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Review

Sialosignaling: Sialyltransferases as engines of self-fueling loops in cancer progression

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ABSTRACT

Background: Glycosylation is increasingly recognized as one of the most relevant postranslational modifications. Sialic acids are negatively charged sugars which frequently terminate the carbohydrate chains of glycoproteins and glycolipids. The addition of sialic acids is mediated by sialyltransferases, a family of glycosyltransferases with a crucial role in cancer progression.
Scope of the review: To describe the phenotypic and clinical implications of altered expression of sialyltransferases and of their cognate sialylated structures in cancer. To propose a unifying model of the role of sialyltransferases and sialylated structures on cancer progression.
Major conclusions: We first discuss the biosynthesis and the role played by the major cancer-associated sialylated structures, including Thomsen–Friedenreich-associated antigens, sialyl Lewis antigens, α2,6-sialylated lactosamine, polysialic acid and gangliosides. Then, we show that altered sialyltransferase expression in cancer, consequence of genetic and epigenetic alterations, generates a flow of information toward the membrane through the biosynthesis of aberrantly sialylated molecules (inside-out signaling). In turn, the presence of aberrantly sialylated structures on cell membrane receptors generates a flow of information toward the nucleus, which can exacerbate the neoplastic phenotype (outside-in signaling). We provide examples of self-fueling loops generated by these flows of information.
General significance: Sialyltransferases have a wide impact on the biology of cancer and can be the target of innovative therapies. Our unified view provides a conceptual framework to understand the impact of altered glycosylation in cancer.

1. Introduction

The sugar portions of glycoproteins and glycolipids are often terminated by sialic acids (Sia): sugars which, owing to their negative electric charge, are crucial in regulating molecular and cellular interactions [1–3]. Sialic acids can be linked to subterminal sugars through an α2-6-bond to N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc); an α2,3 or α2,6 bond to galactose (Gal) or through a α2-8-bond to another sialic acid, forming polysialic acids. Sialyltransferases are a class of glycosyltransferases which catalyze the transfer of sialic acid from a common donor substrate (CMP-sialic acid) to a carbohydrate chain. Sialyltransferases show a certain degree of redundancy, in that the same glycosidic linkage can often be elaborated by different gene products [4] and are crucially involved in cancer progression [5,6]. In this review we have summarized the studies showing the intimate relationship between sialyltransferases and their products with the mechanisms of cell transformation and cancer progression. In particular, we provide examples of how the signaling generated by sialylated molecules at the cell membrane can activate self-amplification loops fueling cancer growth.

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloblastic leukemia; 5-AZA, 5′-azacytidine; BCG, Bacillus Calmette–Guerin; CIN, chromosome instability; DP, degree of polymerization; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial to mesenchymal transition; ER, estrogen receptors; ERE, estrogen responsive element; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; Gal, Galactose; GalNAc, N-acetylgalactosamine; GlcNAc, N-acetylglucosamine; MAPK, mitogen-activated protein kinase; MSI, microsatellite instability; MSS, microsatellite stability; MUC1, mucin-1; N-CAM, neural cell adhesion molecule; PCR, polymerase chain reaction; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PSA, polysialic acid; PST, polysialyltransferase ST8SIA4; Sia, sialic acid; sT, sialyl-T; sTn, sialyl-Tn; Sia6LacNAc, α2,6-sialylated lactosamine; SNA, *Sambucus nigra* agglutinin; STX, polysialyltransferase ST8SIA2; TF, Thomsen–Friedenreich; sLe^a, sialyl-Lewis^a; sLe^x, sialyl-Lewis^x; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

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2. Overall effect of sialylation in cancer

Early studies indicated that the level of sialyltransferase activity is often increased in plasma of cancer patients [7–10] and that the extent of sialylation of cancer cells is associated with their invasive properties [9,11–18]. Former functional studies on the overall effect of sialic acids in cancer biology, using sialidases or sialyltransferase inhibitors sometimes provided contradictory results [19]. For example, the effect of sialidase treatment on collagen IV adhesion was the opposite in murine and human cancer cells [13,14], while sialic acid depletion by the sialyltransferase inhibitor KI-8110 reduced metastasis formation [20] without affecting cell adhesion to extracellular matrix glycoproteins but rather decreasing platelet aggregation [16]. According to other studies, the inhibition of sialic acid incorporation by different compounds impaired adhesion, migration, *in vivo* tumor growth and metastasis formation [21–25].

3. Sialylated structures involved in cancer progression

In this section we describe the structure and biosynthesis of specific sialylated structures and discuss their contribution to cancer biology and progression.

3.1. Thomsen–Friedenreich (TF)-related antigens

Antigens T, Tn and their sialylated variants sialyl-T (sT) and sialyl-Tn (sTn) are small cancer-associated O-linked structures, often referred to as Thomsen–Friedenreich (TF)-related antigens [26], whose structure and biosynthesis are depicted in Fig. 1.

In breast cancer, mucin glycosylation undergoes a characteristic switch from the expression of core 2 structures to the accumulation of T [27] and sTn structures [28,29]. This change is accompanied by a concomitant and apparently paradoxical up-regulation of sialyltransferase ST3GAL1 [30], which converts T in sialyl-T (sT) antigen [31], inhibiting the synthesis of core-2 based structures [32]. ST3GAL1 over-expression in breast cancer is associated with conditions characterizing tumor growth, such as the presence of the inflammatory enzyme cicloxygenase-2 (COX-2) and of its product prostaglandin E2 (PGE2) [33] and hypoxia [34]. On the other hand, the expression of the cell membrane mucin 1 (MUC1), which is frequently altered in cancer [35], down-regulates ST3GAL1 expression in mouse mammary carcinoma cells [36]. Constitutive ST3GAL1 expression by murine mammary epithelium contributes to breast cancer progression. In fact, in PyMT mice, which spontaneously develop breast cancer, the concomitant over-expression of ST3GAL1 in mammary glands results in the development of mammary tumors with shorter latency, although no accumulation of sT antigen was observed [37]. Altogether, these data suggest that the biological effect of ST3GAL1 on cancer progression might not be dependent on the synthesis of its cognate carbohydrate antigen, but rather on its proposed tumor promoter activity [37]. A paradoxical over-expression of both T antigen [38] and sialyltransferases ST3GAL1 and ST3GAL2 [39] has also been reported in colon cancer, with the former associated with lymph node metastasis [39]. In bladder cancer tissues ST3GAL1 mRNA was also elevated, particularly in patients with tendency to recurrence [40].

