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Review

Sialic Acids in Health and Disease

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Abstract: Vertebrate cell surfaces exhibit intricate arrangements of glycosaminoglycan polymers, which are primarily linked to lipids and proteins. Numerous soluble secreted proteins are also decorated with either individual sugar molecules or their polymers. The carbohydrate polymers commonly possess terminal nine-carbon sugars, known as sialic acids. Due to their widespread distribution and strategic positioning, sialic acids play a crucial role in mediating and regulating a wide range of physiologic processes and pathologic conditions. Human- or animal-based investigations predominantly concentrate on the effects of sialic acids during infections, inflammations, vascular disorders, or cancers. Further investigations encompass a variety of applications, including cell–cell interactions, signaling, host–pathogen interactions, and other biological functions associated with nutrition, metabolism, or genetic disorders. Nevertheless, future mechanistic investigations are needed to clarify the specific roles of sialic acids in these varied contexts, so that more effective interventions may be developed.

Keywords: sialic acid; sialoglycoconjugate; sialidase; sialyltransferase; sialylation; desialylation

Academic Editor: Uthayashanker R. Ezekiel

Received: 19 December 2024
Revised: 4 February 2025
Accepted: 7 March 2025
Published: 26 March 2025

Citation: Guerrero-Flores, G.N.; Butler, F.M.; Martinez Marignac, V.L.; Zhang, G.; Pacheco, F.J.; Boskovic, D.S. Sialic Acids in Health and Disease. *Biologics* **2025**, *5*, 10. https://doi.org/10.3390/biologics5020010

1. Introduction

Cell surfaces are covered by a glycocalyx [1] composed of complex carbohydrate polymers (also known as glycans) anchored to cell membranes via glycoprotein or glycolipid linkages [2–5]. Biosynthetically derived from neuraminic acid [6,7], sialic acids represent a family of nine-carbon keto-aldonic acids (nonulosonic acids (NulOs)) [8]. These normally occupy the terminal positions of cell surface glycosaminoglycan moieties [9,10]. They are, however, also present freely in various biofluids or as modifiers of soluble secreted proteins [11–13]. Sialic acids are found in a wide range of animal phyla, including *Platyhelminthes* [14], *Echinodermata* [15], *Cephalopoda* [16], *Crustacea* [17], *Cephalochordata* [18], and *Vertebrata* [19]. In addition, sialic acids are also known to be associated with viruses, bacteria, protozoa, and fungi [20–22]. Consequently, it is not surprising that sialic acids are involved in a large variety of physiologic functions, such as scavenging of reactive oxygen

species (ROS) [23], cell–cell interactions, receptor-binding, and cell signaling [9,13,21]. Further, sialic acids are also recognized to play a central role in some pathologic processes, like cardiovascular disorders and cancer [24–26].

1.1. Analysis of Sialic Acids

Analytical approaches to characterizing sialic acids include separation techniques, such as chromatography [27] and capillary electrophoresis [28], and detection methods such as colorimetry [29] and spectrophotometry [30]. Colorimetry and capillary electrophoresis are relatively straightforward to operate, but tend to have lower sensitivity and specificity compared to other methods [31]. High-performance liquid chromatography (HPLC) is commonly used for the separation of sialic acids [31,32], and is generally combined with ultraviolet [33] or fluorescence detectors [27,34]. Currently, the study of sialic acids is greatly facilitated by the application of mass spectrometric techniques for specific detection and quantification [35–39].

Mass spectrometry can provide qualitative (structural) and quantitative (molecular mass or concentration) information about specific molecules of interest [40]. Mass spectrometers comprise four main components [41,42]: (1) an ion source, enabling ionization of sample molecules; (2) a mass analyzer, which separates ions according to their mass-to-charge ratio (m/z); (3) a detector, which measures the separated ion abundances in the form of electrical signals, and (4) a recording device, which transforms the detector signal into a format suitable for further analysis and processing. The process itself unfolds in its respective stages. (a) The vaporization and ionization of the sample [43,44]. Various approaches may be used for ionization in the gas phase, including electron ionization, chemical ionization, electrospray ionization (ESI), photoionization, inductively coupled plasma, and matrix-assisted laser desorption ionization [45]. (b) Acceleration of ions through an electric field to reach the same kinetic energy [46]. (c) Separation and sorting of ions according to their specific m/z ratios [40,47]. (d) Fragmentation of ions to generate fragments, the distribution of which is characteristic for each molecule. This is typically accomplished in tandem mass spectrometry. (e) Detection and recording of ions, based on the ion abundance and relative intensity [43,45].

