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Sialic acids: An Avenue to Target Cancer Progression, Metastasis, and Resistance to Therapy

Review

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Abstract: **Background:** Sialic acids are alpha-keto acids with nine carbons that are commonly present in the terminal sugars of glycans on glycoproteins and glycolipids on the cell surface. Sialic acids have a role in a variety of physiological and pathological processes by interacting with carbohydrates and proteins, communicating between cells, and acting as cell surface receptors for viruses and bacteria. Several studies have shown the aberrant pattern of sialic acids on cancer cells due to change in their glycosylation status. This pattern may be attributed to various physiological and pathological changes occurring in tumour cells. Hypersialylation in tumours, its involvement in tumour growth, immune evasion and escape from the apoptotic pathway, metastasis formation, and therapeutic resistance have all been fairly well investigated.

Methods: A PubMed search was conducted and published articles in different studies from 2000 to 2020 were included and reviewed. Here, we discuss current outcomes that emphasize the unfavourable effects of hypersialylation on multiple aspects of tumour genesis, immune evasion, metastasis and resistance to therapy.

Conclusion: These recent investigations have found that aberrant sialylation is an essential process for tumour cells to evade immune surveillance and maintain their malignancy. Together, these noteworthy views provide a solid platform for designing and developing therapeutic approaches that target hypersialylation of cancer cells.

Keywords: *chemoresistance • immune evasion • metastasis • sialic acids • tumorigenesis*

1. Introduction

Sialic acids, which have a nine-carbon backbone, belong to the neuraminic acid family and are significant compounds with a wide structural diversity.[1] In general, sialic acids help to stabilise proteins, cell trafficking, cell-cell interaction, and cell-matrix interactions in both vertebrate and invertebrate cells by terminating glycan chains.[2] Eukaryotic cells have specialised machinery that helps in the production, activation, and transport of activated sialic acid by coordinating multiple enzymes. In particular, Golgi resident enzymes, specifically sialyltransferases, integrate activated sialic acids into the terminal monosaccharides of glycoconjugates like glycoproteins and glycolipids. So far, 20 distinct sialyltransferases have been identified; each sialyltransferase is involved in the adding of activated sialic acids to underlying sugars via different glycosidic links, such as α2,3, α2,6, or α2,8.[3]

Furthermore, during tumour transformation and malignant growth, sialic acids are abnormally expressed on the surfaces of tumour cells. Hypersialylation is more commonly found in tumour tissue as compared to normal tissue.[4] Also, the concentration of sialic acids in the

