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REVIEW ARTICLE OPEN

Biological function of sialic acid and sialylation in human health and disease

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Sialic acids are predominantly found at the terminal ends of glycoproteins and glycolipids and play key roles in cellular communication and function. The process of sialylation, a form of post-translational modification, involves the covalent attachment of sialic acid to the terminal residues of oligosaccharides and glycoproteins. This modification not only provides a layer of electrostatic repulsion to cells but also serves as a receptor for various biological signaling pathways. Sialylation is involved in several pathophysiological processes. Given its multifaceted involvement in cellular functions, sialylation presents a promising avenue for therapeutic intervention. Current studies are exploring agents that target sialic acid residues on sialoglycans or the sialylation process. These efforts are particularly focused on the fields of cancer therapy, stroke treatment, antiviral strategies, and therapies for central nervous system disorders. In this review, we aimed to summarize the biological functions of sialic acid and the process of sialylation, explore their roles in various pathophysiological contexts, and discuss their potential applications in the development of novel therapeutics.

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FACTS

- Sialic acids are negatively charged, nine-carbon monosaccharides that play pivotal roles in cellular communication and function.
- Sialylation, a novel post-translational modification driven by adding a sialic acid to the terminal residues of oligosaccharides and glycoproteins, takes part in multiple pathophysiological processes.
- Sialylation not only provides a layer of electrostatic repulsion to cells but also serves as a receptor for various biological signaling pathways.
- Several studies have indicated that sialylation may present a promising avenue for therapeutic intervention.

OPEN QUESTIONS

- How do alterations in the sialylation process impact the development and progression of diseases beyond the currently studied systems?
- What are the underlying molecular mechanisms that link sialylation to neuropsychiatric disorders, and how can these insights be applied to develop novel therapeutic strategies?
- Can sialylation serve as a therapeutic target for diseases (e.g., cancer, stroke, and cardiovascular diseases), and what would be the potential benefits and challenges?

INTRODUCTION

Sialic acid, a member of the nine-carbon monosaccharides with a keto acid functional group [1], is ubiquitous across vertebrate tissues [2]. First isolated by Blix et al. from submaxillary mucin in 1936, it was named "sialic acid" due to its acidic nature and origin from saliva [3]. To date, over 50 distinct sialic acid species have been identified, including N-acetylneuraminic acid (Neu5Ac), N-glycolylneuraminic acid (Neu5Gc), deaminoneuraminic acid (Kdn), and their modified derivatives such as methylation, acetylation, and sulfation at various positions [4]. Among these, Neu5Ac and Neu5Gc are the predominant forms in mammals. In humans, only Neu5Ac is synthesized de novo, as a mutation in the gene of cytidine monophosphate-N-acetylneuraminic acid hydroxylase has rendered humans unable to convert Neu5Ac into Neu5Gc [5] (Fig. 1). However, Neu5Gc can still be found in certain human cells, especially endothelial and epithelial cells, due to dietary intake [6]. The presence of anti-Neu5Gc antibodies in the human body suggests that antigen-antibody interactions involving Neu5Gc may contribute to chronic inflammation and the increased incidence of diet-related carcinomas and other diseases [7]. Moreover, sialic acid-containing structures are integral to numerous physiological and pathological processes through carbohydrate-protein interactions.

Sialylation, the process of appending sialic acid units to the terminal of lipoproteins and glycoproteins, is a novel form of post-translational modification (PTM) [8], making sialic acids as the "bridging" molecules between cells and their extracellular matrix

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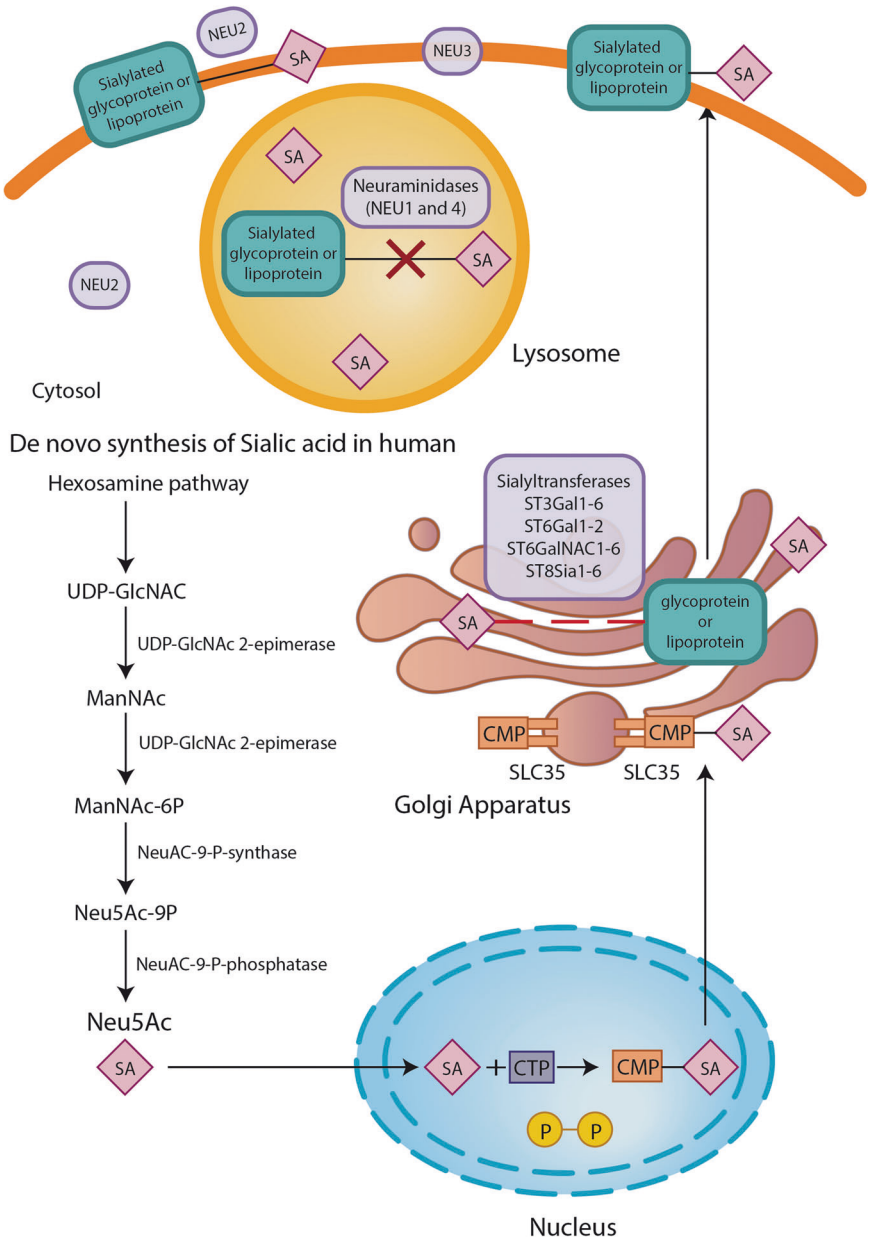


Fig. 1 The biological process of sialylation. SA sialic acid, NEU neuraminidases P-P diphosphate, ST3Gals β-galactoside α-2,3-sialyltransferases, ST6Gals β-galactoside α-2,6-Sialyltranferase, ST8Sias α-2,8-sialyltransferases, CTP cytidine-5′-triphosphate, CMP cytdine 5′-monophosphate, SLC 35 Solute Carrier Family 35, Neu5AC N-acetylneuraminic acid.

