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REVIEW

Sialylation: an Avenue to Target Cancer Cells

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Abstract Tumorigenesis and metastasis are frequently associated with altered structure and expression of oligosaccharides on cell surface glycoproteins and glycolipids. The expression of sialylated glycoconjugates has been shown to change during development, differentiation, disease and oncogenic transformation. Abnormal sialylation in cancer cell is a distinctive feature associated with malignant properties including invasiveness and metastatic potential. The alterations in sialylation is accompanied by changes in sialic acid, sialidase activity, sialyltransferase (ST) activity or sialoproteins. The present review summarizes the reports on alterations of sialic acid, linkage specific STs and sialoproteins, sialidase activity together with different subtypes of ST and sialidases mRNA expressions in various cancers like lung, breast, oral, cervical, ovarian, pancreatic etc. Sialic acids are widely distributed in nature as terminal sugars of oligosaccharides attached to proteins or lipids. The increase shedding of sialic acid observed in malignant tumors may be due to different types of sialidases. The amount of sialic acid is governed by levels of sialidases and STs. Various types of STs are also involved in formation of different types sialylated tumor associated carbohydrate antigens which plays important role in metastasis. The alterations associated with sialylation aids in early diagnosis, prognosis and post treatment monitoring in various cancers. Recently newer drugs targeting different interplays of sialylation have been developed, which might have profound effect in inhibiting sialylation and thus cancer metastasis and infiltration.

Keywords Sialic acid · Sialidase · Sialyltransferase · Sialoproteins · Sialylation

Abbreviations

FUT	Fucosyltransferase
GAL	Galactose
GL	Glycolipids
GP	Glycoprotein
NEU	Neuraminidase
PSA	Prostate specific antigen
SLe	Sialyl lewis
ST	Sialyltransferase
TACA	Tumor associated carbohydrate antigen
TSA	Total sialic acid

Functional activation of newly synthesized proteins requires co-translational and post-translational modifications of proteins and glycosylation is the most frequent modification associated with malignancy. Glycoproteins are proteins with one or more heterosaccharide chains that contain hexose, hexosamine, sialic acid and fucose as predominant sugar moieties. The field of "glycoproteomics" has emerged recently and various studies have identified glycoproteins as cancer biomarkers [1, 2]. The terminal epitopes of glycoproteins have been proposed to play a significant role in cell-cell interaction and cell adhesion, and thus plays an important in malignant transformation. Sialylation is a typical terminal modification that plays a key role during various stages of tumor progression. Sialic acid (N-acetyl neuraminic acid) frequently

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occupies the terminal position on membrane glycoproteins. Sialic acid and their derivatives play roles in a variety of biological processes such cell-cell communication, cell-matrix interaction, adhesion and protein targeting. Abnormal sialylation in cancer cell is a characteristic feature associated with malignant properties including invasiveness and metastatic potential [3]. This review provides comprehensive details on sialylation changes which are accompanied by alterations in sialic acid, sialoproteins, sialyltransferase (ST) activities or sialidase activities in various malignancies.

Alterations in Sialic Acid

Sialic acid residues generally occur at non-reducing terminal positions of the glycoconjugates. Elevated serum total sialic acid (TSA) has been reported in several malignancies like head and neck, breast, endometrial, colorectal, lung, oral cancer etc. [3–5]. Recently there is much advancement in salivary based diagnostics [6, 7]. Recently salivary TSA have been reported to be elevated in breast cancer, oral cancer and also in oral precancerous conditions [8, 9]. It has been also documented that α-2,6 galactose linked sialic acid (GalSA) was downregulated in poorly differentiated non-small cell lung cancer tumors, while it was overexpressed in well differentiated tumors. α-2,6 GalSA have been documented to be responsible for brain metastasis by adhesion of tumor cells to the brain vessels endothelium which enables their transmigration in brain metastastic tumors [10].

Recently, different strategies have been developed to image Sia expression in vivo and the perspectives to translate it from the bench to the bedside [11]. Recently there are therapeutic approaches which targets sialic acids in metastatic tissues [12]. Earlier reports have also suggested that inhibition of serum sialic acid by antineoplastic drugs is due to tumor microenvironment [13].