sTn, a pan-carcinoma antigen expressed by many malignancies [41–45], is usually associated with a worse prognosis [46]. The biosynthesis of sTn largely depends on sialyltransferase ST6GALNAC1, while the contribution of ST6GALNAC2 appears to be negligible [47,48], being more specific for s6T biosynthesis. However, the reduced O-acetylation of sialic acid [49] and the down-regulation of the competing core 1 galactosyltransferase [50,51] also contribute to increased sTn expression in cancer [52]. In bladder cancer, sTn is expressed by 75% of high-grade tumors and correlates with ST6GALNAC1 expression [45]. Moreover, the expression of this carbohydrate antigen, associated with s6T, is a marker of disease-free survival and predicts response to immunotherapy with bacillus Calmette–Guerin (BCG) [45]. In different cancer cell lines, the phenotypic effects of sTn over-expression obtained by forcing ST6GALNAC1 expression, are multiple and only partially overlapping. These include: morphological changes and reduced ability to migrate on extracellular matrix (ECM) components [53], reduced cell adhesion and increased cell migration [54–56], increased metastatic ability [57], decreased intercellular aggregation and increased ECM adhesion, migration and invasion [58], increased cell motility and invasion

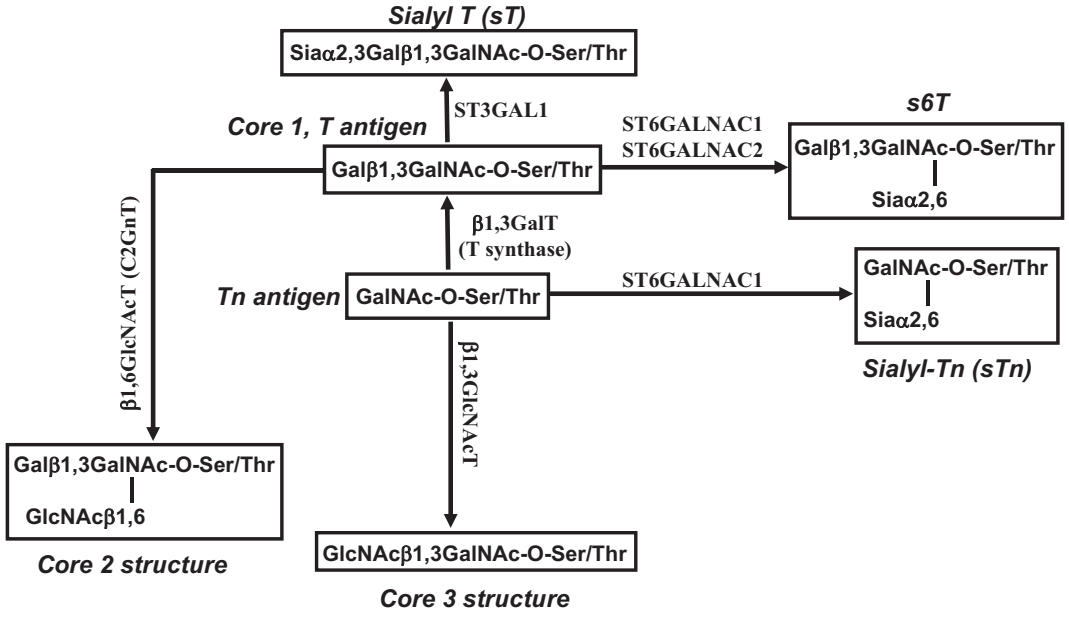

Fig. 1. Structure and biosynthesis of Thomsen–Friedenreich-related antigens. The Tn antigen, originated by the addition of GalNAc to serine or threonine residues of the polypeptide chain, can be transformed in sialyl-Tn antigen by the action of ST6GALNAC1 or can be elongated by the addition of a β1-3-linked galactose, yielding the core 1 structure (T-antigen) or by the addition of a β1-3GlcNAc, yielding the core 3 structure. The T antigen can be further processed by the addition of a GlcNAc β1-6-linked to GalNAc, generating the core 2 structure, or by the addition of sialic acid in α2-3-linkage to Gal, mainly by ST3GAL1, yielding the sialyl-T antigen. Core 1 structure can also be directly sialylated on the GalNAc residue by ST6GALNAC1 or ST6GALNAC2, yielding s6T antigen.

[44]. A possible mechanism through which sTn could enhance tumor growth *in vivo* involves the interaction with Siglec 15, a member of the Siglec family of sialic acid binding lectins [59], expressed by macrophages. sTn binding by the tumor-associated macrophages, which usually display an immunosuppressive M2 phenotype, triggers TGF-β release, establishing a microenvironment favoring cancer growth [60]. The ability of sTn-expressing cells to induce a tolerogenic phenotype of innate immune cells has recently been observed in a different model system [61].

Expression of ST6GALNAC2 displays opposite effects in colon and breast cancer. In colon cancer it is associated with lymph-node metastasis and poor survival [39], while in breast cancer it suppresses brain metastases [62]. The latter effect is due to the replacement of the T antigen with s6T with the consequent block of the binding of galectin-3 to membrane glycoconjugates, a key step in brain metastasis formation [62].

3.2. Sialyl Lewis antigens

Sialyl Lewis^a (sLe^a) and sialyl Lewis^x (sLe^x) are type 1 or type 2 fucosylated antigens terminated by α2,3-linked sialic acid [63], whose structure and biosynthesis are depicted in Fig. 2. Their relevance in cancer mainly originates from their binding to E- and P-selectins expressed on activated endothelial cells [64]. The ectopic expression of sLe antigens by cancer cells allows the adhesion to endothelial cells, promoting metastasis [65], tumor growth and angiogenesis [66]. Experimental