[4]. In mammals, terminal sialic acids are presented either as single entities or as polysialic acid (PolySia) chains on N- and O-linked glycans of glycoproteins and glycolipids. This process occurs through α-2,3- or α-2,6-bonds to galactose (Gal) or N-acetylgalactosamine (GalNAc) units of glycans, or through α-2,8- or α-2,9-bonds to other sialic acid moieties [4, 9] (Table 1). The dynamic addition and removal of sialic acid serve to regulate structural stability and cell recognition and communication [10–12]. For instance, increased terminal sialylation enhances the serum half-life of glycoproteins such as tissue plasminogen activator (tPA) and erythropoietin (EPO) [13–16]. In addition, sialylation of N-glycans prevents their interaction with the asialoglycoprotein receptor, thereby avoiding liver clearance [17].

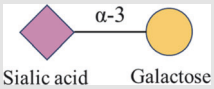
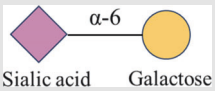
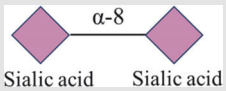
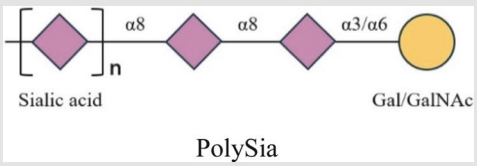
In this review, we summarized the current literature on sialic acid metabolism and its impact on various pathophysiological processes. We further explored the therapeutic potential of targeting terminal sialic acids on sialoglycans in disease conditions. Moreover, we highlighted several unresolved questions regarding the effects of aberrant sialic acid metabolism on cellular activities.

BIOLOGICAL FUNCTIONS OF SIALIC ACIDS

Sialic acids as anti-adhesive molecules on the cell surface

Sialic acid is recognized as an anti-adhesive glycotype, significantly influencing the biophysical properties of sialylated cells. A prime example is the erythrocyte, which is heavily sialylated and negatively charged [18]. The vascular endothelium's luminal surface is similarly rich in sialic acid residues [19], creating a charge repulsion that prevents erythrocyte adhesion and facilitates their unimpeded transit through the circulatory system freely. In the study by Weber et al., the varying degrees of physiologic sialylation on intercellular adhesion molecule-2, highly expressed on platelets and endothelium and a counter-receptor

Table 1. A simplified overview of major sialylation patterns.

Sialylation pattern	Mediated enzyme	Ligation patterns	Representative sialylated molecules
α-2,3 linked	ST3Gals		Sialyl-Lewis X, Sialyl-Lewis A
α-2,6 linked	ST6Gals		Sialyl Tn, APP, VWF
α-2,8 linked	ST8Sias		NCAM, CCR7, CD36, ESL-1, Megalin, NRP2, ST8Sia2, ST8Sia3, ST8Sia4, SynCAM1
			Sialic acids joined internally by α-2,4, α-2,5 O-glycolyl α-2,8, α-2,9, and α-2,8/9 linkages; Polymeric elongation appears at position C8 of a2,3- or a2,6-linked Sia. The value of n varies from 2 to 400.

ST3Gals β-galactoside α-2,3-sialyltransferases, *ST6Gals* β-galactoside α-2,6-Sialyltranferase, *ST8Sias* α-2,8-sialyltransferases, *PolySia* polysialic acid, *Gal* galactose, *GalNAc* N-acetylgalactosamine, *APP* Amyloid precursor protein, *VWF* Von Willebrand factor, *NCAM* neural cell adhesion molecule, *CCR7* C-C chemokine receptor type 7, *ESL-1* E-selectin ligand-1, *NRP2* Neuropilin-2, *SynCAM1* Synaptic Cell Adhesion Molecule 1.

for leukocyte integrins and lymphocyte function-associated antigen-1, could influence endothelial and platelet adhesion behaviors [20].

Sialic acids on receptors

Sialic acids have key roles in intercellular signaling through specific ligands: sialic acid-binding immunoglobulin-like lectins (SIGLECs) and selectins. The interaction between these molecules is facilitated by a salt bridge between arginine and the carboxyl group of Neu5Ac [21]. Upon sialic acid binding, SIGLECs could interact with the DNAX activation protein 12 (DAP12) [22]. Selectins, crucial for leukocyte trafficking to secondary lymphoid organs and infection sites [23], recognize the sialyl-Lewis X (sLex) ligand, which is essential for their interaction with glycoproteins and glycolipids. sLex formation involves the sequential addition of a sialic acid in α-2,3 linkage to a lactosamine unit's galactose residue, followed by the attachment of a fucose residue in α-1,3 linkage to the N-acetyl-glucosamine unit [23].

BIOSYNTHESIS PATHWAY OF SIALYLATION

Sialic acid metabolism is regulated by sialyltransferases and sialidases. Sialyltransferases, located on the type II membrane protein of the Golgi apparatus, catalyze the transfer of sialic acid from a glycosyl donor CMP-Neu5Ac to the terminal positions of oligosaccharides and glycoconjugates. Sialyltransferases are categorized based on the position of sialic acid addition: β-galactoside α-2,3-sialyltransferases (ST3Gals), β-galactoside α-2,6-Sialyltransferases (ST6Gals), and α-2,8-sialyltransferases (ST8Sia). Sialidases, or neuraminidases (NEU), mediate the desialylation process and are classified into four types: NEU1, NEU2, NEU3, and NEU4. NEU1, primarily lysosomal, is involved in exocytosis, immune response, phagocytosis, and elastic fiber assembly. NEU2, predominantly found in the cytosol and plasma membrane, participates in myoblast and neuronal differentiation. Both NEU3 and NEU4 are implicated in neuronal differentiation, apoptosis, and adhesion, with NEU3 localized to the plasma membrane and NEU4 found in lysosomes, mitochondria, and the endoplasmic reticulum [24, 25].

The sialylation-modified cell complex structures, or sialome, are recognized by various sialic acid-binding proteins, initiating multiple sialic acid-dependent signaling pathways [26]. Sialylation is also integral to several physiological functions such as protein conformation regulation, cell proliferation, migration, apoptosis, and cognitive processes [27, 28].

SIALYLATION IN PHYSIOLOGICAL PROCESSES

Sialylation in the immune system

Sialylation plays a multifaceted role in the immune system. It participates in immune responses and leukocyte trafficking through interactions with SIGLECs and selectins. In addition, sialylation of the Fc fragment of antibodies could modulate the function of antibody [29].

Regulation of complement activation by sialic acids. Sialic acids modulate the alternative pathway of complement activation [30]. Factor H, a key mediator in this process, recognizes sialic acids as "self", facilitating their recruitment on the surface of native cells and downregulating the continuous activation of the complement pathway [31]. This mechanism is characterized by the accelerated dissociation of the C3bBb convertase and the promotion of factor I-mediated C3b cleavage [32]. The type of glycosidic linkage of sialic acid to the glycan structure can influence this recognition [33, 34], and alterations in sialic acid side-chain O-acetylation can also affect factor H binding [35]. Notably, the binding of O-acetylated sialic acids on murine erythrocytes may limit the control of alternative complement pathway activation, as these modified forms are less effective targets for factor H binding [36].