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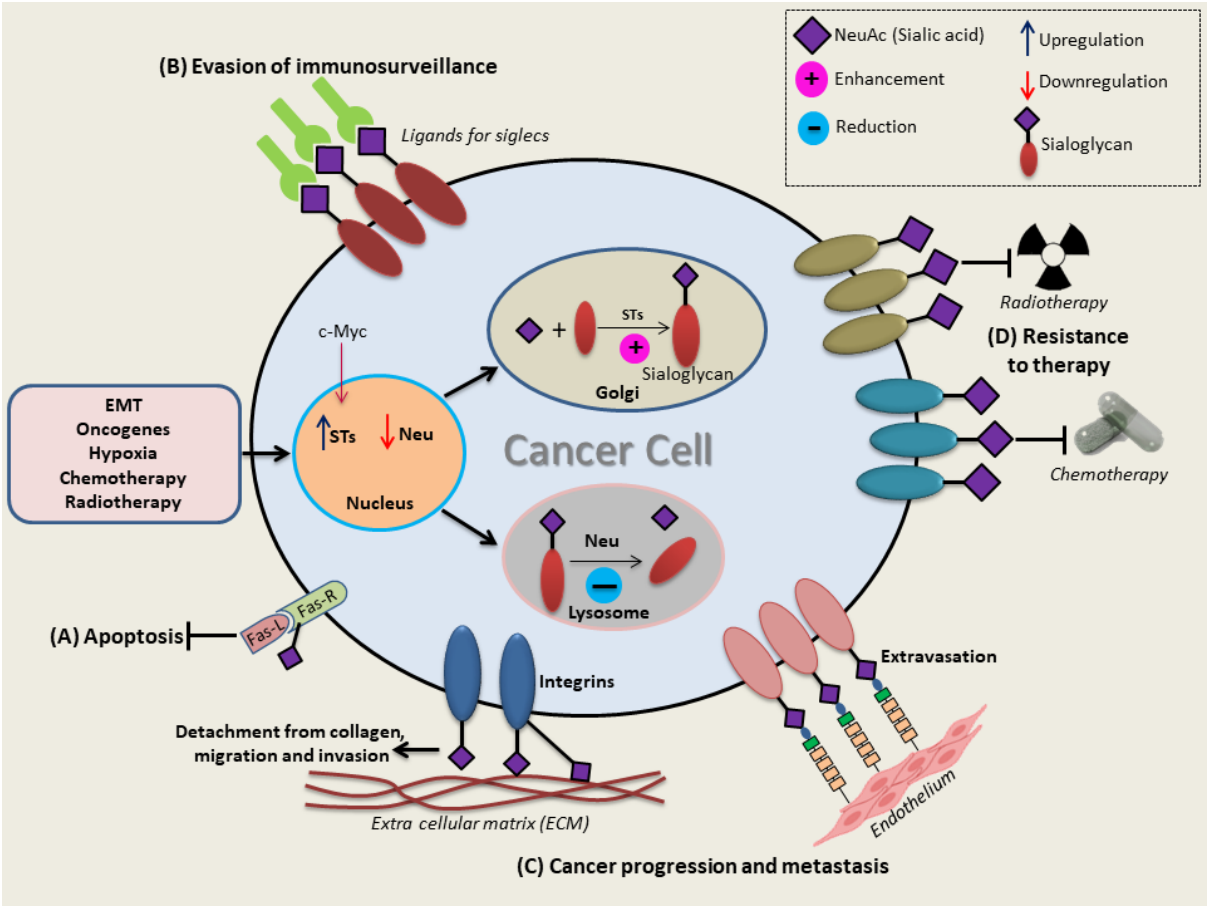


Figure 1: In cancer cells, factors such as oncogenes, hormones, and therapy increase the expression of sialyltransferases while decreasing the expression of sialidases (Neu). As a result, sialoglycan synthesis by sialyltransferases in the Golgi system is increased, while sialoglycan hydrolysis by sialidases in the lysosome is decreased, resulting in the accumulation of hyposialylated structures on the cell membrane. The Fas receptor's apoptotic signalling is impaired by unusually elevated sialoglycan expression (A). The integrins hypersialylation facilitates binding to the extracellular matrix (ECM) or selectins, allowing migration/tissue invasion and metastasis formation (C), and assisting immune evasion in cancer (B) and mediating resistance to therapy (D).

blood and glycolipid-bound sialic acids is substantially given rise to various malignancies.[5] Aside from that, hypersialylation aids in the progression of cancer and leads to a poor prognosis. Unusual metabolic alterations and/or abnormal expression of sialyltransferases or sialidases are also the major drivers of increased sialic acid content in tumour cells.[6,7] In addition, the study discovered that in cancer, sialic acid metabolism is elevated, as is glucose uptake, which is a resource for sialic acid production. Intriguingly, knocking down the *CMAS* (Cytidine Monophosphate *N*-acetylneuraminic Acid Synthetase) gene, a crucial factor in sialic acid metabolism, suppressed the production of the activated form of sialic acid and, as a result, reduced the establishment of metastasis.[8] Furthermore, abnormal or aberrant expressions of sialyltransferases on tumour cells enhance sialylation on glycoconjugates, allowing cancer cells to evade the immune-mediated attack, increase tumour cell proliferation and metastasis, aid in tumour angiogenesis, and help in apoptosis resistance by high expressions of sialylated glycan on Fas receptors and cancer therapy, illustrated in Figure.1.[4] A dense layer of tumour-associated carbohydrate antigens, including sialyl Lewis A (SLeA), sialyl Lewis X (SLeX), STn, and GM2 antigens, coats the cell surface of tumour cells.[9] We review and summarise the effects of abnormal sialic acid expression on tumour cell immune evasion, cancer growth, metastasis formation, and therapeutic resistance in this article.