Technical advantages of mass spectrometry include high sensitivity, specific selectivity, and small sample requirements [35,48]. Consequently, mass spectrometry has become the preferred approach for sialic acid research [49]. As a result of continuing advancements, specific sialic acids are now being studied in a variety of organisms and human tissues. Moreover, their potential roles in human health and disease are also being investigated.

1.2. Structures of Sialic Acids

Sialic acids constitute a family of more than 50 distinct molecules, 15 of which have been identified in human tissues [9,24]. The differences between sialic acids are based on particular *N*-linked or *O*-linked modifying groups, such as *N*-acetyl-, *N*-glycolyl, and *O*-acetyl, or, less frequently, the *O*-lactyl, *O*-methyl, and *O*-sulfate groups (Figure 1) [10,25,50]. The modifications confer distinct properties to the nine-carbon sugars, which support their specific physiologic functions [12]. Two major structural features include an often-modified amino group at position 5 and a carboxyl group at position 1. This carboxyl group, with its characteristic pKa of about 2.2, confers a negative charge on the sialic acid within a wide physiologic pH range [10,13]. Esterification of the hydroxyl groups at positions 7, 8, or 9 with acetic acid, in the form of *O*-acetylation, occurs less frequently [10]. Other known modifications include sulfation or methylation at position 8, or lactylation at position 9. Substitutions may occur at multiple sites, as illustrated by 7,8,9-tri-*O*-acetyl-*N*-acetyl- and *N*-glycolylneuraminic acid [8,9,51].