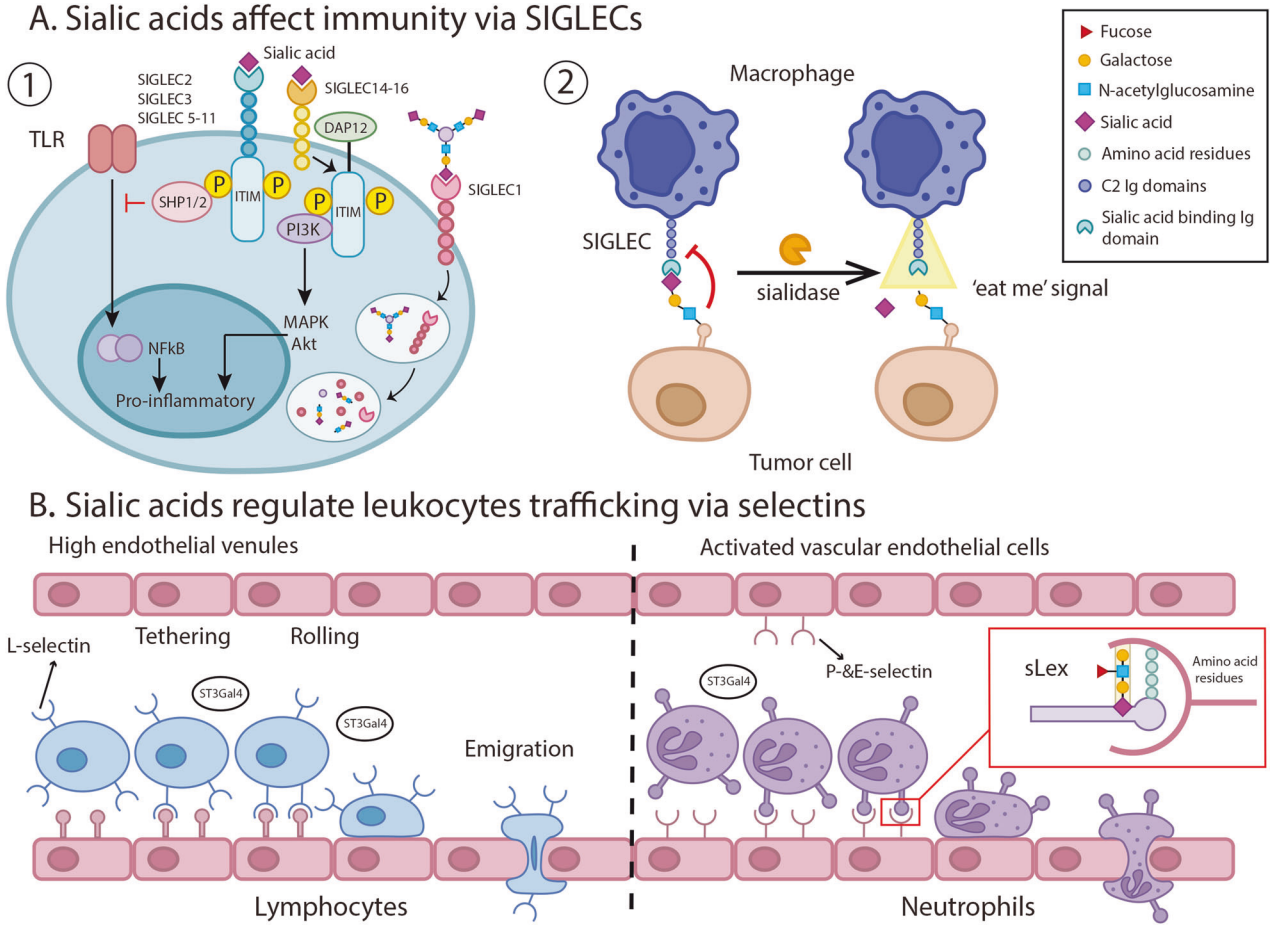


Fig. 2 Regulatory roles of sialic acids in the immune system. A Modulation of Immune Responses by SIGLECs; **B** Leukocyte Trafficking Facilitated by Sialic Acid. SIGLECs sialic acid-binding immunoglobulin-like lectins, SHP Small Heterodimer Partner, ITIM immunoreceptor tyrosine-based inhibition motif, TLR toll-like receptor, DAP12 DNAX activation protein 12, SLex sialyl-Lewis X, PI3K phosphoinositide-3 kinase.

Ficolins, soluble activators of the complement lectin pathway, also recognize sialic acids, particularly on sialylated bacteria, representing a host response to molecular mimicry [37–39].

Sialic acids and their ligands in the immune system. SIGLECs, a family of sialic acid-binding proteins predominantly found in immune cells such as leukocytes and macrophages, are known to regulate inflammatory signals [31, 40, 41]. In sepsis models, SIGLEC-G and SIGLEC-E stimulation has demonstrated significant anti-inflammatory potential, suggesting the therapeutic value of SIGLEC-targeting treatments [42–44]. SIGLEC agonists also modulate adaptive immune responses, for example, SIGLEC-G binding to CD24 on antigen-presenting cells can mitigate T-cell-mediated responses in graft-versus-host disease models [45]. In humans, SIGLECs are categorized into two groups: SIGLEC-1 (Sialoadhesin), SIGLEC-2 (CD22), SSIGLEC-4 (MAG), SIGLEC-15 [46], and the CD33-related SIGLECs (SIGLEC-3, SIGLEC 5-11, SIGLEC-14, and SIGLEC-16) [47]. Sialylation of SIGLEC-1 can induce internalization of SIGLECs and antigens, initiating immune responses by presenting antigens to dendritic cells (DCs) or B cells. Conversely, sialylation of SIGLEC-2, 3, and 5-11 can suppress proinflammatory signals by modulating toll-like receptor signaling, while SIGLEC-14, -15, and -16 activation by sialic acids can stimulate proinflammatory responses via the MAPK and AKT signaling pathways [46] (Fig. 2). In tumor cells, the removal of sialic acid residues from glycans leads to the exposure of galactose residues, which in turn generate "eat me" signals recognized by both professional and non-professional phagocytes, including microglia [48] (Fig. 2).

Another sialylated ligand, sLex, is found in CD45RO$^+$ memory-phenotype subsets of human T cells and is upregulated on CD45RA$^+$ naïve human CD4$^+$ and CD8$^+$ T cells following accepting T cell receptor stimulation [49]. Upon stimulation with cytokines such as IL-2 in combination with IL-12 or IL-15, CD4$^+$ and CD8$^+$ T cells expressing the sLex antigen in human peripheral blood mononuclear cells are rapidly activated in an antigen-independent manner. Importantly, sLex-positive human CD8+ T cells have been shown to significantly enhance reverse antibody-dependent cellular cytotoxicity (ADCC) compared to sLex-negative cells [49]. These observations suggest that sLex-expressing memory CD4$^+$ and CD8$^+$ T cells contribute to early-stage immunity through the provision of IFN-γ and cytotoxicity.

Leukocyte trafficking and selectin ligands. Selectin ligands play crucial roles in modulating leukocyte trafficking, a process vital for immune defense and surveillance. Leukocyte migration across body compartments involves capture, rolling along blood vessels, firm arrest on the endothelial lining, and leukocyte modification [50] (Fig. 2). The initial steps of capture and rolling are mediated by interactions between selectins and α-2,3-sialylated carbohydrate determinants on selectin ligands. ST3Gal5 has been shown to influence chemokine-triggered leukocyte arrest by expanding the role of α-2,3 sialylation in leukocyte rolling and subsequent arrest [51]. Sialylation by ST3Gal4 is also essential for leukocyte trafficking,

with ST3Gal4$^{-/-}$ mice exhibiting reduced adhesion during inflammation. Collectively, the evidence underscores the importance of sialylation of selectin ligands on chemokine receptors in maintaining the integrity of leukocyte trafficking processes.

Sialylation of antibody Fc fragments. Sialic acid binding to the Fc fragment of antibodies significantly modulates their effector functions [52]. Human IgG contains predominantly α-2,6-linked sialic acid residues [53, 54], whereas recombinant IgGs with α-2,3-sialylation have been successfully expressed in Chinese Hamster Ovary cells. Mouse myeloma cells are capable of producing recombinant IgGs with both α-2,3-linked and α-2,6-linked sialic acid residues, without raising concerns regarding immunogenicity [17]. Elevated Fc sialylation has been demonstrated to reduce the ADCC activity, potentially due to suppressed binding affinity [52].