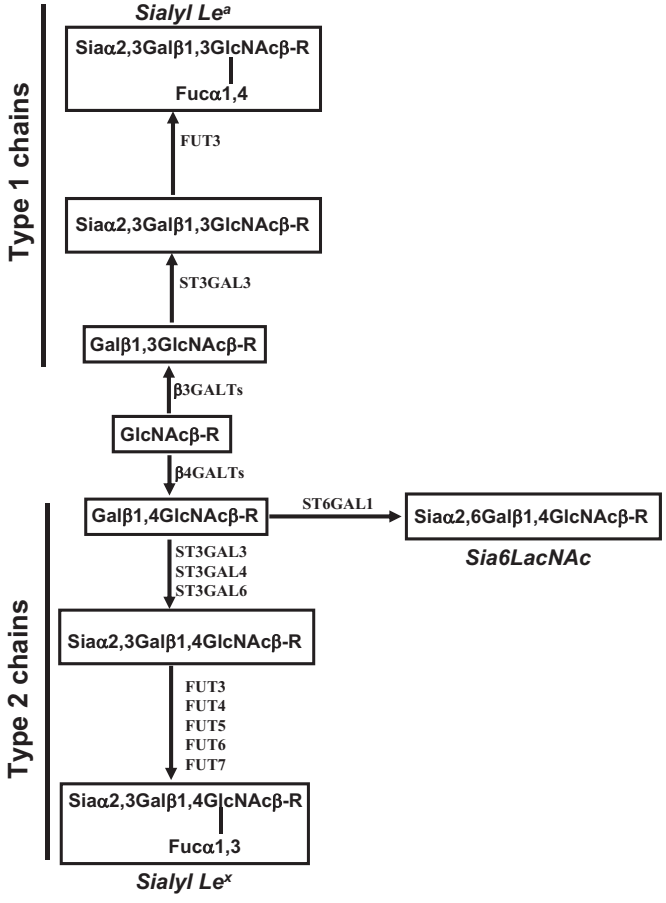

Fig. 2. Structure and biosynthesis of sialy Lewis antigens and Sia6LacNAc. Substitution of GlcNAc by a β1,3-linked galactose leads to the basic unit of type 1 chain, while substitution with a β1,4-linked galactose leads to lactosamine, the basic unit of type 2 chains. α2,3-sialylation of type 1 or 2 chains by the indicated sialyltransferases forms the substrates for the successive addition of fucose, which is mediated by FUT3 in sLe^a biosynthesis and by FUT3, -4, -5, -6, or -7 in sLe^x biosynthesis. The α2,6-sialylation of type 2 chains by ST6GAL1 leads to the formation of Sia6LacNAc.

manipulation of α2,3-sialyltransferases [67–72] and/or α1,3/4 fucosyltransferases [73–75] indicates that both enzymes classes can determine the level of sLe biosynthesis, even though this does not necessarily imply a regulatory role *in vivo* for those enzymes. Studies on mRNA expression of sialyltransferases in clinical specimens had reported partially conflicting conclusions [76–78]. The lack of a clear relationship between sialyl-/fucosyltransferase modulation and sLe expression in colon cancer [76] suggests that in this malignancy, the *de novo* expression of sLe antigens might be due to other mechanisms (reviewed in [79,80]). TNF-α stimulates the expression of selectin ligands through different mechanisms: in lung cells through stimulation of ST3GAL4 [72,81], in prostate cancer cells through up-regulation of ST3GAL3 and other glycosyltransferases [82]. Epithelial to mesenchymal transition (EMT), a crucial event in metastasis formation of epithelial tumors, induced by EGF or bFGF treatment of colon cancer cells, produced expression of sLe^x/sLe^a antigens [83] through the transcriptional activation of sialyltransferases ST3GAL1, -3- and -4 (and of FUT3), mediated by c-myc [83]. The transcription of ST3GAL6, also involved in sLe^x biosynthesis, is increased by treatment with 5-aza-2′-deoxycytidine, a drug which inhibits DNA methylation [84]. It is likely that the altered pattern of methylation of tumors influences the expression level of sialyltransferases involved in the biosynthesis of sialylated tumor antigens. In breast cancer, high ST3GAL3 mRNA expression, together with low ST6GAL1, are associated with worse prognosis [85,86]. Breast cancers are grouped according to the expression of the estrogen receptors (ER). The privileged expression of sLe^x by ER-negative tumors is consistent with the over-expression of a group of glycosyltransferases, including ST3GAL6, FUT3, and FUT4 [87]. Although expression of sLe^x is not directly associated with survival, patients displaying a double sLe^x/ER positive phenotype are at higher risk of metastasis to bone where E-selectin, the countereceptor of sLe^x, is constitutively expressed [87].

3.3. Polysialic acid

Long linear arrays of sialic acid residues joined through an α2-8-linkage which decorate the N-linked chains of the neural cell adhesion molecule (N-CAM) [88] and of a few other glycoproteins are referred to as polysialic acid (PSA). The biological properties of PSA depend on the degree of polymerization (DP), which is high in embryonic and fetal brain but low in the adult [89]. High DP PSA exerts a strong inhibitory effect on intercellular adhesion [90,91], allowing the tissue plasticity which characterizes immature nervous system. PSA regulates both homophilic interactions between N-CAM molecules and heterophilic interactions between N-CAM and other cell adhesion molecules [92]. The biosynthesis of PSA is mediated by two sialyltransferases, ST8SIA2 (also known as STX) [93] and ST8SIA4 (also known as PST) [94], which display only partially overlapping properties in that only ST8SIA2 is dependent on development while ST8SIA4 synthesizes longer PSA chains [95].

High DP PSA is re-expressed in a variety of human cancers [96] mainly, but not exclusively, of neuroectodermal origin [97,98] and is usually associated with malignancy. In a seminal study on neuroblastoma cells, the DP of PSA was found to be greater than 55 [99]. *In vitro*, the presence of PSA increased cell growth and migration [100,101], while in immunodeficient mice PSA expression facilitated the growth of glioma cells in the brain [102] and increased metastasis formation [103], although it reduced the subcutaneous growth of lung cancer cells in nude mice [104]. The increased cell motility associated with high DP PSA can be explained by at least two different mechanisms: through decreased E-cadherin-mediated intercellular aggregation [92] and by decreased number of cell-substratum focal adhesions [105]. The contribution of the two polysialyltransferases to PSA re-expression is tissue-dependent [98,102,106]. Bone marrow detection of ST8SIA2 mRNA in neuroblastoma patients predicts metastatic progression [107]. The therapeutic inhibition of PSA biosynthesis has been pursued

with different approaches [108]. In colon cancer, polysialyltransferases are expressed without a concomitant expression of PSA [104], because of the lack of N-CAM. Even though PSA has been associated with malignancy, N-CAM expression is associated with reduced invasion [109,110]. This could explain why the concomitant transfection of lung adenocarcinoma cells with both polysialyltransferases and N-CAM cDNAs reduced *in vivo* growth [104]. Consistently, although neuroblastoma patients with higher levels of polysialylated N-CAM presented more often metastasis at diagnosis, those without polysialylated N-CAM had a poor five year survival [111].