2. Mechanisms leading to aberrant sialylation/hypersialylation

So far, three important mechanisms that lead to aberrant sialylation in cancer cells have been identified. The overexpression or the altered expressions of sialyltransferases are hypothesized to be the first

mechanism, leading to increased sialylation of glycans and the development of tumour-associated carbohydrate antigens.[7] Furthermore, proto-oncogenes such as Ras and c-Myc were shown to control transcription factors of certain sialyltransferases. Moreover, enhanced α2, 6 sialylations of β1 integrin (Ras) and high expression of SLex/a antigens (c-Myc), both accelerated tumour cell motility.[10,11] Additionally, hypoxia and high hormone levels were discovered to stimulate ST3GAL1 (ST3 beta-galactoside alpha-2,3-sialyltransferase 1) expression, which supports selectin binding and appearance in the bloodstream.[7]

Almaraz and colleagues postulated a second mechanism in which increased availability of precursor CMP-Sialic acids or the overexpression of genes involved in sialic acid production results in enhanced metabolic flux and sialic acid accumulation on cancer cells.[7,12] Rather than having their sialylation levels drastically elevated, glycoproteins involved in extracellular matrix (ECM) interactions and cell motility were discovered to be hypersialylated. It's still unclear if this is a tumour-specific occurrence. Some findings, on the other hand, imply that metabolic alterations in the course of sialic acid synthesis in the tumour microenvironment can induce cancer cells to hypersialylate, changing the expression of markers involved in tumour cell migration and metastasis.

Sialidases, also known as neuraminidases (NEU), can remove sialic acids from glycans enzymatically, hence regulating sialoglycan degradation, shedding, and plasticity. This third mechanism is enhanced tumour cell sialylation produced by differential expression of sialidases or neuraminidases (NEU). Currently, four well-known sialidases have been identified. NEU1 and NEU4 are found in the lysosome, while NEU2 and NEU3 are found in the cytosol and plasma membrane, respectively. In malignancies, expression of NEU1, 2, and 4 is reduced, increasing sialoglycans. While NEU3 has been reported to be elevated in various cancer cell types, the functional implications of sialylation are still unknown.[13]

2.1. Sialic acids and cancer cells' immune evasion

Immune cells that scour host cell surfaces for malignant abnormalities or infections recognise the particular glycan structures that protrude from the cell surface as among the first assemblies they detect. The majority of immunological cells express several distinct carbohydrate-binding receptor families that control their function. Among the numerous carbohydrates found in cell surface glycans, the sialic acid sugar family is critically relevant.[14] According to the data, sialic acid modulates immunological homeostasis and suppresses incorrect immune activation to prevent or restrict host cell damage. While some studies have shown that the thick layer of sialic acid on the cancer cells obscures surface antigens and makes it difficult for the immune system to recognise them.[15] Also, some of the findings verified that removing sialic acid from tumour cells with sialidase boosted their immunogenicity and slowed their growth in immune-competent animals, which backed up the theory. As a result, in some animal tumour models, sialidase-treated tumour cells are being used as a preventative and therapeutic vaccination.[14] Consequently, these findings suggest that sialic acid plays a significant role in tumour immunology and could be used as a target for cancer immunotherapy. In the current scenario, advancements in the research of immunology and glycobiology have rekindled attention in sialoglycans and revealed their immunomodulatory potential beyond antigen masking.

The sialoglycans are thought to have a role in distinguishing between self and non-self host cells, as well as preventing complement activation by attracting the complement regulatory protein factor H to the cell surface. Factor H has the polyanionic binding sites that aid in the binding of negatively charged molecules such as sialoglycans, glycosaminoglycans, and other compounds on the surface of host cells. In addition, the protein C3b is a surface-bound complement activating factor that blocks the deposition of factor-H, which leads to the initiation or the activation of the alternative complement pathway. This controlling framework suggests that improper activation or destruction of sialylated host cells should be avoided.[16] Although the complement system role is not fully known, cancer cells' escape mechanism, aided by complement activation by controlling their membrane with sialoglycans, has been well known.[17,18]