Prior studies have found that intravenous IgG fractions containing α-2,6-linked sialic acid residues in the Fc region exhibit enhanced anti-inflammatory properties [55, 56]. It may be explained that this involves the binding of Fc-sialylated IgG to mouse SIGNR1 or its human counterpart, DC-SIGN, which may contribute to the anti-inflammatory effects by upregulating the inhibitory Fc receptor FcgRIIB on macrophages and DCs [57, 58]. However, this hypothesis has been subject to recent scrutiny, with other factors also being considered. For instance, sialylated glycans constitute about 15% of total N-glycans in intravenous IgG, while Fab glycans, which can be more complex and carry both α-2,3-linked and α-2,6-linked sialic acid residues, account for 15–30%. The contribution of Fab glycans with different sialylation patterns to the anti-inflammatory effects of intravenous IgG is not yet clear but may be significant. In addition, the reduced cell-killing ability of Fc-sialylated antibodies could also contribute to their anti-inflammatory properties, although the exact mechanisms require further investigation. Furthermore, sialylation of IgG can decrease its binding affinity to insoluble or cell surface antigens, an effect not observed with soluble antigens [52]. The negative charge of sialic acid residues may alter the overall charge of the antibody molecule, lowering its isoelectric point and affecting antigen binding.

The sialylation of the IgG Fc fragment has also been linked to negative effects. Following immune checkpoint blockade therapy for hepatocellular carcinoma, effector T cells can induce IgG sialylation through an IFN-γ-ST6Gal-I-dependent pathway [59]. Sialylated IgG primarily targets DC-SIGN macrophages, which, upon stimulation, can elevate ATF3 through Raf-1, inhibiting the cGAS-STING pathway and suppressing type-I-IFN-mediated anti-tumor immunity [59].

Sialylation and protease sensitivity. Sialylation increases the sensitivity of antibodies to proteases, potentially due to the negative charge of sialic acid residues. Since many proteases are acidic, sialylated antibodies may reduce the effective pI of these enzymes [17]. Structural changes in the CH2 domains of antibodies due to sialylation could also enhance sensitivity. The limited space in the CH2 domain may be affected by the bulkier sialic acid residues, leading to structural and functional alterations. The addition of sialic acid could cause a bulge in the Fc fragment, increasing amino acid flexibility and improving the accessibility of antibodies to proteases.

Sialylation and dendritic cells. Sialylation impacts the maturation and function of DCs [60]. Sialidase treatment of DCs and sialyltransferase knock-out mice models have shown increased DC maturation [60–63]. In the absence of sialylation, human monocyte-derived DCs exhibit increased bacterial phagocytosis [61–63]. Polysialylation of CCR7 [64] in mature DCs is essential for CCL21 ligand recognition and chemokine-mediated migration. In addition, polysialylation of neural cell adhesion molecule (NCAM) in natural killer (NK) cells influences the fate of DCs, with polysialylated NK cells binding to DC-SIGN ligands and protecting SIGN-expressing DCs from NCAM-positive NK cell-mediated cytotoxicity [65].

Sialylation and stem cell pluripotency

Sialylation is a critical process for establishing and maintaining stem cell pluripotency. Undifferentiated human induced pluripotent stem cells (iPSCs) exhibit higher levels of ST6Gal1 expression compared to non-pluripotent cells [66]. Knockdown of the ST6Gal1 gene or the use of sialyltransferase inhibitors can negatively impact the efficiency of somatic cell reprogramming. Several cell adhesion molecules, including E-cadherin, integrins, and catenins, are sialylated glycoproteins [67]. Aberrant sialylation can disrupt the interactions between these adhesion molecules and their receptors, blocking signal transduction related to cell differentiation and thus preserving stem cell characteristics.

Sialylation in sperm development and fertilization

Sperm exhibit millions of sialylation sites [68], and the levels of sialylation and sialidase activity undergo dynamic changes during the processes of sperm maturation, capacitation, and sperm-egg binding [69, 70], which are closely related to successful fertilization and embryonic development [8, 71].

Sperm are anatomically divided into the head, neck, and tail regions, with different types of SIGLECs. These proteins are significantly expressed in the principal piece of the sperm, facilitating tail-specific functions through sialylation-mediated intracellular communication [72]. Since sperm flagellar proteins are glycoproteins rich in sialylation [73], treatment with sialidase significantly reduces the activity of their forward motility proteins [74]. In the human testis, the sialic acid metabolism pathway is more prevalent in Sertoli cells compared to other testicular cells. Sialyltransferases, including ST3Gal1 and ST6 GalNAC6, are expressed at higher levels in male reproductive tissues [75], indicating the vital role of sialylation in male fertility.

Glycoproteins with high sialylation levels, such as beta-defensin 126 (DEFB126), are necessary for the smooth entry of sperm into the female reproductive tract to meet the eggs [76, 77]. The specific roles of sialylation include: creating a negatively charged surface on the sperm, reducing resistance in the negatively charged cervical mucus; interacting with SIGLECs and other recognition molecules on the epithelium of the fallopian tube and immune cells, preventing sperm from being attacked in the female reproductive tract, and maintaining temporary storage in the fallopian tubes; and during sperm capacitation in the female reproductive tract, a gradual decrease in the degree of sialylation on the sperm surface occurs. Ultimately, sperm recognize the zona pellucida receptor of the egg through their sialylation, initiating the acrosome reaction and facilitating fertilization [75]. In addition, PolySia is suggested to potentially regulate sperm development by affecting the communication between germ cells and Sertoli cells [78]. Polysialic acid can bind various growth and nutritional factors [79], which may benefit the survival of male reproductive cells [80]. Furthermore, polysialylated-neural cell adhesion molecule (PSA-NCAM) is widely expressed in mammalian testes, epididymal smooth muscle cell clusters, and mature human sperm [75, 81], although the exact mechanisms remain unclear [82].

Sialylation in maintaining platelet function

A case of thrombocytopenia with macrothrombocytopaenia has been documented in a 70-year-old patient with a deficiency in sialylation ability [83]. Despite normal platelet precursor and megakaryocyte counts and morphology, the increased platelet size suggests cellular fragmentation defects. Similar findings are observed in Bernard-Soulier syndrome, a macrothrombocytopenia caused by a deficiency in the major sialic acid carrier, platelet surface glycoprotein Ib [23, 84, 85].