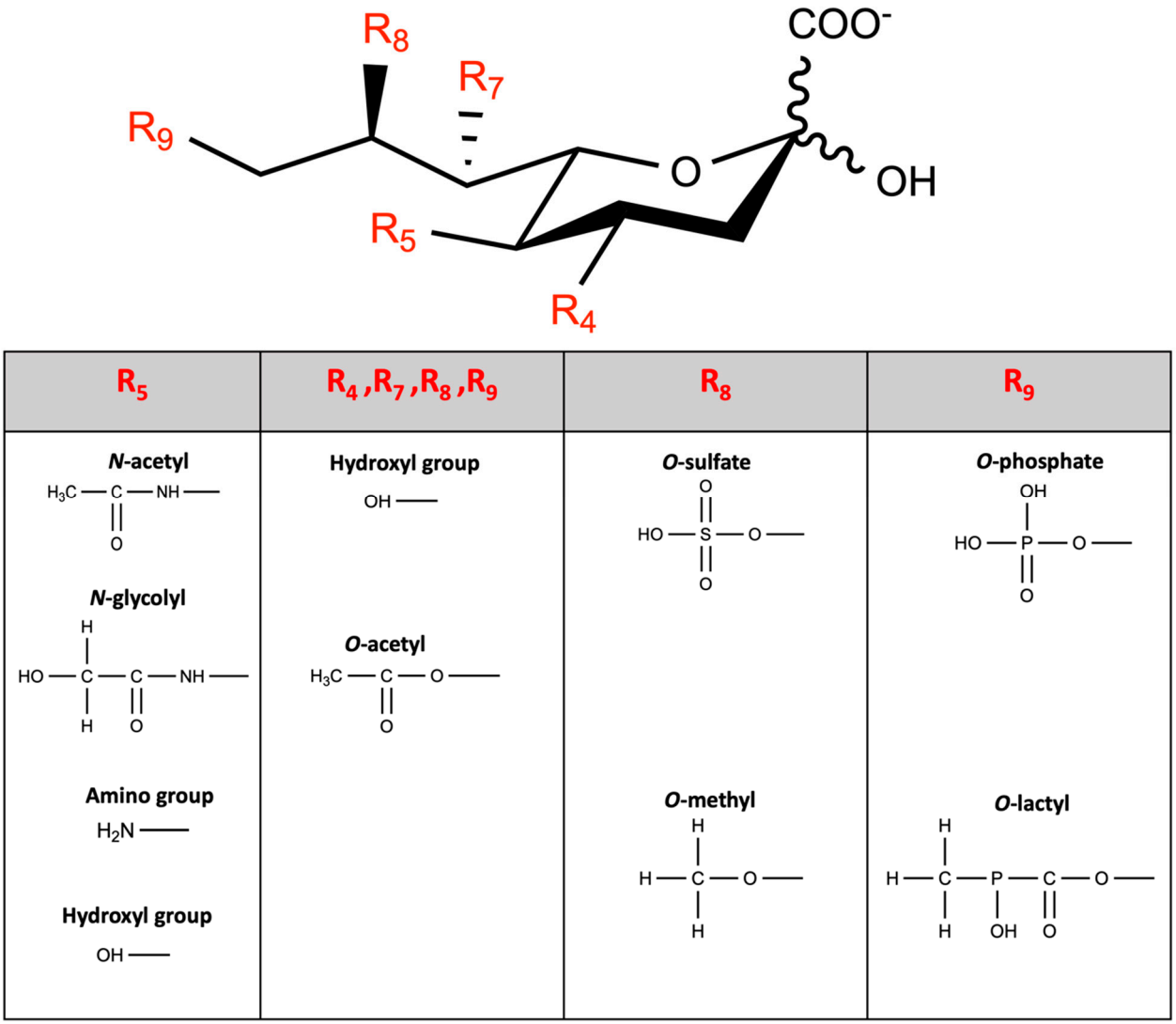

Figure 1. The molecular structure of sialic acid and its variants under various physiologic conditions. Sialic acids are characteristically carboxylate at group C1, attached to the C2 anomeric carbon. The wavy lines in C1 signify that the specific α or β anomeric configuration is not specified. The most common natural substituents (positions indicated in brackets) are a glycerol-like side chain (C7, 8, and 9) projecting out of the ring, and an acylated amino group at C5. Different groups with methyl, lactyl, acetyl, glycolyl, or sulfate can additionally diversify sialic acids. Prepared with ChemDraw, ver.: 23.1.2.7.

Widely distributed in a variety of human tissues and fluids [52], sialic acids exhibit particular functional roles associated with their specific structural features [10]. The most common member of this family is *N*-acetylneuraminic acid (Neu5Ac), with an acetylated amino group at position 5 (Figure 2) [7,50]. Neu5Ac can be converted to a less common *N*-glycolylneuraminic acid (Neu5Gc) by cytidine monophosphate-N-acetylneuraminic acid hydroxylase (Cmah), which hydroxylates the acetyl group [9,50,53]. Another sialic acid member, mainly found in its free form [10,54,55], and generally expressed at lower levels than Neu5Ac or Neu5Gc in mammalian tissues, is 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid (KDN) [8,36,55,56]. More in-depth structural and stereochemical sialic acid analyses are presented elsewhere [6,10,25,57–60].

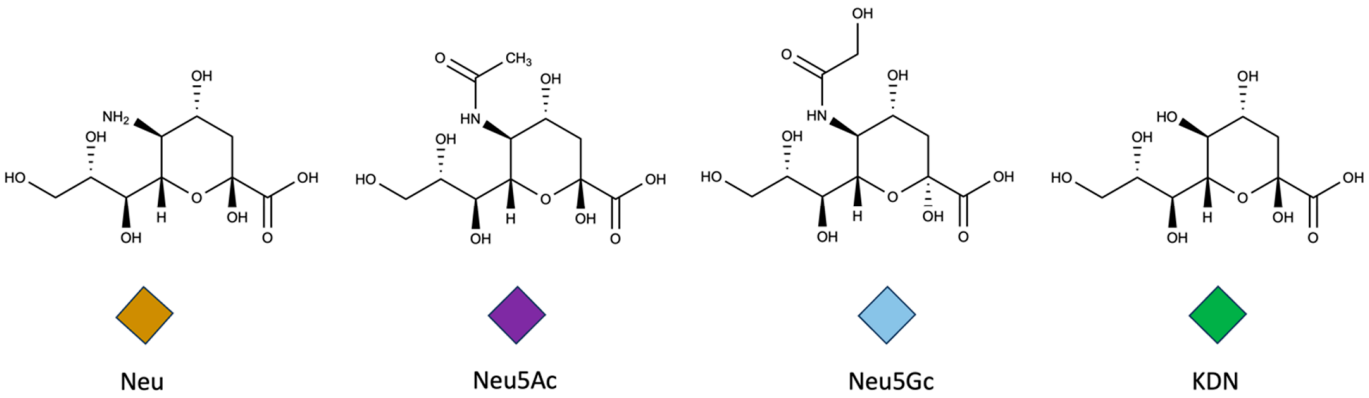

Figure 2. The structures of the most common sialic acids. The graphical representation of these glycans was developed according to the Symbol Nomenclature for Glycans (SNFG) guidelines. Prepared with ChemDraw, ver.: 23.1.2.7. Neu, neuraminic acid; Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid (Neu5Gc); KDN, 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid.