Natural killer (NK) cells are effector lymphocytes in the innate immune system that control the progression of many types of tumours and the resulting tissue damage. To be more specific, NK cells recognise and kill tumour cells that do not express MHC class I. Tumour cells have the potential to avoid NK-cell mediated killing processes either by producing inhibitory ligands of NK cells or by downregulating the production process of activation ligands and hence limits the current NK cell-mediated therapies.[19] So far, two NK cell-mediated immune evasion approaches were found, both of which entail tumour cell hypersialylation. The high sialoglycan coating on cancer cells prevents physical contact with NK cells and masks the activating ligands on

tumour cells.[20] Furthermore, by inhibiting cytotoxicity, hypersialylation of tumour cells reduced the development of connections between NK cells and tumour cells. This result is connected to reduced identification of ligands for the activating NK cell receptor NKG2D on sialylated tumours, most likely due to charge repulsion caused by the high negative charge of sialylated membranes and/or the hypersialylation of NKG2D ligands themselves. Second, numerous studies demonstrate that tumour sialoglycans interfere with NK cell function by initiating immunological inhibitory signalling via Siglec receptors, which inhibits NK cell function. Siglec-7 is expressed by the majority of NK cells, while Siglec-9 is expressed by roughly 40% of NK cells. Siglec-7 recognises α2, 8-linked sialic acids that are primarily expressed on NK cells, central nervous system cells, and tumour cells such as melanoma, glioma, and neuroblastoma. Several studies have found that binding of tumour α2, 8-linked sialic acids, such as GD3, to Siglec-7 reduces NK cell activation and function, allowing tumour cells to avoid NK cell-mediated death.[21,22] Like NK cells, Natural killer T (NKT) cells have a significant role in innate immunity. However, little attention has been paid to the expression of Siglec by NKT cells. Nevertheless, one study discovered that melanoma antigen containing sialic acid can bind to the NKT cell receptor CD1.[23]

Furthermore, tumour sialoglycans have an impact on adaptive immune cells. Tumour sialoglycans that aid tumours avoid cytotoxic T lymphocytes (CTLs) by blocking their stimulation and limiting their killing capabilities. CTLs kill tumour cells in two ways: granule-mediated cytotoxicity and Fas-mediated cytotoxicity, both of which are influenced by abnormal sialoglycan expression on tumour cells.[24] The α2, 6-sialylation of FasR hindered Fas-associated adaptor molecule (FADD) binding to the FasR death domain, impeded the assembly of the death-inducing signalling complex (DISC) and blocked apoptotic signalling, according to a recent study.[25] In addition, depending on the altered parameters, the tumour microenvironment was shown to play pro- and anti-tumorigenic effects in myeloid cells. Surprisingly, the dual actions of myeloid cells were discovered due to the production of sialic acids on tumour cells. Given this, tumour sialoglycans allow macrophages to recognise and absorb them in one way, but they can also deviate macrophages towards a more pro-tumorigenic phenotype in another. Siglec-1, which detects α2, 3-linked sialic acids and is expressed on macrophages as sialoadhesin/CD169, and a conserved Siglec hindrance the C-terminal immunoreceptor tyrosine-based inhibitory motif (ITIM). Also, they help to phagocyte the dead tumour cells and also assist in cross-presenting the antigens to CTLs. Hence, Siglec-1 positive macrophages considered to be useful in developing immune responses against cancer cells.[14, 26]

Dendritic cells (DCs) are essential antigen-presenting cells in the mammalian immune system that can activate T lymphocytes to attack tumour cells. To accomplish this, developed DCs must present naive T lymphocytes with tumour antigens as well as co-stimulatory chemicals. Secreted or tumour-bound sialoglycans have been shown to inhibit the start of antitumour T cell responses via modulating DC activation and maturation. For example, to counteract DC activation, overexpression of co-stimulatory molecules CD80/86, and IL-12 production, gastric, pancreatic, and prostate cancer cells create GD1a, a disialoganglioside. As a result, DC pulsed with GD1a failed to trigger Th1 effector cell growth but enhanced immunosuppressive regulatory T cell differentiation (Tregs). Other tumour-derived gangliosides, such as GD2 (found in neuroblastoma) and GM3/GD3 (found in melanoma), have been shown to block DC activation, IL-12 production, and subsequent effector T cell activation. GM3/GD3 has also been shown to inhibit the activation and migration of tissue-resident Langerhans cells as well as trigger death in melanoma cells.[14, 27]