3.4. Sia6LacNAc

The transfer of α2,6-linked sialic acid to lactosaminic chains (Fig. 2), mediated by β-galactoside α2,6-sialyltransferase (ST6GAL1) generates α2,6-sialylated lactosamine (Sia6LacNAc). Lectins from *Sambucus nigra* (SNA), *Trichosanthes japonica* [112] or *Polysporus squamosus* [113] have been widely used to detect Sia6LacNAc in normal and cancer tissues. The fucosylated variant of Sia6LacNAc recognized by antibody ST2H [114] and the CDw75 antigen [115] are also the product of ST6GAL1. Although widely expressed by normal tissues ST6GAL1 is a cancer-associated glycosyltransferase. After the first description of ST6GAL1 elevation in colon cancer tissues [116], successively confirmed by several groups [117–119], the enzyme and/or its product was found to be increased in a variety of malignancies (reviewed in [5,120]), as reported in Table 1. In colon cancer, increased SNA reactivity [121] and ST6GAL1 expression [122] have been reported to be predictive markers of poor prognosis. Colon cancers can be grouped according to two main transformation pathways. The majority display inactivation of the APC gene, mutation of K-ras and other changes. These cases usually show chromosomal instability (CIN) but microsatellite stability (MSS). The minority of the cases shows the inactivation of DNA repair genes, resulting in microsatellite instability (MSI), and a consequent inactivation of crucial tumor suppressor genes. The increased SNA reactivity of colon cancer cases is mainly associated with the MSS phenotype [123], probably because of the known dependence of ST6GAL1 on Ras activation (see Section 5.1), a key event in MSS progression.

While in rodent hepatoma ST6GAL1 was elevated [124,125], among liver cancer patients only a small group displayed increased ST6GAL1 expression [126,127], while the few patients with decreased expression [126] showed poor differentiation and prognosis [128]. Also in breast cancer, increased ST6GAL1 expression was displayed only by a group of patients, mainly of grade III [85].

An association between α2,6-sialylation and invasive growth was suggested by early studies [129–131]. However, to study the functional implications of the overexpression of ST6GAL1 and/or its cognate Sia6LacNAc structures, we [132] and successively others [133–135] obtained stable ST6GAL1 transfectants in different cell lines. These models showed increased α2,6-sialylation of β1-integrins and increased binding to extracellular substrates in epithelial cancers [133,134,136–138]. The α2,6-sialylation of β1-integrins modulates intracellular signaling (as described in Section 5.2) and is involved in a self-fueling loop (as described in Section 5.3). In addition, α2,6-sialylation of β1-integrins can reduce the binding of galectin-3 [139] a lectin which, in some

Table 1
Human cancers displaying elevated ST6GAL1 and/or Sia6LacNAc.

Tissue of origin	Enzyme protein	mRNA	Sia6LacNAc	References	Remarks
Colon	Activity[a]	–	–	[116]	
	–	–	SNA	[236,237]	Low reactivity in adenomas
	Activity	–	–	[118]	Increased in metastasis
	Activity	–	SNA	[238]	
	–	PCR	–	[77]	Detected in metastasis
	Mab[b]	–	–	[119]	
	Mab	–	–	[122]	Worse prognosis
	–	–	SNA	[121]	Worse prognosis
	–	–	*T. japonica*	[112]	Only differentiated carcinomas
	Activity	PCR	SNA	[239]	
	–	PCR	–	[76]	
	Activity	–	Anti CDw75	[117]	
	–	–	SNA	[123]	Reactivity mainly in MSS cases
	–	–	SNA	[240]	Increased reactivity of some plasma proteins
	Activity	–	–	[241]	
Stomach	–	PCR	–	[242]	
	Activity	PCR	–	[243]	Associated with local recurrence
	–	–	Anti CDw75	[244]	Worse prognosis
AML[c]	Activity	–	–	[245]	Increased in blasts
ALL[d]	–	PCR	CD22[e]	[170]	Increased mRNA and Sia6LacNAc structures
Choriocarcinoma	Activity	PCR	–	[246]	
Cervix	–	PCR	–	[247–249]	
	–	PCR	–	[250]	
Ovary	–	PCR	–	[251]	
Brain	Polyclonal Ab	Northern	SNA	[252]	Increased only in non-neuroectodermal tumors
Liver	Mab	–	CD22	[127]	
	Activity	PCR, i.s. hyb[f]	SNA	[126]	Increased in a minority of cases
	–	PCR	Anti CDw75,		Sia6LacNAc gangliosides slightly increased
	–	–	Viscumin	[253]	ST6GAL1 mRNA unchanged
	Activity	–	–	[128]	Decreased activity correlates with poor prognosis
Breast	–	PCR	–	[85]	Associated with grade III
	–	–	Anti CDw75	[254]	
Mouth	Activity	–	SNA	[255]	
	Activity	–	SNA	[256]	Detected in serum
Cutaneous cancers	Mab	–	–	[257]	Associated with invasion

[a] ST6GAL1 expression has been measured as enzyme activity.
[b] ST6GAL1 expression has been measured with a monoclonal antibody.
[c] AML: acute myeloblastic leukemia.
[d] ALL acute lymphocytic leukemia.
[e] Sia6LacNAc has been detected using a soluble form of the Sia6LacNAc-specific siglec CD22.
[f] *In situ* hybridization.

circumstances, can exert a pro-apoptotic effect [140], resulting in prevention of apoptotic death and increased malignancy. However, ST6GAL1 expression reduced the tumorigenic potential and the multilayer growth of the colon cancer cell line SW948 [137] and the invasive growth of glioma cells [135,141–143]. Mammary tumors developed by PyMT mice (Section 3.1) in a ST6GAL1-null background displayed increased differentiation but the same growth rate as those grown in the PyMT mice expressing ST6GAL1 [144], although ST6GAL1-negative tumors exhibited altered expression of genes associated with focal adhesion signaling and had decreased phosphorylation of focal adhesion kinase, a downstream target of β1-integrins. The ST6GAL1 protein has been reported to be associated with the stem phenotype of both normal and cancer cells [145]. As detailed in Section 5.2, ST6GAL1-mediated sialylation prevents VEGF-independent angiogenesis [146,147]. Association of ST6GAL1 with radiation resistance and with drug resistance is discussed in Section 4. Altogether, these data indicate that the relationship between Sia6LacNAc and invasive growth is complex and probably strongly cell- and tissue-dependent.

