Together, these mechanisms suggest that platelets may play a key role in regulating cancer cell glycosylation, with potential consequences for metastatic behavior. Nonetheless, further studies are required to clarify the precise mechanisms and relative contributions of these pathways.

Clinical implications of glycosylation alterations in cancer

Altered glycosylation as a biomarker for the development of cancer

Most diagnostic and prognostic biomarkers currently used in oncology are glycan antigens or glycoproteins overexpressed in the blood of cancer patients, such as CA125/MUC16 for ovar-

ian cancer, CA19.9 for pancreatic cancer, and CEA or CA72.4 for colorectal cancer.[31,142-144] However, their clinical use is limited by low sensitivity and specificity, as they are often absent in early disease stages and can be elevated in non-cancerous or inflammatory conditions.[142] Cancer-associated alterations in glycosylation lead to profound changes in the glycan structures of cell surface and secreted glycoproteins, prompting efforts to identify cancer-specific glycoforms as improved biomarkers.[145-147] For example, while α-fetoprotein is elevated in several physiological and pathological conditions, its fucosylated form is highly specific for hepatocellular carcinoma.[32,142] Similarly, CD43 exhibits cancer-specific glycosylation involving the Tn antigen, which can be selectively recognized by monoclonal antibodies for early diagnosis.[148] In ovarian cancer, acute-phase proteins such as haptoglobin, α1-acid glycoprotein and α1-antichymotrypsin display increased SLe^X-rich glycoforms, and patient IgG contains elevated agalactosylated and fucosylated glycans.[149] In PDAC, aberrant O-glycosylation of MUC4 results in truncated Tn and sialyl-Tn antigens,[150] distinguishing malignant from normal tissue.[151]

EVs derived from cancer cells also exhibit distinct glycosylation signatures that influence immune evasion, cell targeting, and metastasis, making them promising non-invasive biomarkers detectable using lectins or glycan-binding probes.[152] Large-scale glycoproteomic studies further highlight cancer-specific glycosylation patterns exemplified by analyses of patient sera: ovarian cancer is associated with elevated levels of branched and sialylated N-glycans, whereas liver cancer shows the opposite trend.[153-156] Similarly, increased sialylation, fucosylation, and N-glycan branching have been reported in the serum of patients with pancreatic cancer and in prostate cancer, altered fucosylation and accumulation of specific N-glycans, including N,N′-diacetyllactosamine and high-mannose structures, are observed in both tissues and blood.[153,157] Recently, a glycosignature based on differential GT expression has been proposed as a prognostic tool in pancreatic ductal adenocarcinoma.[158]

Glycosylation alterations: therapeutic target in cancer?

Deregulated glycosylation plays a central role in cancer progression and metastasis, providing tumor cells with survival and invasive advantages. This has prompted interest in targeting GTs and specific glycan structures as potential therapeutic strategies. Several compounds that inhibit N- or O-glycosylation have shown promising effects *in vitro* and in preclinical cancer models. Swainsonine (SW), a natural alkaloid, inhibits α-mannosidases involved in N-glycan processing, leading to the accumulation of high-mannose structures. Early studies demonstrated that SW reduces tumor invasiveness in melanoma models without major toxicity, partly by enhancing NK and LAK cell–mediated cytotoxicity.[159-161] Tunicamycin is the most widely used N-glycosylation inhibitor in basic cancer research. It blocks the first step of N-glycosylation by inhibiting GPT, resulting in ER stress, activation of the unfolded protein response, and apoptosis. Tunicamycin enhances the sensitivity of cancer cells to chemotherapies and targeted therapies.[162-164] It also disrupts N-glycosylation of EGFR, promoting their degradation and inhibiting downstream signaling involved in proliferation, survival, and angiogenesis.[163-166] *In vivo* studies in head and neck and breast cancer models have confirmed its ability to reduce tumor growth.[170-172]

Benzyl-O-GalNAc is commonly used to inhibit O-glycosylation by competing with UDP-GalNAc. This treatment induces accumulation of truncated O-glycans (T and Tn antigens) while reducing sialylated selectin ligands, thereby impairing tumor cell adhesion to endothelial cells and platelets.[167-169] This reduces metastatic potential in several cancer models. Additionally, altered O-glycosylation affects intracellular trafficking, causing mislocalization of glycoproteins and further limiting their function. However, the glycan changes induced by this inhibitor vary between cell types.[169,170]