Collectively, studies in the field of glyco-immunology, contribute to our understanding of the tumour sialoglycan-mediated immune escape mechanisms. Tumour sialoglycans, for example, have been demonstrated to disrupt physical interactions with immune receptors, inhibiting ligands on the cancer cell surface by masking or reducing the immune system's most important killing mechanism. However, further investigations are needed to acknowledge the impact of various tumour sialoglycans on immune cell activity, as well as the role of sialic acid in detecting lectin and other important receptors on immune cell subsets and in tumour immunology.

2.2. Sialic acids and cancer progression and metastasis

Infiltrations, as well as metastasis, are two essential biological pathways in cancer that determine the forms of malignancy. In which the tumour microenvironment shows a major role in the evolution and establishment of a malignancy's form, growth, and invasiveness. Cell surface glycans, particularly sialic acids, play a vital role in cell invasiveness, tumour cell ability to spread via the circulation, and distant metastasis among many variables implicated in cancer progression.[28]

The significance of sialic acid in malignancy progression and metastasis is based on a study that

found that increased expression of α2, 3-linked sialic acids promotes stomach cancer and is connected to a poor prognosis. The measure of α2, 3 linked sialic acids, which were detected by Maackia Amurensis Lectin I (MAL-I), was significantly overexpressed in MGC-803 cells, according to the glycan profiling modifications of gastric cancer growth mechanism study. Furthermore, ST3GAL4 (ST3 beta-galactoside alpha-2, 3-sialyltransferase 4) is linked to the creation of α2, 3 sialic acids, which promotes cell migration and invasion in gastric cancer cells. Furthermore, MAL-I staining in gastric cancer tissue revealed that increased expression of α2, 3 sialic acids were linked to lymph node metastases, cancer staging, and overall survival of the study participants. As a result, these outcomes contribute to a better understanding of the role of α2, 3 sialic acids in the growth and metastasis of gastric cancer, as well as the potential for the development of new cancer therapeutic approaches.[29]

Remarkably, another study has discovered and addressed the importance of sialylation in the progression of prostate cancer. ST3GAL3 (ST3 beta-galactoside alpha-2, 3-sialyltransferase 3) gene expression increased in tandem with the rise in α2, 3-linked sialic acid residues on α2 subunits of α2β1 integrin receptors. Cell surface α2, 3-sialylation of two integrin subunits revealed integrin α2β1-dependent cell adherence to collagen type I in the cancer microenvironment. Furthermore, the study found that the sialylated integrin receptor was responsible for the interaction with the carbohydrate moiety of asialo ganglioside GM1 (AsGM1), and it also explained how AsGM1 and α2β1 integrin receptors form complexes. These findings add to our understanding of the role of sialic acid in the organisation and function of key membrane components during the invasion and metastatic processes.[30]

ST6GAL1 (ST6 beta-galactoside alpha-2, 6-sialyltransferase 1) is highly expressed in numerous malignancies, including breast cancer, hepatocellular cancer, and colon cancer. ST6GAL1 mRNA levels increased considerably in lung cancer cell lines and tissue, while ST3GAL1, ST6GALNAC3 (ST6 N-acetylgalactosaminide alpha-2, 6-sialyltransferase 3) and ST8SIA6 (ST8 alpha-N-acetyl-neuraminide alpha-2, 8-sialyltransferase 6) were significantly reduced. Furthermore, forceful downregulation of ST6GAL1 reduced the protein levels of Jagged1, DLL-1, Notch1, Hes1, Hey1, matrix-metalloproteinase (MMPs) and vascular endothelial growth factor (VEGF) in A549 and H1299 cells *in vitro*, suppressing their proliferation, migration, and invasion abilities. ST6GAL1 knockdown also decreased tumorigenicity of NSCLC cells in athymic nude mice via the Notch1/Hes1/MMPs pathway in an *in vivo*. Surprisingly, modifying α2, 6-sialylation is associated with lung cancer progression, implying that ST6GAL1 may mediate the invasiveness and tumorigenicity of NSCLC cells *in vitro* and *in vivo* via the Notch1/Hes1/MMPs pathway.[31]