STs are the enzymes capable of transferring sialic acid to glycoconjugates and sialidase is involved in breaking down of sialic from sialyloglyconjugates. Cellular sialic acid contents are mainly controlled by ST and sialidases. However, in cancer there is an alteration in sialylation pattern, which is mainly accompanied through changes in sialyloglyconjugates by ST and sialidase enzymes.

Alterations in Sialidase Activity

The major function of sialidase (neuraminidase) enzyme is to hydrolyze glycosidic linkages between sialic acid and glycosyl residue of complex oligosaccharide and glycoconjugates. Earlier studies have observed higher sialidase activity in serum and tissue of various cancers [14]. In cancer patients increased sialic acid levels might be due increased serum/tissue sialidase activity. Increased sialic acid also contributes to process of metastasis.

A recent study from our laboratory has reported elevated salivary sialidase activity in patients with OPC and oral cancer patients [9].

There are four type of sialidase NEU1, NEU2, NEU3 and NEU4. The major subcellular localization of NEU1 is lysosomal, NEU2 is cytosolic, NEU3 is on plasma membrane and NEU4 is in lysosomes or in mitochondria and ER [14].

Alterations of NEU1 in Cancer A decrease in *NEU1* expression has been observed in various cancers. It has been observed that over-expression of the human *NEU1* gene suppressed cell migration and invasion in the colon adenocarcinoma HT-29 case, whereas its knockdown resulted in the opposite [15]. Earlier reports have documented that introduction of *NEU1* sialidase into B16 melanoma cells resulted in suppression of pulmonary metastasis and tumor progression, with increased sensitivity to apoptosis [14].

Alterations of NEU2 in Cancer It has been earlier reported that when the human *NEU2* gene was introduced into leukemic K562 cells, it induced a significant reduction in anti-apoptotic factors Bcl-XL and Bcl-2, which further resulted in increased sensitivity to apoptotic stimuli. Studies have also shown that introduction of rat *NEU2* gene into a B16-BL6 mouse melanoma cell lines and colon adenocarcinoma cells, caused a marked reduction in metastasis [14].

Alterations of NEU3 in Cancer Increased expression of NEU3 has been reported in various cancers including colon, renal, ovarian, and prostate cancers; also a decreased expression has been noted in acute lymphoblastic leukemia [14].

Alterations of NEU4 in Cancer Earlier reports have indicated decreased *NEU4* mRNA levels in human colon cancer. When DLD-1 and HT-15 colon adenocarcinoma cells were transfected with *NEU4*, it resulted in acceleration of apoptosis and decreased invasiveness and cellular motility [14]. Earlier reports have shown that targeting *NEU4* by siRNA resulted in marked inhibition of apoptosis and promotion of cellular invasiveness and motility. A recent report has documented that glioblastoma stem cells (GSCs) demonstrated marked upregulation of *NEU4*. Moreover, it has been observed that increase in NEU4 activity in more differentiated GBM cells by the NEU4 agonist thymoquinone, causes increased expression of *OCT-4* and *GLI-1* [16].

Drugs Targeting Sialidase

A recent study has suggested that targeting NEU1 sialidase with oseltavimir phosphate inhibits the cancer cell survival in

pancreatic cancer with acquired chemoresistance. Thus, oseltavimir phosphate was shown to be a potent therapeutic agent for pancreatic cancer resistant to drug therapy i.e. cisplatin or gemcitabine alone or in combination [17]. Earlier it has been observed that *NEU3* siRNA resulted in decreased expression of MMP-2 and MMP-9 which caused mark reduction in invasion and metastasis [18]. Oseltavimir and Zanamivir are drugs frequently used for targeting sialidase enzyme. Alkyne-hinged 3-fluorosialyl fluoride (DFSA) containing an alkyne group has been reported to be a target-specific irreversible inhibitor of sialidases. The main advantage of the ester-protected analog DFSA was its cell membrane-permeability, which was shown to form covalent adducts with virus, bacteria, and human sialidases [19].