3.5. Gangliosides

Gangliosides are sialic acid-containing glycosphingolipids, whose expression is often deranged in cancer. The two sialyltransferases which mainly control ganglioside biosynthesis are ST3GAL5 (GM3 synthase) which synthesizes GM3, precursor of all ganglio-series glycolipids, and ST8SIA1 (GD3 synthase) which synthesizes GD3, precursor of b-series gangliosides (Fig. 3). In general, it appears that malignancy is positively associated with the expression of GD3 [63,148,149] and negatively with that of GM3 [150–153]. A high level of GD3 characterizes melanoma, while neuroblastoma typically exhibit a high GD2/GD3 ratio, owing to high levels of B4GALNT1 (GD2 synthase) [154]. Neuroblastoma cells grown as nude mice xenografts express higher levels of ST8SIA1 and of b-series gangliosides [155], while knock-down of ST8SIA1 by antisense vector inhibited tumor growth and angiogenesis [156–158]. Enhanced malignancy in ST8SIA1-expressing cells can be due to interaction of GD3 or GD2 with integrins [159], growth factor receptors [160–162] and Src kinases [163] (Fig. 4) (discussed in detail in Section 5.2). A recent study [164] reports that ganglioside GD2 is a marker of breast cancer stem cells and that ST8SIA1 is a crucial regulator of GD2 expression. In this tumor, ST8SIA1 is regulated by NFkB and estradiol [165] (see Section 5.1). In considering the phenotypic effects of ST8SIA1 expression it should be considered that this enzyme also provides the basis for the biosynthesis of more complex gangliosides, such as GQ3 and GP3 [166]. A therapeutic approach of lung cancer based on ST8SIA1 suppression by RNA interference has been proposed [149].

The growth inhibitory effects of GM3 are supported by several observations. First, the growth-suppressing activity of GM3 is so strong that it can normalize the neoplastic phenotype induced by the expression of the viral oncogene v-Jun in fibroblasts [150] (Fig. 5); second, the expression of GM3 can induce cell death [167]; third, fibroblasts from ST3GAL5-KO mice, lacking a- and b-series gangliosides, show MAPK activation [168], indicating that the mere absence of GM3 even in the absence of GD3 is sufficient to activate the MAPK pathway. However, in oncogene-transformed cells a near complete ganglioside depletion results in a dramatic inhibition of *in vivo* growth in syngeneic animals [169]. Although ST3GAL5 and GM3 are usually associated with reduced malignancy, some observations suggest the opposite relationship [170–173]. The association between malignancy and ST8SIA1/GD3 also presents some exceptions [174–176].

Sialyltransferases involved in the biosynthesis of more complex gangliosides are prominently involved in some cancers. ST6GALNAC5, which synthesizes GD1α (Fig. 3), is a crucial mediator of breast cancer metastasis to the brain [177] because the ectopic expression by breast cancer cells of this enzyme, which is normally restricted to the brain, enhances their adhesion to brain endothelial cells and their passage through the blood–brain barrier. In other malignancies ST6GALNAC5 plays an opposite role. In fact, the CpG islands of its promoter are frequently hypermethylated in colon adenomas and carcinomas [178] while its over-expression in glioma cells lead to reduced malignancy [179]. The expression of ST6GALNAC6, another sialyltransferase involved in the biosynthesis of higher disialogangliosides, also shows down-regulation in cancer [180].

4. Sialyltransferases in resistance to chemotherapy and radiotherapy

Resistance to radio- and chemotherapy which are, beside surgery, the most widely used cancer therapies is a major reason of cancer death. A role of sialyltransferases in causing resistance to these treatments is

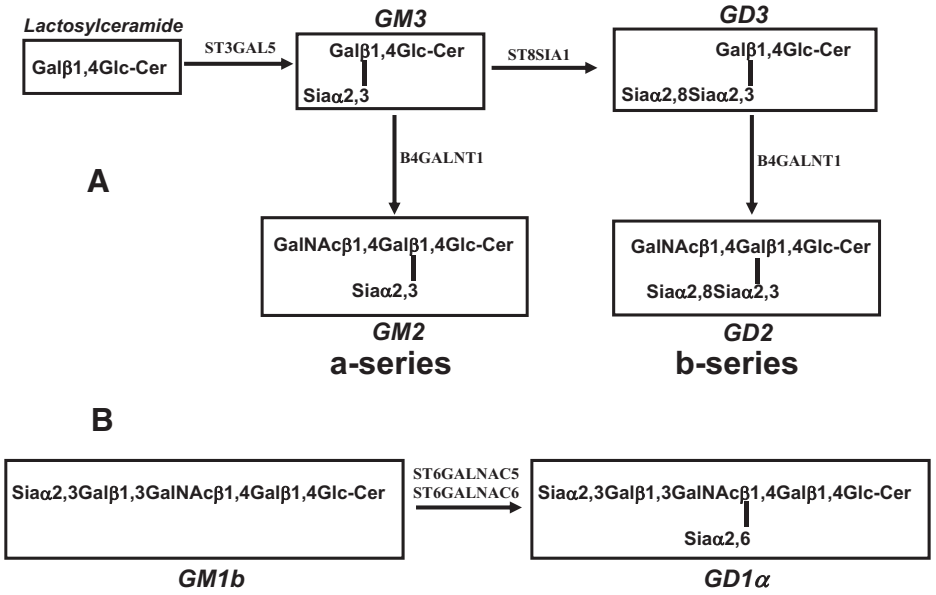

Fig. 3. Simplified representation of ganglioside biosynthesis. A: sialylation of lactosylceramide, mediated by ST3GAL5, is the first step of all ganglio-series ganglioside biosynthesis. The addition of a second, α2-8-linked sialic acid by ST8SIA1, yields GD3, which is the first member of b-series gangliosides. The addition of GalNAc on GM3 or GD3 by B4GALNT1 (GM2/GD2 synthase) yields GM2 and GD2, respectively. B: biosynthesis of the brain metastasis-associated ganglioside GD1α by ST6GALNAC5/ST6GALNAC6.