Changes in epithelial-mesenchymal transition (EMT) are linked to altered sialoglycan expression during tumour growth. During TGF-induced EMT in GE11 cells, ST6GAL1 transcription and α2, 6-sialylated *N*-glycans are upregulated. TGFβ-induced EMT was greatly suppressed by knocking down ST6GAL1, which was accompanied by an increase in E-cadherin expression, a key factor in epithelial cell adherens junctions, in an *in vitro* experiment. Overexpression of ST6GAL1, on the other hand, causes an increase in cell surface E-cadherin turnover and additional TGFβ-induced EMT.[32]

Aberrant sialylation has been linked to tumour growth, invasiveness, and metastatic potential, although the biological importance and molecular processes must be investigated further. Surprisingly, some research has concentrated on sialidases and the impact they have on tumour growth. In general, the metastatic ability of malignancies increases when sialidases/ neuraminidases are downregulated. A recent study found that downregulating NEU1 in bladder cancer cells caused abnormal sialic acid expression, which was linked to cancer growth. NEU1 overexpression, on the other hand, increased apoptosis and decreased proliferation in bladder cancer cells. Furthermore, the integrin α5β1 interaction was disrupted, and the Akt signalling pathway was inhibited.[33] NEU3 was previously shown to be linked with the plasma membrane and engaged in the apoptotic pathway in colon cancer. In addition, NEU4 downregulation aided the invasive capabilities of human colon malignancies.[34]

Overall, our findings suggest that changes in glycosylation patterns, notably, sialylation levels and concentrations of sialic acids, could be valuable markers for cancer development as well as possible molecules that regulate cancer spread by targeting specific machinery. However, more research is required to investigate the role of an individual and/or combined effects of sialyltransferases in cancer growth and metastasis.

2.3. Sialic acids and resistance to therapy

Through a variety of processes, cancer cells develop resistance to treatments such as chemotherapy, radiation, and other targeted therapies, which is a major hurdle to treating the disease. Many studies have recently shown that overexpression of sialyltransferases

and abnormal sialylation contribute to therapeutic resistance. A retrospective study has looked into 169 cases of ductal carcinoma of the breast that had undergone chemotherapy. The findings revealed that despite chemotherapy, upregulation of sialomucins and sialyltransferase ST3GAL5 was found in surgical specimens in patients who died within five years. As a result, the study concluded that uncontrolled sialylation was a probable cause of aggressive chemoresistant breast tumours.[35] The effect of sialylation on epidermal growth factor receptor (EGFR) phosphorylation and resistance to tyrosine kinase inhibition was proven utilising biochemical techniques. According to the findings, abnormal sialylation altered EGFR activation and sensitivity to tyrosine kinase inhibitors (TKIs) that prevent EGFR phosphorylation. In addition, sialylation of EGFR inhibited EGF binding and EGFR dimerization, suppressing EGFR phosphorylation. As a result, these findings suggest that the sialylation pathway is important in TKI-mediated EGFR phosphorylation and its related network during tumorigenesis.[36]

Endogenous gene regulators known as microRNAs have been linked to the development of multidrug resistance. The abnormal sialylation profile on the surface of leukaemia cells has been demonstrated for its potential function in leukaemia multidrug resistance. The researchers also looked at the expression profiles of α2, 3-sialyltransferases and miR-4701-5p in three chronic myeloid leukaemia (CML) cell lines and CML patients' bone marrow mononucleated cells. ST3GAL1 expression was shown to be altered in vitro and in vivo, and this was linked to Adriamycin drug resistance.[37] Furthermore, ST6GAL1 was elevated in ovarian cancer, and the high expression of this enzyme was linked to poor patient prognosis. ST6GAL1 was found to increase EGFR activation and protect ovarian cancer cells against Gefitinib-mediated cell death. As a result, the discovery of ST6GAL1 as an EGFR regulator sheds new light on the role of aberrant sialylation in growth factor signalling and chemoresistance.[38]

Altogether, these findings suggest that overexpression of sialyltransferases or hypersialylation of cancer cells aids in the control of chemotherapy efficacy and confers resistance to anticancer drugs. Furthermore, it was postulated that sialic acids could have a role in cancer therapeutic resistance.