1.3. Synthesis

In mammals, the synthesis of sialic acids involves more than 30 genes, encoding enzymes, and transporters allocated in various cellular compartments [61]. The synthesis of Neu5Ac begins in the cytosol with glucose, which enters the hexosamine biosynthetic pathway (HBP). This pathway phosphorylates glucose using ATP to produce the key metabolite uridine-5′-diphospho-N-acetylglucosamine (UDP-GlcNAc) [60,62]. Then, the epimerase domain of UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE) mediates the formation of the uncharged monosaccharide *N*-acetylmannosamine (ManNAc) [63], with simultaneous cleavage of UDP [64–66]. ManNAc is phosphorylated by the kinase domain of GNE, leading to ManNAc-6P [67]. Sialic acid synthase (NANS) converts ManNAc-6P to Neu5Ac-9P in a condensation reaction with phosphoenol-pyruvate (PEP) [51], and subsequently, *N*-acetylneuraminic-acid-phosphatase (NANP) mediates the dephosphorylation to produce free Neu5Ac [68]. The free monosaccharide is activated in the nucleus by coupling with cytidine monophosphate (CMP), via the action of CMP-N-acetylneuraminate synthetase (CMAS), producing CMP-Neu5Ac [10,69]. Then, the CMP-Neu5Ac is added to lipid or protein to form glycans in the Golgi apparatus [70,71], or transferred to carbohydrate chains of nascent glycoconjugates by sialyltransferases (Figure 3) [10,13,24,72]. At this point, the bound Neu5Ac may be further altered via *O*-acetylation or *O*-methylation [73], before the glycoconjugate is transferred to the cell surface [72].

The main precursor for KDN biosynthesis is mannose (Man). The synthetic pathway comprises a series of reactions, similar to those for the biosynthesis of Neu5Ac (Figure 4) [60,74–76]. (1) Man + ATP → Man-6-P + ADP; (2) Man-6-P + PEP → KDN-9-P + P_i; (3) KDN-9-P → KDN + P_i. Reaction 1, catalyzed by a hexokinase, represents the 6-*O*-phosphorylation of mannose to form D-mannose-6-phosphate (Man-6-P). Reaction 2, catalyzed by KDN-9-phosphate (KDN-9-P) synthetase, condenses Man-6-P and PEP to form KDN-9-P. Reaction 3, catalyzed by a phosphatase, involves dephosphorylation of KDN-9-P to yield free KDN [12,55,74].