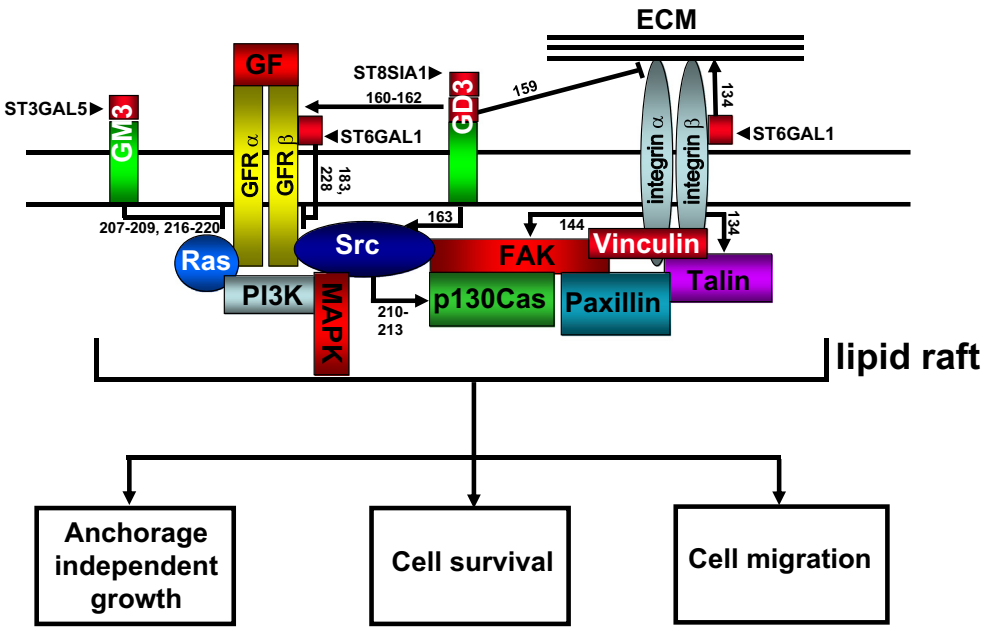

Fig. 4. Schematic representation of glycosylation-modulated interactions in a lipid raft. In these cholesterol-rich specialized membrane microdomains, growth factor receptors (GFR) (yellow), integrins (light blue) and gangliosides coexist. Disialoganglioside GD3 (sialic acid is represented by red squares) stimulates cell growth through at least two partially overlapping mechanisms: first through enhanced localization of Src kinase family members in lipid rafts, resulting in stronger signaling of FAK/p130Cas; second, through the constitutive activation of the growth factor receptor c-Met, which stimulates MAPK and PIP3 signaling. On the other hand, monosialoganglioside GM3, inhibits ligand-dependent phosphorylation of growth factor receptors (GFR). The presence of α2,6-linked sialic acid on β1 integrins strengthens the binding to extracellular matrix (ECM) components and to talin. Arrows indicate activation signals. Arrowheads indicate the addition of sialic acid residues by specific sialyltransferases. Numbers close to arrows refer to some pertinent citations.

supported by several observations. ST6GAL1 expression confers drug resistance to ovarian cancer cells [181] and leukemia cells [182], while in a colon cancer cell line it reduces sensitivity to the EGFR kinase-specific inhibitor gefitinib [183]. On the other hand, human T cell lymphoblastic leukemia cells resistant to the drug desoxyepothilone B displayed reduced expression of ST6GAL1 [184]. Sialyltransferase ST8SIA4 is one of the glycosyltransferases over-expressed in a drug-resistant variant of the erythroleukemia cell line K562 [185] and in multidrug resistant variants of acute myeloid leukemia cells [182]. These changes affect expression of P-glycoprotein and of multidrug resistance-related protein 1 through modulation of PI3K/Akt signaling. Interestingly, Akt activation appears to be at the basis of ST6GAL1 and ST8SIA2 induced chemoresistance in hepatocarcinoma cell lines [186].

ST6GAL1 is also crucially involved in radiation resistance. In fact, exposure to ionizing radiations resulted in increased expression of ST6GAL1 in animal tissues and cultured cell lines [187,188], while forced expression of ST6GAL1 cDNA in colon cancer cell lines induced radiation resistance [188]. The increased signaling through α2,6-sialylated β1-integrins results in activation of paxillin and Akt signaling [189,190], promoting cell survival [191].

5. Cancer associated glycans and signaling pathways

Neoplastic transformation is usually due to altered regulation of genes regulating cell growth (oncogenes and tumor-suppressor genes). The carbohydrate structures described above are aberrantly expressed in cancer mainly because genetic and epigenetic changes alter oncogene/tumor suppressor gene regulation which, in turn, perturbs glycosyltransferase expression. Through the synthesis of cancer-associated carbohydrate structures, this generates a flow of information from the nucleus to the cell surface (inside-out signaling). On the other hand, membrane molecules decorated by cancer-associated glycans convey aberrant signaling pathways targeting gene expression, generating an information flow from the cell membrane to the nucleus (outside-in signaling). In some cases, these bi-directional information flows form self-fueling loops, as shown in Fig. 5.

5.1. Inside-out signaling: genetic and epigenetic changes leading to sialyltransferase modulation

ST6GAL1 provides a very good example of a glycosyltransferase which is directly controlled by an oncogene. The positive effect of Ras signaling on ST6GAL1 expression has been known since the '90s [192–194]. More recently, it has been shown that both oncogenic N-ras and H-ras stimulate ST6GAL1 transcription through RalGEF signaling [195] and that in a colonocyte cell line Ras drives the α2,6-sialylation of β1-integrins through ST6GAL1 over-expression [136]. Consistently, ST6GAL1 shows negative regulation by the tumor suppressor transcription factor RUNX3 [196]. On the other hand, it has been reported that ST6GAL1 expression is stimulated by caveolin-1 [197] a gene with a prevalent tumor suppressor activity.

Transfection of medulloblastoma cells with the muscle-specific transcription factor Pax3 induces polysialylation of N-CAM through increased expression of ST8SIA2 but not of ST8SIA4 [198].