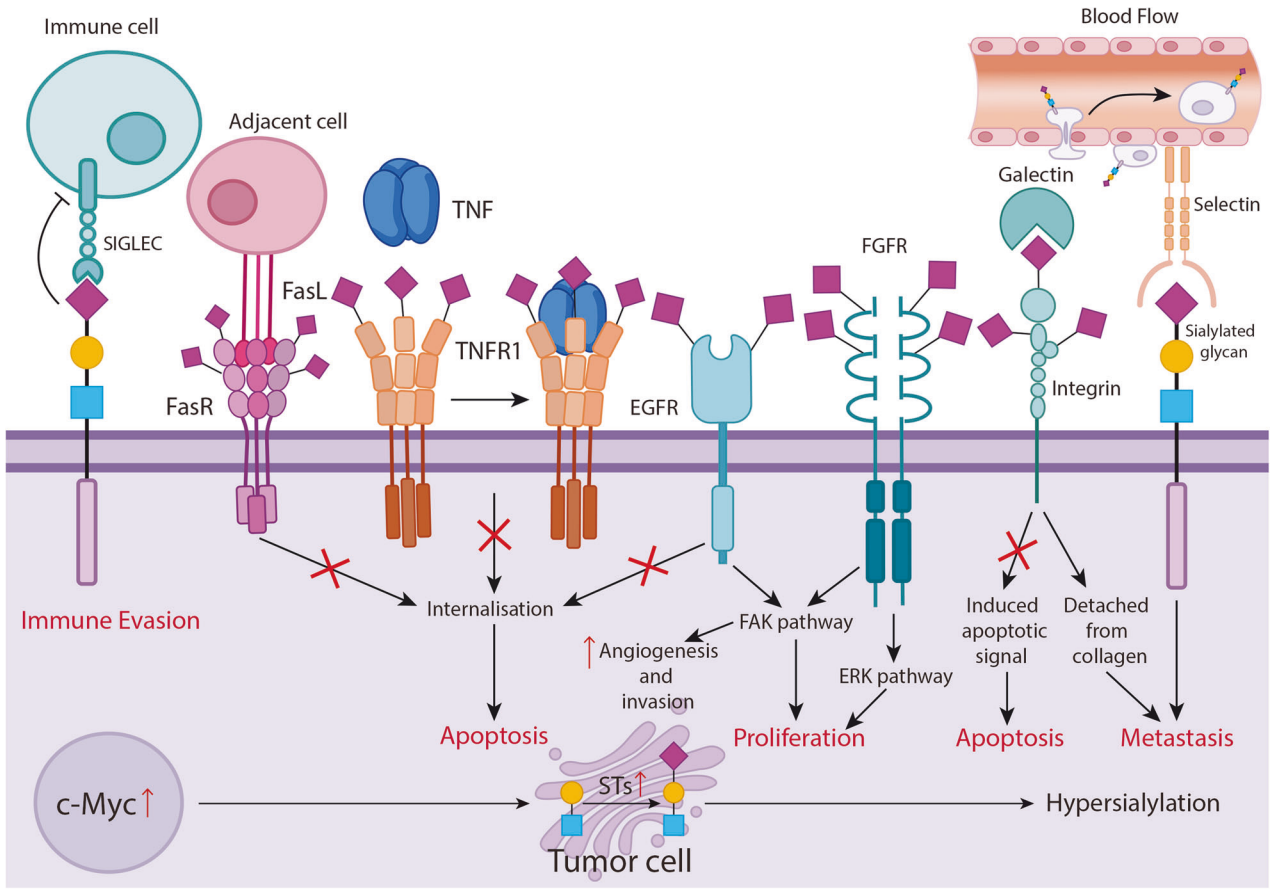


Fig. 3 Impact of Sialylation on Cancer Progression. SIGLECs sialic acid-binding immunoglobulin-like lectins, FasR Fas receptor, TNFR tumor necrosis factor receptor, FGFR fibroblast growth-factor receptor, ERK extracellular signal-regulated kinase, FAK focal adhesion kinase, EGFR epidermal growth factor receptor, STs Sulfotransferases.

These indicate a potential role for sialylation in platelet disorders.

Von Willebrand factor (VWF), a crucial molecule in the coagulation system, undergoes complex PTMs before being secreted into plasma. VWF monomers, which contain numerous N-glycan and O-glycan structures, are capped with terminal sialic acid residues that impart a negative charge [86]. Notably, the sialylation status of VWF is heterogeneous and dynamic; VWF from endothelial cells is fully sialylated, whereas this level is significantly lower in VWF from platelets. This difference may be due to varying activities of their sialyltransferases in cells.

Sialylation significantly influences VWF function in multiple ways, including its activity, susceptibility to proteolysis, and clearance [86]. Federici et al. demonstrated that treatment of VWF with neuraminidase can remove over 95% of the total sialic acid content [87]. When using inhibitors to suppress the function of this enzyme's activity, desialylation did not have directly influence on the multimer pattern [88]. However, in platelet-rich plasma, desialylated VWF can induce spontaneous platelet aggregation and effectively modulate platelet adhesion to collagen under shear conditions [87].

SIALYLATION IN PATHOLOGICAL PROCESSES

Roles of sialylation in cancer

Cancer progression. Hypersialylation, characterized by alterations in sialic acid levels, sialidase activity, sialyltransferase activity, or sialoproteins [89], has been observed in most tumor cells. This elevated sialylation level enhances tumor cell resistance to apoptosis and promotes proliferation. Tumor cells often upregulate ST6GAL1, leading to increased α2-6-sialylation of the Fas receptor (FasR) and tumor necrosis factor receptor 1, which suppresses cancer apoptosis and facilitates the formation of secondary tumor sites [90]. In addition, sialylation of integrins can block apoptotic signals, preventing tumor cell death [91] (Fig. 3). In various malignancies, elevated levels of serum or plasma total sialic acid are detectable during tumor initiation, progression, and treatment [92–95]. The hypersialylation state of tumor cells may accelerate cancer progression through mechanisms such as cell-cell repulsion, altered binding to the extracellular matrix, enhanced migration, and invasion, all of which contribute to metastasis formation and poor disease prognosis.

Cancer metastasis. Metastasis can be summarized in four steps: escaping from the primary site, survival in the bloodstream, lymphatic transfer, and attachment to new distal sites [96]. Sialylation plays a vital role in each of these processes. For instance, α2-6-sialylation of the epidermal growth factor receptor (EGFR) has been shown to regulate the epithelial-mesenchymal transition (EMT) of cancer cells [97], influence membrane retention, regulate integrin tension, and affect focal adhesion and cell motility [98, 99]. Increased α2-6-sialylation of β1 integrin enhances its binding to collagen I, promoting tumor migration and invasion [100]. Similarly, α2-6-sialylation of the fibroblast growth factor receptor (FGFR) amplifies signals through extracellular regulated protein kinases 1/2 (ERK1/2) and focal adhesion kinase (FAK) [101]. α2,3-Sialylated CD44 promotes adhesion to hyaluronic acid [102], further accelerating cancer cell motility and metastasis. Poor prognosis in patients is often associated with the sialylation of tumor-associated carbohydrate antigens like Sialyl Tn

(STn), which can enhance cancer invasiveness [103, 104]. Under hypoxic conditions, PolySia maintains tumor cell migration [105], as the hypoxic microenvironment promotes the polysialylation of NCAM, increasing the motility of glioblastoma cells [106] (Fig. 3).

However, the role of sialylation in cancer metastasis may be complex and different among various malignancies. In estrogen receptor-positive breast cancers, high levels of ST6GalNAc2 increase the sialylation of core 1 antigen, reducing the binding of galectin-3 and thus tumor metastasis. In contrast, estrogen receptor-negative breast cancers with low ST6GalNAc2 exhibit higher endothelial cell adhesion and metastasis [107]. In addition, sialic acid-containing GM3 can reduce phosphoinositide-3 kinase (PI3K)-AKT signaling, increasing the migration and invasion of breast and colon cancer cells [108].

Immune evasion. Sialic acids play a crucial role in cell-environment interactions and are integral to self-recognition through self-associated molecular patterns. An upregulation of sialoglycans on the surface of malignancies creates an "antigenic masking" effect, significantly influencing tumor immunogenicity and enabling the concealment of tumor-associated antigens [109]. The dense layer of sialoglycans on the tumor cell surface generates steric and electrostatic barriers, effectively masking underlying glycans and protein epitopes to evade immune cell recognition [64].

During tumor progression, sialic acid-binding antigens can act as "don't eat me" signals that interfere with macrophage function [110, 111], and these signals can also be transmitted to NK cells and T cells, inhibiting their activity. Heavy glycosylation of tumor-derived MUC1 can prevent the degradation of sialic acids in endosomes, thereby creating a barrier to antigen presentation by DCs [112].