Despite encouraging experimental results, most glycosylation inhibitors exhibit significant toxicity toward normal tissues. Consequently, although glycosylation is clearly involved in cancer progression, no glycosylation-targeted therapies are currently approved for clinical use. Using these drugs as such is not feasible because of their toxicity and lack of target specificity. Several groups have investigated platelet inhibition using antiplatelet agents to reduce tumor growth and metastasis in both mouse models and human studies.[113,171,172] Heparin (UFH/LMWH), a glycosaminoglycan polysaccharide composed of repeating disaccharide units β-D-GlcA-(1→4)-α-D-GlcN(SO_3^-), has been widely used in CAT.[108] Preclinical murine studies show that LMWHs significantly reduce primary tumor growth or enhance anti-tumor effects when combined with chemotherapy.[113,173] However, in clinical settings, their effect on tumor development and metastasis remains weak or absent, with to date an unclear mechanistic.[174]

Major technological advances have been made in antibody engineering. It is now possible to envisage the use of antibodies conjugated to drugs. The ultimate goal would be to generate an antibody–drug conjugate that targets both a cancer-specific glycosylated moiety and the protein backbone of a glycoprotein, thereby selectively targeting cancer cells. This approach, however, would require the development of a specific antibody for each type of cancer. Nevertheless, as described in this review, certain similarities exist among different cancer types, which may help overcome this limitation. A pan-cancer approach focusing on cancer-associated glycosylation appears to be a realistic strategy. Mucins seem to be particularly attractive targets; however, despite numerous studies on MUC1, some disappointments have been reported. Nevertheless, an antibody–drug conjugate, DS-3939a, targeting MUC1 carrying short cancer-associated glycans such as Tn and sialyl-Tn, has recently been developed.[175] This antibody is conjugated to a DNA topoisomerase inhibitor and has shown efficacy *in vitro* and *in vivo* using patient-derived xenograft models.[175] It is currently being evaluated in phase I/II clinical trials. Other approaches, targeting either up to three proteins (including MUC1 and CEA; NCT03384316) or a single protein (NCT01720836), are currently being evaluated in Phase I/II clinical trials.[176] These studies provide a foundation for the future development of therapies directed against glycoprotein targets.

Glycosylation is far more than a simple post-translational modification. As reviewed here, the biological significance of a given glycan structure cannot be considered in isolation — it is inseparable from the nature of its carrier, whether a protein or a lipid, and from the broader glycan context in which it is dis-

played. This complexity must be fully embraced if glycosylation is to be effectively exploited as a therapeutic target in cancer. Selectively disrupting cancer-associated glycan remodeling, particularly at the platelet–tumor cell interface, represents a promising yet demanding strategy. Its success will likely depend on combinatorial approaches, associating glycan-targeting moieties with cytotoxic or immunomodulatory agents within antibody–drug conjugates or similar platforms, in order to achieve the selectivity that global glycosylation inhibitors have so far failed to provide.

Meeting this challenge will require the full mobilization of modern computational and bioinformatic tools. Molecular modeling and molecular dynamics simulations are increasingly powerful means to predict glycan–protein and glycan–lectin interactions at atomic resolution and should be systematically integrated into the rational design of glycan-targeting therapeutics. Alongside these approaches, specialized glycobiological databases — including GlyGen and UniCarbKB — provide invaluable, curated information on glycan structures, glycosylation sites, and their associated proteins, and constitute essential resources for the field.

Leveraging this combined framework represents a necessary step toward the development of more selective and effective glycan-based therapeutic strategies in oncology.