Sialyltransferases display modulation by estrogens. Estradiol stimulates ST3GAL3 but inhibits ST6GAL1 in breast cancer cells [199]. The core promoter of ST8SIA1 contains two putative estrogen response elements (ERE) to which the transcription factor NFkB binds, stimulating transcription of ST8SIA1 [200]. However, in ER-positive breast cancer cells estradiol binding to ERE inhibits NFkB binding, resulting in down-regulation of ST8SIA1 transcription [165] and explaining the up-regulation of ST8SIA1 transcription in ER-negative breast cancers. Interestingly, in prostate carcinoma cells NFkB positively regulates the transcription of sialyltransferases ST3GAL1, -2 and -6 [201]. Sialyltransferases ST3GAL1, -3 and -4 are down-regulated by the metastasis-suppressor gene nm23-H1 [202] but are up-regulated by c-myc [83]. Although in porcine kidney cells, ST3GAL1 is transcriptionally regulated by TGF-β/SMAD3 signaling [203], in a human colon

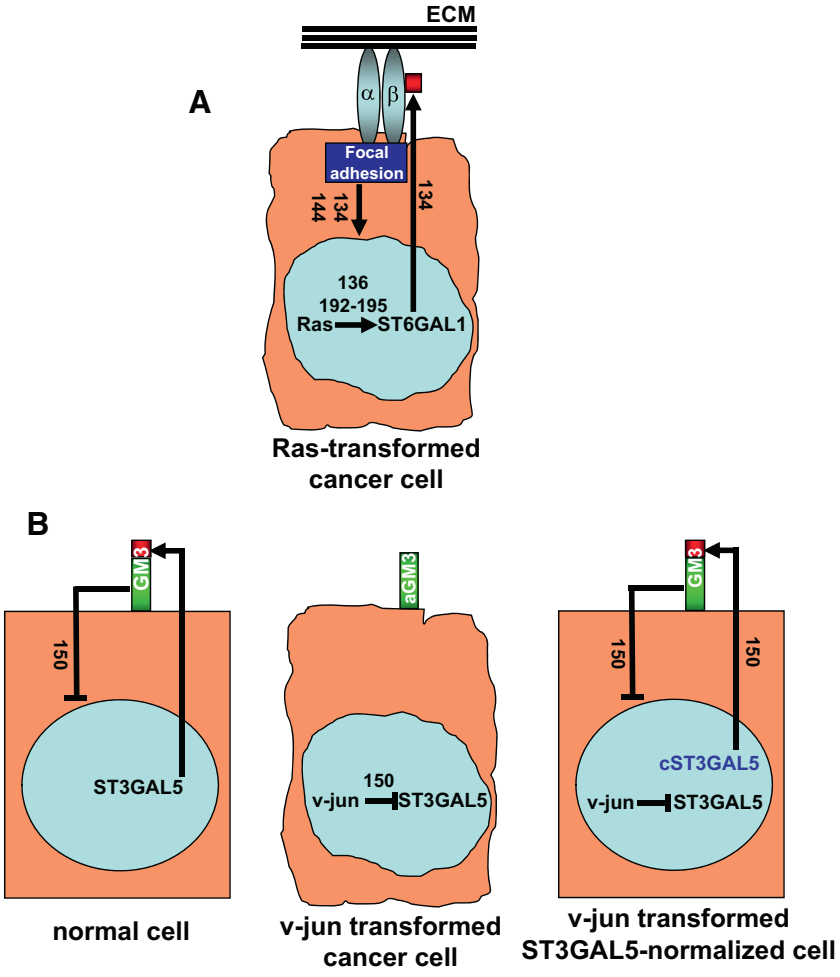

Fig. 5. Examples of outside-in/inside-out loops. A: In a Ras-transformed cell (irregular cell and nucleus shape), ST6GAL1 over-expression leads to α2,6-sialylation of integrin β1-chains (red square). This modification increases binding to ECM and downstream FAK signaling. B: a normal cell expresses ST3GAL5 and ganglioside GM3 which are associated with a normal phenotype (regular cell and nucleus shape). The expression of v-jun oncogene leads to cell transformation (irregular cell and nucleus shape), inhibition of ST3GAL5 and replacement of GM3 with asialo-GM3 (aGM3). However, the constitutive expression of ST3GAL5 (cST3GAL5, blue) by transfection, restores GM3 biosynthesis with normalization of the cellular phenotype. Numbers close to arrows refer to pertinent citation.

cancer cell line TGF-β receptor 2 signaling modulates sialylation without affecting the mRNA levels of known sialyltransferases [204].

Treatment of HCT15 colon cancer cells with the demethylating drug 5-azacytidine (5-AZA) activates ST3GAL6 and expression of sLe^x on MUC1 [84], while in prostate cancer cells, androgens induce transcriptional activation of ST3GAL2 through demethylation of its promoter [205].

5.2. How the expression of sialylated glycans on the cell membrane signals to cell interior (outside-in signaling)

The lipid rafts are cholesterol-rich membrane microdomains in which growth factor receptors, integrins and gangliosides coexist, favoring their interactions. The sialylation of plasma membrane glycoproteins, including integrins and growth factor receptors, modulates their activity and consequently the origin of the signaling pathways toward the nucleus (outside-in signaling). In addition, the activity of these receptors can be indirectly modulated by gangliosides. Examples of these mechanisms, depicted in Fig. 4, are described below.

c-Met is the receptor of the hepatocyte growth factor (also known as scatter factor) and is crucial for cancer cell motility and metastasis [206]. In a breast cancer cell line, the constitutive expression of ST8SIA1 and of gangliosides GD3 and GD2 results in proliferation in the absence of serum [161,162] because of the constitutive activation of c-Met [160] and in the stimulation of MAPK and PIP3 signaling [160]. On the other hand, interaction of c-Met with monosialogangliosides GM3 and GM2 resulted in inhibition of its signaling and of cell motility [207–209]. c-Met activation can also be induced by the ST3GAL4-induced expression of sLe^x, leading to phosphorylation of FAK and Src proteins [70]. Thus, the activation of c-Met signaling is the common downstream effect of the expression of different sialyltransferases.