Sialylation in neurological disorders

The concentration of sialic acid is highest in mammalian central nervous system (CNS), with 65% in gangliosides, 32% in glycoproteins, and 3% free sialic acid [113]. Most sialic acids are incorporated into gangliosides, while polySia is linked to glycoproteins such as NCAM in the CNS [44]. The expression of PolySia is predominantly detected in four types of cells including migrating neuroblast cells (e.g., olfactory neuronal precursors), extending cells (neurons and Schwann cells), synapses in synaptic plasticity regions, and neural stem cells (subventricular zone) [44, 114]. In brain, the rapid changes of sialylation in cell-surface may occur physiologically, usually induced by the transfer of NEU1 or NEU4 to the cell surface [115]. Acute stress could induce the rapid decrease of polysialylation in olfactory bulb and prefrontal cortex in mice, which is mediated by sialidases from microglia and astrocytes [116]. Moreover, neural activity instantly increases the activity of sialidase activity on neuronal and astrocytic surface, causing neuronal desialylation, which in turn modifies memory formation [117].

Alzheimer's disease. Alzheimer's disease is characterized by the deposition of Aβ peptides in the brain, which is central to the "amyloid cascade hypothesis" of the disease's development [118]. Sialylation in the Golgi apparatus modulates the functions of the amyloid precursor protein (APP) [28]. Overexpression of ST6Gal-I in Neuro2a cells enhances α-2,6-sialylation of APP, increasing the extracellular levels of Aβ peptides, sAPPβ, and sAPPα. Conversely, Aβ peptide secretion is significantly reduced in cells lacking ST6Gal-I [119]. The N-glycans on APP are essential for this enhanced secretion, and a correlation between α-2,6-sialylated APP and sAPPβ levels has been observed in the mouse brain [119].

Genetic variants of SIGLEC genes may also contribute to Alzheimer's disease by affecting microglial cell functions. Microglia express SIGLEC-3/CD33, and its polymorphisms are associated with varying risks of Alzheimer's disease. The inhibitory SIGLEC receptors, mediated by TYRO protein tyrosine kinase-binding protein (TYROBP), can suppress phagocytosis and promote oxidative burst, inflammation, migration, and proliferation [44]. In addition, loss-of-function mutations in triggering receptor expressed on myeloid cells 2, which is upregulated by CD33-related SIGLEC receptors, are linked to a nonresponsive microglial phenotype and an increased risk of Alzheimer's disease [120].

Multiple sclerosis. Multiple sclerosis is an autoimmune disease involving the CNS, where B cells play a significant role [121]. CD22 and SIGLEC-G/SIGLEC-10 on B cells are crucial for maintaining B cell tolerance, and their deficiency can lead to autoimmunity. Antigen-specific B cell tolerance may be induced by targeting SIGLECs on the B cell receptor or antigen complex. SIGLEC-2/CD22 or SIGLEC-G-displaying nanoparticles can suppress antigen-specific B cell activation, leading to B cell apoptosis [122–124].

Acute nervous system injury. Local overexpression of PolySia can promote axonal regrowth and neural connectivity [125–128]. Similarly, PolySia-expressing Schwann cells enhance Purkinje axonal regeneration post-injury [126]. However, long-term overexpression of PolySia may impede myelination or remyelination [125, 129–131], as it acts as a 'repulsive strut' on unmyelinated or demyelinated axons. PolySia-mimicking peptides, such as tegaserod or 5-nonyloxytryptamine oxalate, have been developed to foster repair in the spinal cord [132, 133] and peripheral nerve injuries [134–136]. This strategy has been recently confirmed by a collagen–laminin scaffold-based tissue engineering approach [137].

Prion diseases. Prion diseases are transmissible neurodegenerative disorders caused by misfolded sialoglycoprotein, the prion protein (PrPC) [138, 139]. PrPC undergoes PTMs, including the addition of sialic acids to N-linked glycans and a glycosylphosphatidylinositol (GPI) anchor [140, 141]. Sialic acids are linked to the termini of these N-linked glycans through α2-3 or α2-6 linkages, and variations in N-linked glycan structure result in numerous PrPC glycoforms [141, 142]. Recent studies have shown that PrPC molecules with unsialylated GPIs are refractory to conversion into PrPSc [143]. Experiments involving the injection of partially desialylated PrPSc, which exposes more galactose, have demonstrated an inability to induce prion disease in animal models [144–146]. Notably, animals infected with partially desialylated PrPSc were found to be free of prions in their brains [145, 146].

In PrPSc particles, glycans are oriented outward, with terminal sialic acid residues contributing to the negative charge on the PrPSc surface [147–149]. This negative charge leads to electrostatic repulsion between sialic acid residues, imposing structural constraints on PrPSc replication [150]. A portion of heavily sialylated PrPC is less likely to be converted into PrPSc, with the degree of exclusion being strain-specific. Treatment of PrPC with sialidases, which remove these structural constraints, can increase the replication rate of PrPSc in PMCAb cells, with the extent of increase varying widely between different strains [144, 150]. Furthermore, PrPSc-induced toxicity is influenced by PrPC molecules with sialylated GPI anchors [151, 152]. Aggregation of PrPC with sialylated GPIs can cause injury to synapses in vitro by activating cytoplasmic phospholipase A2 in cultured neurons [151, 152]. However, the precise relationship between the sialylation status of N-linked glycans on PrPSc and its toxicity is not fully understood [138, 153, 154].

Sialylation in cardiovascular diseases

In the context of atherosclerosis, mouse model experiments have shown that the administration of Neu5Ac can reduce atherosclerosis in hyperlipidemic mice [155–157]. Treatment with Neu5Ac in Apoe$^{-/-}$ mice decreased atherosclerotic plaque

formation and hepatic lipid accumulation, associated with upregulation of hepatic proteins involved in reverse cholesterol transport and downregulation of inflammatory markers [157]. ApoB, a major component of very-low-density lipoprotein and low-density lipoprotein (LDL), contains sialylated glycosylation sites that are typically modified with complex N-linked glycans terminated with sialic acid [158]. Patients with CVDs have elevated plasma LDL levels with reduced sialic acid content [159, 160]. These hyposialylated LDL particles are more readily taken up by cells from the human aorta, leading to increased intracellular cholesterol ester accumulation [161–163]. Compared to normal LDL, hyposialylated LDL is more immunogenic, promoting the production of proatherogenic autoantibodies [164–167] and accelerating atherosclerosis.

In mouse models, the manipulation of neuraminidase function affects the extent of atherosclerosis. NEU1, a crucial component of the atherogenic action of elastin-derived peptide, stimulates monocyte migration, reactive oxygen species production, LDL oxidation, and vascular smooth muscle cell proliferation [168–170]. Atherosclerotic lesions are significantly reduced in Apoe$^{-/-}$ mice with mutated NEU1 compared to those with only Apoe knockout [171], with fewer macrophages, T cells, and smooth muscle cells indicating reduced inflammation and cell recruitment in the plaque. Suppression of NEU1 also decreases left ventricular dysfunction following ischemia/reperfusion injury [172]. Demina et al. [173] confirmed that the deficiency of NEU1 and NEU3, but not NEU4, attenuates atherosclerosis in mouse models. In addition, increased plasma neuraminidase activity is observed in patients with myocardial infarction [174].

In patients with atheroma or atherosclerosis, sialyltransferase activity is upregulated compared to healthy individuals [175]. In Apoe$^{-/-}$ mice, the deficiency of ST3Gal4 reduces atherosclerotic plaque size and macrophage numbers without affecting plasma cholesterol levels [176]. A genome-wide association study has revealed that single nucleotide polymorphisms in ST6Gal1 are associated with multiple inflammatory disorders, including CVDs [177]. The expression level of ST6Gal1 in the aortic endothelium is inversely related to atheroma formation in Apoe$^{-/-}$ mice [178]. This evidence suggests that sialyltransferases might be potential targets for the prevention and treatment of atherosclerosis.