Alterations in Sialyltransferases

STs are enzymes that transfer sialic acid to nascent oligosaccharides. Each ST is specific for a particular sugar substrate. STs adds sialic acid to the terminal portions of the sialylated glycolipids (gangliosides) or to the N- or O-linked sugar chains of glycoproteins. The amount and type of sialylation of tumor cell membrane depend on the activity of a number of different STs. Sialic acid is linked either through α-2,3 or α-2,6 linkage to subterminal galactose or α-2,8 linkage to another sialic acid forming polysialic acid catalyzed by specific ST. The various STs are named according to sialyl linkages they form (ST3GAL, ST6GAl, ST6GALNAC and ST8Sia). ST families are further sub-divided into 20 sub-families in mammals, which can be distinguished on the basis of oligosaccharide sequence they use as acceptors and anomeric linkage they form with the penultimate sugar residue [20].

Expressions of STs are often de-regulated in various cancers like colorectal, liver, gliomas, gastric, oral cancer etc. [3, 9, 20].

Earlier studies from our laboratory have reported alteration in enzyme activities of α-2,3 and α-2,6 STs in serum and saliva of patients with OPC and oral cancer patients and its significance in treatment monitoring [3, 9].

During neoplastic transformation, the activity of the Golgi-localized STs is usually increased and as a consequence, cancer cells express more heavily sialylated tumor associated carbohydrate antigen (TACA) at their surface. The various ST plays role in formation of TACA in various cancers [20]. *ST3GAL1* plays role in formation of sT antigen, *ST3GAL4* in sLe^X formation, *ST6GAL1* in CD75s and ST2H formation, *ST6GALNAC1* in sTn antigen etc. The common glycan alterations observed in various cancers are increased $sLe^{x/a}$, increased Tn epitopes, increased sialyl Tn epitopes, increased sialyl T antigens and increased α-2,6 sialylation [21]. The tumors expressing a high level of certain types of TACAs exhibit greater metastasis and progression than those expressing low level of TACAs [21]. These TACAs also serve as basis for development of anti-cancer vaccines [22].

Novel Drugs Involved in Inhibition of Sialyltransferase Enzyme

The different strategies targeting sialylation like the use of chemical inhibitors of ST and specific antisense oligodeoxynucleotides silencing ST gene expression have been developed to analyze the role of sialylation in cancer progression and metastases. It may serve as new potent anti-inflammatory, immunosuppressive and anti-metastatic agents for future therapeutic applications. Efforts have been made to design and synthesize specific ST inhibitors such as substrate (both donor- and acceptor based) analogs or compounds with a structural mimetic of transition-state [23]. However, although these compounds are efficient inhibitors of ST activities in vitro, they are usually less effective in vivo due to a poor permeability across cell membranes. There are very few ST inhibitors with a cell-permeable property reported so far. Soyasaponin I, a ST inhibitor isolated from soybean saponin, has been shown to be CMP-Neu5Ac competitive inhibitor of *ST3GAL1* in vivo. Lithocholic acid analogues which have similar steroid-related structure as Soyasaponin I, have been found to be noncompetitive inhibitors of Galβ1-3GalNAc α-2,3 STs. AL10, a lithocholic acid derivative was earlier shown to inhibit adhesion, migration and invasion of *ST3GALI* over-expressing A549 and CL1.5 human lung cancer cells. The ST inhibitor KI-8110 (5-fluoro-2′,3′-isopropylidene-5′-O-(4-N-acetyl-2,4-dideoxy-3,6,7,8-tetra-O-acetyl-1-methoxycarbonyl-D-glycero-α-D-galactooctapyranosyl)uridine), has been shown to successfully lower pulmonary metastatic potential of murine NL-17 colon adenocarcinoma cells by inhibiting platelet-derived growth factor-(PDGF) dependent growth of cancer cells. Recently, a novel sialytransferase inhibitor Lith-O-Asp has been developed that suppresses Fak/Paxillin signaling and cancer angiogenesis and metastatic pathways [24].

The competitive inhibitors of *O*-glycosylation such as benzyl-N-acetyl-α-D-galactosaminide (BGN) have been shown to hinder *O*-linked oligosaccharide sialylation of cancer cells and it has been reported that BGN treatment resulted in reduction of CD44 *O*-linked glycan sialylation and enhanced metastatic ability of B16BL6 melanoma cells [25]. Recently, fluorescent inhibitors i.e. anionic mimetics of CMP-Neu5Ac have been developed, which are potent cell-permeable polarization probes that inhibit cellular sialylation [26]. Earlier studies have reported that anticancer effect of the epidermal growth factor receptor (EGFR) kinase inhibitor, gefitinib, was increased in *ST6GAL1* deficient colon cancer cells. In contrast, overexpression of *ST6GAL1* reduced the cytotoxic effect of gefitinib [27]. It has been also suggested that fluorinated analogs of sialic acid and fucose can be taken up and metabolized