GD3 can also stimulate cancer cell growth by direct interaction with cell signal transducers located on the internal side of the plasma membrane. GD3 promotes the association between FAK and p130 [210,211], enhancing signaling [212,213] because of a stronger involvement of the Src kinase family member Yes which, in GD3-expressing cells, localizes in raft domains even before serum treatment [163]. The negative effect of ganglioside GM3 on the cell growth and on the activity of growth factor receptors has long been known [214,215]. A large body of data points to the interaction between GM3 and the ERBB membrane receptors family [216]. GM3 interacts with the GlcNAc termini of N-linked chains of ERBB1 (EGF receptor, EGFR), inhibiting its ligand-dependent activation [217–220], while the interaction of GM3 with the EGFR/ERBB2 heterodimer induces its retention in lipid rafts in a phosphorylated form [221–223]. The expression of ST3GAL5 and of GM3 in non small cell lung cancer results in an increased number of EGFR molecules and increased sensitivity to the EGFR-tyrosine kinase gefitinib [224]. It has been proposed that the GM3-mediated inhibition of EGFR signaling is due to the inhibitory activity of protein kinase C-α on EGFR [225]. On the other hand, normal human fibroblasts not expressing ST3GAL5

exhibit an over 90% reduction of the ganglioside content and a concomitant strong inhibition of EGFR signaling [226]. GM3 inhibits the pro-angiogenic activity of VEGF [152] through direct interaction with the VEGFR-2 receptor [227]. Apart from ganglioside contribution, glycosylation of EGFR can directly modulate its activity. In a lung cancer model, sialylation and fucosylation of EGFR resulted in a reduced, rather than increased, tendency to receptor dimerization and phosphorylation after EGF binding [228]. Consistently, in a colon cancer cell line, inhibition of ST6GAL1 resulted in increased growth and EGFR signaling upon EGF binding and increased sensitivity to the EGFR inhibitor gefitinib [183]. An opposite effect was displayed by ST3GAL1, whose expression enhanced gefitinib sensitivity [224]. However, α2,6-sialylation can also indirectly stimulate ERBB2/ERBB3 signaling. In fact, inhibition of ST6GAL1 by miR-199a reduced sialylation and the expression of a tumor suppressor which inhibits ERBB2/ERBB3 signaling [229].

Integrins are heterodimeric membrane glycoproteins mainly involved in binding to extracellular matrix components. After binding, integrins form focal adhesion complexes, activating signal transduction pathways downstream of growth factor receptors (Fig. 4). The integrin/growth factor receptor crosstalk provides the cells with environmental signals necessary for proliferation [230,231]. The ST6GAL1-mediated sialylation of integrin β1-chains reinforces the integrin-based signal transduction, as shown by increased binding of talin [134] and phosphorylation of focal adhesion kinase [144] and provides a survival signal through activation of paxillin/Akt [190]. Integrin function can also be modulated by interactions with the sugar portions of gangliosides. In fact, gangliosides GD3 and GT1b inhibit the binding of α5β1 integrin to fibronectin by direct binding of their carbohydrate portion with that of integrin α5 subunit [159] while GM3, in association with tetraspanin and CD9 interacts with β1 integrins and inhibits cell motility [232,233].

Induction of tumor angiogenesis is mainly regulated by VEGF-mediated stimulation of VEGF receptors. Inhibition of this interaction by the anti-VEGF-A monoclonal antibody bavacizumab is a widely used anti-cancer therapy. However, the existence of a glycosylation-dependent, VEGF-independent mechanism of VEGFR stimulation, which can be at the basis of bevacizumab resistance has been recently described [146,147]. According to this mechanisms, in the tumor hypoxic conditions exacerbated by anti angiogenic treatment, ST6GAL1 was down-regulated, while N-acetylglucosaminyltransferase-V (MGAT5, responsible for β1,6-branching) was up-regulated. The coordinate modulation of the two enzymes leads to a remodeling of the N-linked chains of VEGFR2 which favors its binding by galectin-1 which, in turn, results in VEGFR signaling in the absence of its ligand. Thus, the ST6GAL1-mediated sialylation of VEGF receptors exerts a key role in preventing angiogenesis and tumor progression [146,147].

N-CAM provides another example of a cell adhesion molecule which modulates intracellular signaling through its PSA chains. Removal of PSA from N-CAM of neuroblastoma cells activates extracellular signal-regulated kinase (ERK), leading to reduced proliferation and neuronal differentiation [234].

5.3. Inside-out/outside-in loops

Examples of positive or negative inside-out/outside-in loops are provided in Fig. 5. In the positive loop shown in A, a Ras mutation activates ST6GAL1, leading to α2,6-sialylation of β1 integrins, stronger binding to ECM and increased FAK signaling. In the negative loop shown in B, cell transformation by the viral oncogene v-jun inhibits sialyltransferase ST3GAL5 and ganglioside GM3 expression, resulting in increased growth rate and anchorage independent growth [150]. Forced expression of ST3GAL5 results in the normalization of the transformed phenotype [150]. These data provide proof of the principle that aberrant oncogene expression results often in a deranged glycosylation pattern (inside-out), which in turn, modifies the gene expression of cancer cells (outside-in).

6. Concluding remarks

Glycosylation, among other postransductional modifications, is increasingly appreciated as a tool through which nature modifies the functional properties of the molecules without the need to alter the genetic code. In this review we have reported the alterations of significant sialylated structures and/or the level of expression of their cognate sialyltransferases, finding not always consistent results. This may depend on the fact that in many studies the level of glycosyltransferase expression was inferred from that of the corresponding RNA, although it is known that the RNA/protein quantitative relationship could be poor. Moreover, multiple mechanisms contribute to determine the actual level of a sialylated structure, including masking by substituents, competition between glycosyltransferases and role of sialidases. Amplification loops fueled by sialylated molecules which we discuss in this review are reminiscent of other amplification loops described in tumors, like that originated by Src, ErbB2 and PEAK1, recently described in pancreatic cancer [235]. The self-fueling loops where aberrant sialylated structures sustain cancer growth make sialyltransferases and/or their products attractive targets for innovative therapeutic treatments. However, based on experimental evidences, the use of sialyltransferase inhibitors or sialidases appears not sufficiently specific for clinical application, at the moment. More detailed knowledge of the mechanisms linking sialylation and cellular transformation, which is necessary to warrant the success of therapeutic approaches, will be the focus of future investigations.

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