Sialylation in virus infection

Sialylation significantly influences viral binding and replication mechanisms. Viruses, such as the influenza virus, bind to sialylated glycans on host cells via hemagglutinin (HA), a process that facilitates membrane fusion and endocytosis. This interaction is mediated by a highly conserved receptor-binding domain on HA, which specifically recognizes α-2,6 linked sialic acids present in human influenza strains [179]. The binding between HA and sialic acid typically occurs through weak hydrophobic and hydrogen bonds, with an affinity measured in the millimolar range for monovalent interactions [180]. However, when multiple HA monomers are involved, the binding affinity increases dramatically, suggesting that multivalent interactions between HA and terminal sialic acid residues are crucial for viral attachment and infection [181–183].

Neuraminidase (NA), another glycoprotein on the influenza virus surface, facilitates the cleavage of HA-sialic acid bonds [180], thereby enhancing viral infectivity. NA cleaves the links between the virus and heavily sialylated mucins in the upper respiratory system [184], which act as decoys. Like HA, NA also preferentially interacts with sialoglycans in α-2,3 or α-2,6 conformations [185].

Hemagglutinin esterase (HE) and hemagglutinin-esterase-fusion protein (HEF) are additional surface glycoproteins that interact with sialic acid. HE is found in coronaviruses, while HEF is present in influenza viruses. These proteins combine the functions of HA and NA, binding to specific 9-O-acetylated sialic acids to enable the release of viral progeny from host cells and evade heavily sialylated decoy cells through receptor destruction activity [186].

Sialylation in psychiatric disorders

Genome-wide association studies have linked genetic variants of the ST8Sia2 gene, or its loss-of-function mutations, with several major psychiatric conditions, including schizophrenia [139, 187, 188], bipolar disorder [139], and autism [189, 190]. Patients with schizophrenia often exhibit decreased levels of polySia-NCAM [191–193]. Mouse models lacking ST8Sia2 display schizophrenia-like behaviors, such as cognitive dysfunction, impaired prepulse inhibition, and heightened sensitivity to amphetamine-induced locomotion [194]. These findings suggest that structural or functional impairments in polySia may contribute to the development of schizophrenia [188].

SIALYLATION IN NOVEL THERAPEUTIC STRATEGIES

Anti-cancer therapy

Current research suggests that the use of neuraminidase to remove sialic acid from the tumor cell surface can enhance tumor immunogenicity [96]. Therefore, developing drugs that disrupt sialic acid metabolism and its associated signaling pathways is a viable strategy (Supplementary Table).

Blockade of sialylation. One approach to anti-cancer therapy involves inhibiting sialyltransferases to block sialylation. Most current sialyltransferase inhibitors are analogs of sialic acids and CMP-sialic acids [195, 196]. A prominent example is 3Fax-Peracetyl Neu5Ac (P-3Fax-Neu5Ac), a sialic acid mimetic that, when modified at the C-5 position, can enhance its potency [197]. P-3Fax-Neu5Ac has been shown to inhibit cancer cell migration and proliferation [198, 199] and, in vivo, to enhance cytotoxic CD8+ T cell-mediated anti-tumor responses [200–202]. In addition, soyasaponin I, another sialyltransferase inhibitor, primarily suppresses cellular ST3Gal activity, reducing tumor cell invasiveness [203]. Other inhibitors, such as 8-keto-sialic acid [204] and endogenous CMP-Neu5Ac [205], are also being investigated for their effects on sialic acid metabolism.

Targeting sialic acid's ligand-receptor interactions. Therapies that target interactions between sialic acid and its receptors, such as selectins and SIGLECs, are under investigation. Uproleselan, which blocks E-selectin, has been shown to limit tumor cell extravasation and adhesion, significantly reducing metastasis [206]. Fucoidan [207], a P-selectin targeted agent, may benefit patients with prostate cancer resistant to docetaxel chemotherapy. Glycopolymers with P-selectin affinity are being explored to prevent melanoma spread [208]. These inhibitors also block E-/P-selectin-mediated signaling in tumor cells, offering additional anti-cancer effects.

As for SIGLECs, its interactions with sialic acid are considered glyco-immune checkpoints for tumor cells [209–212]. Antibodies against SIGLEC-7 and SIGLEC-9 can suppress the conversion of macrophages into tumor-associated macrophages and reprogram the immunosuppressive tumor microenvironment, enhancing anti-cancer immunity [213]. SIGLEC-9 antibodies, in particular, can suppress the inhibitory effects of cytotoxic CD8+ T cells [214, 215], promoting T cell receptor signaling, cytotoxicity, and cytokine production. Antibodies targeting SIGLEC-15 can also enhance anti-tumor immunity and limit cancer progression. The use of SIGLEC-7, SIGLEC-9, and SIGLEC-15 antibodies may provide an alternative therapeutic option for patients resistant to PD-L1/PD-1 blockades [213–217].

Conjugating antibodies with sialidase. To overcome the reduced efficacy of PD-L1 antibodies due to glycosylation, an artificial PD-L1 antibody-sialidase conjugate has been developed. This

conjugate enhances the blockade efficiency of PD-L1, augmenting anti-cancer activity through T-cell reactivation [218]. Similar effects have been observed with a HER2 antibody-sialidase conjugate, which improves antibody affinity and degrades tumor-derived sialoglycans, boosting the anti-tumor immune response [211]. A corresponding clinical trial (NCT05259696) is investigating the safety, pharmacodynamic effects, and antitumor activity of E-602, a bi-sialidase fusion protein targeting immunosuppressive sialoglycans [219].

Sialic acid modification in anti-cancer vaccine development. Sialoglycans, often overexpressed in tumors, are potential targets for novel cancer vaccines. The low immunogenicity of GM3, a sialylated ganglioside expressed by tumor cells, has been addressed by modifying the sialic acid residue [220]. Sialic acid-modified sTn antigenicity has also been shown to elicit high titers of antigen-specific IgG antibodies [221], making Tn-based glycoconjugates promising candidates for vaccination strategies. Cancer-therapeutic vaccines targeting sialic acid are in development, with a synthetic sTn-keyhole limpet hemocyanin vaccine (Theratope®) having completed clinical trials and shown to improve survival in advanced breast cancer [222]. In addition, carbohydrate vaccines, including a pentavalent vaccine (Globo-H-GM2-sTn-TF-Tn) and a heptavalent vaccine (GM2-Globo-H-Lewis Y-Tn-sTn-TF-Tn-MUC1), have successfully elicited IgG and/or IgM responses in ovarian cancer patients [223, 224].

Stroke treatment

Traditional stroke treatments include thrombolytic therapy with tissue plasminogen activators and surgical clot removal. However, these methods can lead to rapid increases in reactive oxygen species and subsequent ischemia-reperfusion damage [225, 226]. Antioxidants, such as selenium nanoparticles, are being investigated for stroke treatment [227]. Angelica polysaccharide, derived from the Chinese herb Angelica Sinensis, has been studied as a drug delivery system and for its neuroprotective effects against hypoxia-induced apoptosis and autophagy in neural stem cells [228].

Modifying drug delivery systems with sialic acid can improve hydrophilic properties and enhance brain drug delivery efficiency due to the negative charge of the sialylation process [229, 230]. For instance, sialic acid-modified angelica polysaccharide and MSAOR@Cur nanoparticles have shown potential in improving brain infarction and neurological outcomes. The nanoparticle is designed to cross the blood-brain barrier and uses sialic acid-modified angelica polysaccharide as a hydrophilic end, with an oxalate bond linking resveratrol and curcumin to enhance drug delivery [231].