2.4. Sialic acids as targets for cancer immunotherapy

The thick covering of sialic acids on the surface of tumour cells aided and protected them from immune system destruction. Years ago, some studies used bacterial sialidases to remove sialic acids from the surface of tumour cells, and later sialidase-tumour-treated cells were used to vaccinate cancer patients in clinical trials, although the results were inconsistent.[7,28] The use of bacterial sialidases has been utilised to remove sialic acids from cancer cells for a long time and is still commonly employed today. Cancer cells, on the other hand, can replenish sialic acids on the cell surface after enzymatic clearance, severely limiting the use of sialidase in cancer therapy.[39]

Siglec is a family of lectins that recognize sialylated glycans on cancer cell glycoproteins and glycolipids and is expressed on the surface of immune subtypes in the tumour microenvironment. Siglec controls the immune system and aids cancer cells in escaping the immune system by forming a network of cancer cell sialic acids. STn and sialyl T are well known cancer-associated sialoglycans that have been linked to the deactivation of NK cells and the production of regulatory T cells, as well as the defective maturation and activation of macrophages and dendritic cells.[28]

Targeting inhibitory Siglec members and their receptors, which are thought to be critical, as well as possible immunological checkpoints to target malignancies, has been the focus of recent studies. To inhibit the pathways and improve feasible therapeutic methods, it is necessary to understand the Siglec ligands and their expression on cancer cells. Some of the targeted approaches to eliminate Siglec ligand expression on cancer cells are valuable for research and clinical development, while the evaluation of checkpoint inhibitors, as well as the transfer of engineered NK cells to eliminate Siglec, could be an effective way to improve current NK cell-based cancer treatments.[22][40] Studies incorporating comprehensive profiles of patients' tumour "glyco-code" are critical for better understanding particular glycan structures and developing novel tactics for tailored immunotherapy, as well as targeting sialic acid to improve patient response to immunotherapies.

3. Conclusion and future perspectives

We have briefly discussed and summarised limited and selected studies in this review, and we have highlighted the various roles of sialic acids and their role in tumour progression, immune surveillance escape, metastasis formation, and resistance to apoptosis and chemotherapy. As a result, we conclude that cancer therapy that targets sialic acids and their receptors is highly effective. Because increased concentrations

of sialic acids on the surface of tumour cells mask the antigenic sites of glycoproteins due to aberrant sialylation and/or hypersialylation, removing such sialic acids using the sialidases enzyme is anticipated to develop a promising cancer management strategy in the future. Interestingly, the surface sialidase co-expression in chimeric antigen receptor T Cells (CAR-T) has recently been shown to be successful in the treatment of tumours.[4,41]

Furthermore, according to a new perspective on cancer treatment, engineering glycans and eliminating sialic acids by altering extracellular vesicles and replacing them with Lewis Y glycans changed the mechanism of tumour cell presentation to dendritic cells.[42] In addition, Siglec-15, an antibody against sialic acid-binding protein and T cell depressor, is predicted to apply to cancer immunotherapy and offers an additional treatment approach for patients resistant to current anti-PD1/PD-L1 therapy.[43] Henceforth, future research on developing treatment strategies by diminishing sialic acid levels, targeting sialyltransferases, or directing the inhibitory sialic acid receptor in combination with immunotherapy will make a significant contribution to improving the ineffective management of cancer patients as well as improving their quality of life.

Abbreviations

Sialyltransferases are named according to the HUGO recommendations; CMP: Cytidine monophosphate; IgG: Immunoglobulin G; NKG2D: Natural killer group 2D; PD-1: programmed cell death protein-1; PD-L1: programmed death-ligand1.

Authors' contribution

MG, PKJ, and VDBM designed this review outline. MG contributed to the papers collection, analysis, and interpretation of data. MG and PKJ wrote the manuscript. VDBM and VC read and approved the final manuscript.

Conflict of interest

The author declare that they have no conflicts of interest.

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