List of abbreviations

Asn – Asparagine
BCR – B-cell receptor
CA19.9 – Carbohydrate antigen 19-9
CA72.4 – Cancer antigen 72.4
CA125 – Cancer antigen 125
CAFs – Cancer-associated fibroblasts
CAT – Cancer-associated thrombosis
CEA – Carcinoembryonic antigen
CD – Cluster of differentiation
CCL22 – C-C motif chemokine ligand 22
C1GALT1 – Core 1 β1,3-galactosyltransferase 1
DGAGT1 / GPT – UDP-N-acetylglucosamine:dolichyl-phosphate N-acetylglucosamine-phosphotransferase
DNA – Deoxyribonucleic acid
ECM – Extracellular matrix
EGFR – Epidermal growth factor receptor
EMT – Epithelial–mesenchymal transition
ER – Endoplasmic reticulum
ERK – Extracellular signal-regulated kinase
EV – Extracellular vesicles
FGF – Fibroblast growth factor
FN1 – Fibronectin 1
Fuc – Fucose
FUT – Fucosyltransferase
Gal – Galactose
GalNAc – N-acetylgalactosamine
GALNT – N-acetylgalactosaminyltransferase
GlcNAc – N-acetylglucosamine
GPT – GlcNAc-1-P Transferase
GT(s) – Glycosyltransferase(s)
HGF – Hepatocyte growth factor
HIFα – Hypoxia-inducible factor α
ICAM-1 – Intercellular adhesion molecule 1
iC3b – Inactive C3b (complement system)
IFN – Interferon
IgG – Immunoglobulin G
IL – Interleukin
LAK – Lymphokine-activated killer cells
LMWHs – Low molecular weight heparins
MAC-1 – Integrin αMβ2 (CD11b/CD18)
Man – Mannose
MGAT / GnT – N-acetylglucosaminyltransferase
MMP – Matrix metalloproteinase
mRNA – Messenger RNA
MUC – Mucin
NM23 – Metastasis suppressor nucleoside diphosphate kinase
NK cells – Natural killer cells
OST – Oligosaccharyltransferase
PD-1 – Programmed cell death protein 1
PDAC – Pancreatic ductal adenocarcinoma
PD-L1 – Programmed death-ligand 1
PDGF – Platelet-derived growth factor
PECAM/CD31 – Platelet endothelial cell adhesion molecule
Poly-LacNAc – Poly-N-acetyllactosamine
PSGL-1 – P-Selectin Glycoprotein Ligand-1
Sda antigen – GalNAcβ1-4(NeuAcα2-3)Gal epitope
Ser – Serine
$SLe^{X/A}$ – Sialyl Lewis X / Sialyl Lewis A
Siglec – Sialic acid–binding immunoglobulin-like lectin
STAT – Signal transducer and activator of transcription
sTn – Sialyl Tn antigen
SW – Swainsonine (α-mannosidase II inhibitor)
T antigen – Thomsen antigen (Galβ1-3GalNAc)
TAMs – Tumor-associated macrophages
TANs – Tumor-associated neutrophils
TCIPA – Tumor cell-induced platelet aggregation
TCR – T-cell receptor
TF – Tissue factor
TGF – Transforming growth factor
Thr – Threonine
TIMPs – Tissue inhibitors of metalloproteinases
TME – Tumor microenvironment
TNF – Tumor necrosis factor
TRAIL – TNF-related apoptosis-inducing ligand
Tn antigen – Thomsen-nouveau antigen (GalNAc-O-Ser/Thr)
UDP – Uridine diphosphate
VEGF – Vascular endothelial growth factor
Wnt – Wingless/INT signaling molecules
Xyl – Xylose
ZEB1 – Zinc finger E-box-binding homeobox 1
2F-Fuc – 2-fluoro-fucose
5-Aza-dC – 5-aza-2’-deoxycytidine

List of cell lines

MCF-7 – Human breast adenocarcinoma
MDA-MB-231 – Human breast cancer
MDA-MB-435S – Human melanoma/breast cancer–like line
PC3 – Human prostate adenocarcinoma
WM9/WM239/WM793 – Human melanoma
WM1205Lu – Human metastatic melanoma (lung-seeking)

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Online supplementary material:

Table 1. Glycosylation alterations in cancer: causes and consequences for inflammation and metastasis.

Table 2. Platelet-mediated glycoprotein remodeling in cancer cells as a driver of inflammation and metastasis.

Figure 1. Overview of the N-Glycosylation process. Figure created using Biorender and Servier Medical Art, respectively available at https://www.biorender.com/ and https://smart.servier.com/

Figure 2. Overview of O-Glycan biosynthesis.