Respiratory virus infection

Sialylation's involvement in virus infection has led to the development of drugs targeting interactions between sialic acid and viral surface glycoproteins. Oseltamivir and zanamivir, NA inhibitors, prevent virus spread by inhibiting NA from cleaving bonds between HA and terminal sialic acids on host sialoglycan chains. This action restricts the release of viral progeny from infected cells and prevents the virus from escaping heavily sialylated decoy mucins in the upper respiratory tract [232]. (Supplementary Table).

In addition, inhibitors target to the interactions between HA and sialic acid have also been developed. Peptides that mimic sialic acids, such as Ala-Arg-Leu-Pro-Arg, have been developed to block HA interactions [233]. However, the therapeutic potential of polymerized sialic acid analogs is limited by solubility and cytotoxicity issues [234]. To overcome these challenges, negatively charged liposomes have been used to deliver high-affinity HA-binding sialic acid analogs like sialylneolacto-N-tetraose [235, 236]. These decoy liposomes can suppress viral infectivity by forming multivalent bonds with the HA receptor-binding domain.

DAS-181 (Fludase), a sialidase mimic, is under phase III clinical trials for its potential to block virus infection [237]. It binds to sialylated cell surface polysaccharides [238] and hydrolyzes both α-2,3 and α-2,6 linked terminal sialic acids, demonstrating efficacy against various strains of influenza, parainfluenza, and metapneumoviruses. While DAS-181 has shown relatively few side effects, the development of antibodies against it after long-term use is a concern [239].

Sialyltransferase inhibition represent another antiviral strategy. Inhibiting cell surface sialylation can block virus infection by preventing viral binding to sialoglycans [240]. siRNAs silencing ST6Gall expression have been shown to reduce the infectivity of human influenza strains without affecting cell viability [241]. Existing sialyltransferase inhibitors include a variety of compounds discovered in natural products [242]. However, the antiviral effects of sialyltransferase inhibitors have not been confirmed in in vivo studies [243], indicating a need for further research on sialyltransferase subtype selectivity.

Chloroquine is another small molecule inhibitor of sialic acid expression with broad-spectrum antiviral activity. It inhibits quinone reductase 2, structurally similar to enzymes involved in sialic acid biosynthesis [244, 245]. Chloroquine's antiviral effects are also associated with the blockade of sialic acid, as it binds to sialic acids and sialoglycans [246], preventing virus attachment.

Central nervous system disease treatment

SIGLEC-targeting therapies are now being explored for their potential in treating inflammatory CNS injuries, such as multiple sclerosis. B cell-depleting anti-CD20 therapies have shown success in this disease. SIGLEC agonists, particularly CD22 and SIGLEC-G/SIGLEC-10, are crucial for maintaining B cell tolerance, as their deficiency leads to B cell hyperactivation and autoimmune phenotypes in mice. Inducing antigen-specific B cell tolerance by recruiting SIGLECs to the B cell receptor/antigen complex is a promising strategy. Experiments have shown that antigen-bearing polymers or liposomal nanoparticles with synthetic SIGLEC-2/CD22 or SIGLEC-G ligands can significantly suppress the activation of antigen-specific B cells, leading to B cell apoptosis [122, 123, 247]. (Supplementary Table).

In spinal cord injury treatment, preclinical data indicate that local overexpression of polySia promotes axonal regrowth and neural connectivity. Overexpression of polySia or engineered Schwann cells expressing polySia has also been shown to facilitate Purkinje axonal regeneration after brain injury. This suggests that re-expressing polySia in damaged adult CNS tissues may support neural cell remodeling and repair. Research on polySia-mimicking peptides, such as tegaserod and 5-nonyloxytryptamine oxalate, is advancing rapidly, showing potential in promoting repair of spinal cord and peripheral nerve injuries in animal models.

Furthermore, the human inhibitory SIGLEC receptor SIGLEC-11 has been shown to alleviate immune-mediated neuronal cell damage. SIGLEC-11, when ectopically expressed in cultured mouse microglia, prevents microglial phagocytosis of apoptotic neuronal material and reduces lipopolysaccharide (LPS)-induced inflammation [248]. The SIGLEC-11 ligand, polySia with an average degree of polymerization of 20 (polySia avDP20), also suppresses phagocyte and macrophage oxidative burst functions in LPS-exposed environments [249], highlighting the potential of polySia-based and SIGLEC agonistic approaches in limiting acute nervous system injury.

Effects of sialic acid on stabilizing nanocarriers

To stabilize nanocarriers in the bloodstream, polysialylation has been employed using compounds bearing one or more sialic acid moieties. Most research has focused on incorporating sialic acid onto the surfaces of liposomes. Ganglioside GM1 is an early

application of a surface modifier used to stabilize nanocarriers [250]. It can be integrated into the liposome bilayer, presenting sialic acid molecules on the nanocarrier surface. The use of GM1 can significantly reduce reticuloendothelial system uptake of liposomes in mice [251]. The effectiveness of this approach is influenced by liposome size [252], with liposomes between 90 and 200 nm being most suitable for tumor cell accumulation [253]. Other chemical moieties, such as fucose residues, can also affect sialic acid activity, with the presence of fucose increasing reticuloendothelial system uptake of glycoprotein-conjugated liposomes. In addition, pH levels can influence the stability and drug release profile of sialic acid-modified liposomal formulations [254].

CONCLUSIONS AND PERSPECTIVES

Sialic acids participate in various facets of cell biology. On the cell surface or glycocalyx, sialic acids act as cytoprotectors, with fundamental functions that include signal transduction via receptors like SIGLECs and selectins, and anti-molecular adhesion due to their negatively charged surface. Sialylation plays a crucial role in immune system regulation, including complement activation, leukocyte trafficking, dendritic cell maturation, and modulation of antibody effects. It also contributes to maintaining stem cell properties and fertility. However, sialic acids can be exploited by pathogens and malignant cells. Dysregulation of sialylation has been linked to cancer progression, CNS diseases, viral infections, atherosclerosis, and CVDs. Thus, novel therapeutic strategies targeting the sialylation process are being developed. Inhibitors of sialyltransferases, selectins, and SIGLECs have been tested in animal models of cancer, and sialidase-conjugated antibodies for anti-cancer therapy are entering clinical trials. Modifying drug delivery systems with sialic acid holds potential for treating stroke-induced brain reperfusion injury. In addition, strategies that mimic sialidase or block interactions between sialic acid and viral surface glycoproteins are under investigation for antiviral therapy. Blocking sialic acid-binding receptors and supplementing polysialic acid may offer promising methods for CNS disorder treatment.

Despite advancements in sialylation research, numerous questions remain. First, while sialic acids are ubiquitous, studies on their pathophysiological roles are limited to a few systems. Most research focuses on cancer biology and the nervous system, with potential roles in other systems (e.g., digestive and urinary systems) yet to be explored. Second, although there is a link between aberrant sialylation and psychiatric diseases, the specific mechanisms are not well understood. Third, in the fields such as CVDs, prior researches are primarily focused on understanding sialylation's role in pathological or physiological processes, with its therapeutic potential remaining unclear. Lastly, most current approaches targeting sialylation are in the pre-clinical stage.

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AUTHOR CONTRIBUTIONS

WGZ and SHF conceptualized and developed the design of the article, interpreted relevant literature, and wrote the original manuscript. YZ and LJG conducted the review & editing steps of the manuscript. WGZ was responsible for funding acquisition and validation. All authors have read and approved the final submission.

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COMPETING INTERESTS

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