resulting in a global, family-wide shutdown of sialyl or fucosyltransferases and remodeling of cell surface glycans. These inhibitors substantially decrease the expression of the sialylated and fucosylated ligand sLe^X on myeloid cells, which resulted in loss of selectin binding and impaired leukocyte rolling [28]. There is much advancement in development of various glycan antagonists and inhibitors of ST and FUCT. ZP103 was observed to be a potent inhibitor of glycosyltransferase involved in sLe^x biosynthesis. Several O-linked and N-linked glycan inhibitors have been developed that are monosaccharide inhibitors or enzyme inhibitors, acceptor analogs or blocking glycan-protein interactions [29]. The profound effect of these inhibitors on different interactions of sialylation in cancer is indeed noteworthy, which might aid in better prognosis of cancer patients.

Inhibition of Different Sialyltransferases by Using Antisense or Small Hairpin RNA

Specific inhibition by antisense or small hairpin (Sh) RNA has also been utilized to analyze the role of ST in cancer. Earlier studies have reported that antisense silencing of the G_{D3} synthase (ST8Sia I) in F-11 rat neuroblastoma cells decreases cell proliferation, angiogenesis, vascular endothelial growth factor (VEGF) production and tumor growth in nude mice [20]. Significant decrease in the cell growth and invasion activity has been observed in lung cancer cells, when stably transfected with a G_{D3} synthase RNAi expression vector [30]. Similarly, G_{D3} synthase antisense knockdown induced a decreased rate of cell growth in the hamster melanoma AbC-1 cell line [20]. It has been depicted that G_{M3} synthase (*ST3GAL5*) silencing in 4 T1 highly metastatic mouse mammary tumor cells significantly inhibits cell migration, invasion and anchorage-independent growth in vitro, and lung metastasis in vivo. This has been suggested due to activation of PI3K/Akt pathway and nuclear factor of activated T cells (NFAT) inhibition [31]. Earlier reports have indicated that silencing of *ST6GAL1* inhibits the ability of HT-29 human colon cancer cells to form colonies in soft agar and to invade the extracellular matrix [32]. Transfection of MDA-MB-435 breast cancer cells with *ST6GAL1* cDNA was shown to up-regulate cell surface α-2,6 sialylation with concomitant increase in cell migration and reduce cell–cell adhesion, whereas antisense *ST6GAL1* RNA was shown to significantly reduce collagen IV and cell-extracellular matrix adhesion. The results suggested that cell surface α-2,6 sialylation contributes to extracellular matrix adhesion of tumor cells. Earlier reports have documented that suppression of ST by antisense DNA reduces invasiveness of human colon cancer cells in vitro [32].

Alterations in Sialoproteins/Sialoglycoproteins

Alterations in tissue and serum sialylated glycoproteins have been observed in various cancers like ovarian, breast, glioma, liver, etc. [2, 3]. A recent study from our laboratory indicated altered salivary α-2,3 and α-2,6 sialoproteins in patients with OPC and oral cancer patients [9].

Earlier it has been reported that the levels of core-fucosylated biantennary glycans and α-2,3 linked sialic acids were significantly increased in prostate cancer patients as compared to patients with benign prostate hyperplasia [33]. Earlier evidences have reported that cancer cells can become more aggressively malignant in metastatic transformation via metabolic flux through sialic acid pathway [34].

Therapeutic Approaches Earlier studies have documented that fluorinated sialic acid analogues blocks the synthesis of sialoglycans in murine melanoma cells. The result documented P-3F(ax)-Neu5AC as a powerful glycomimetic capable of inhibiting aberrant sialylation, which can be used for anticancer therapy [35].

In conclusion, the present review summarizes the changes associated with sialylation in various cancers and its applicability in diagnosis, prognosis and post treatment monitoring. The newer drugs targeting different interplays of sialylation might have profound effect in inhibiting sialylation and thus cancer progression, metastasis and infiltration. The progress made in the field of drugs targeting sialylation seems to remodel the glycome in cancerous cell, which can prove wonders in inhibiting cancer invasion and metastasis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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