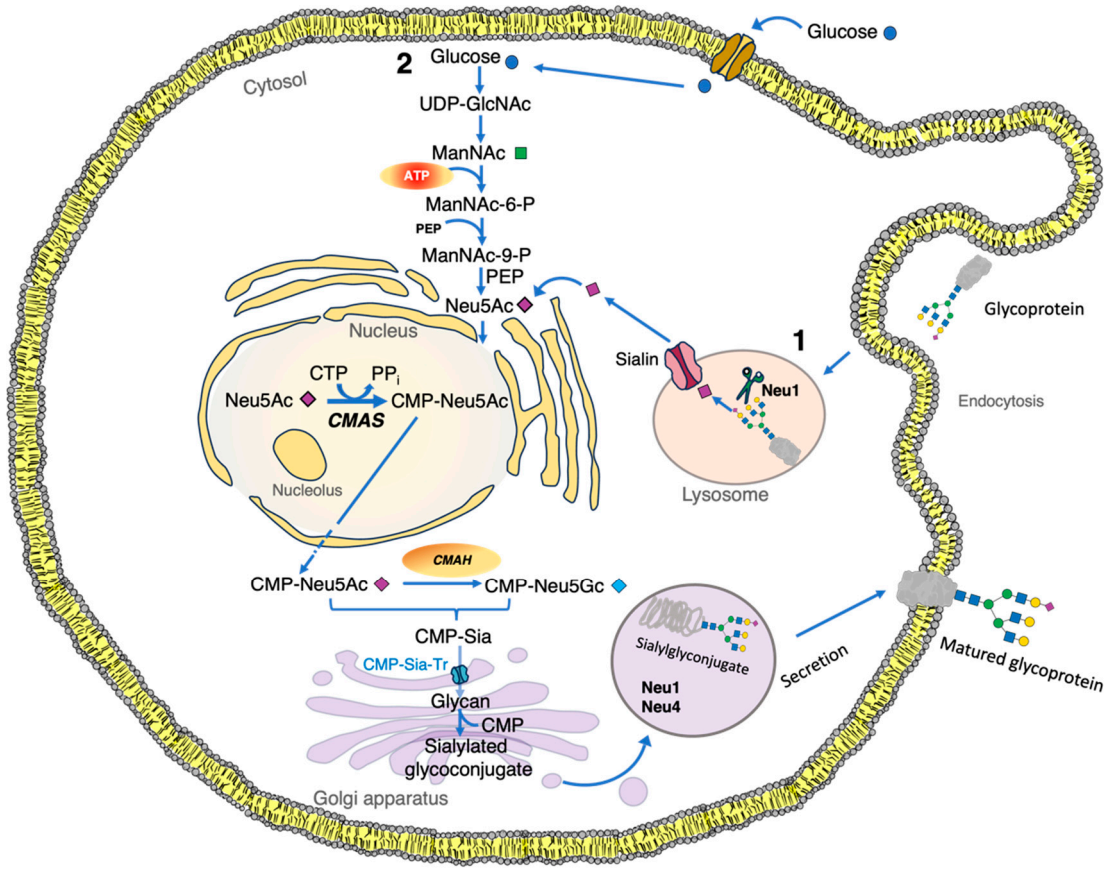

Figure 3. Sialic acid metabolism in eukaryote cells. (1) Sialic acid molecules found in the cytosol of eukaryotic cells are obtained from exogenous sources, such as glycolipids or glycoproteins. (2) Sialic acids can be produced from cytosolic UDP-GlcNAc molecules, biosynthesized from glucose in the hexosamine pathway. Finally, in the lysosome, after Neu1 hydrolyzes the terminal sialic acid residue from glycoconjugates, the sialylated glycoconjugate is transported by the sialin transporter encoded by the SLC17A5 gene. CMAH, cytidine monophospho-*N*-acetylneuraminic acid hydroxylase; CMAS, CMP-*N*-acetylneuraminate synthetase; CMP, cytidine-5′-monophosphate; CMP-Sia-Tr, CMP sialic acid transporter in the Golgi apparatus, encoded by the SLC35A1 gene; CTP, cytidine-5′-triphosphate; ManNAc, *N*-acetylmannosamine; ManNAc-6-P, *N*-acetylmannosamine 6-phosphate; ManNAc-9-P, *N*-acetylmannosamine 9-phosphate; Neu1, neuraminidase 1; Neu4, neuraminidase 4; PEP, phosphoenolpyruvate; PP_i, pyrophosphate; Sia, sialic acid; Sialin, sialic acid transporter in the lysosome; UDP-GlcNac, uridine diphosphate *N*-acetylglucosamine.

1.4. Functions

Sialic acids are involved in a variety of physiologically important functions [24,77], such as (a) antioxidant protection [78], (b) cell surface interactions [1], (c) infant bone development and skeletal growth [79], (d) immune recognition [80], (e) brain development [79,81], and (f) learning and memory [82].

In GNE myopathy patients and in a GNE mutant mouse model, muscles were hyposialylated and proteins were highly modified via *S*-nitrosylation, while oxidative stress-responsive genes were significantly upregulated [83]. In both cases, reactive oxygen species (ROS) production was elevated with cellular hyposialylation [83]. However, increasing overall sialylation through the intake of extrinsic sialic acid reduced ROS and protein *S*-nitrosylation. Additionally, the oral antioxidant *N*-acetylcysteine ameliorated muscle atrophy and weakness in *GNE*-mutant mice [83,84]. Together, this line of evidence demonstrates that overall sialylation is associated with increased antioxidant protection and improved reserve capacity to handle incidental ROS.

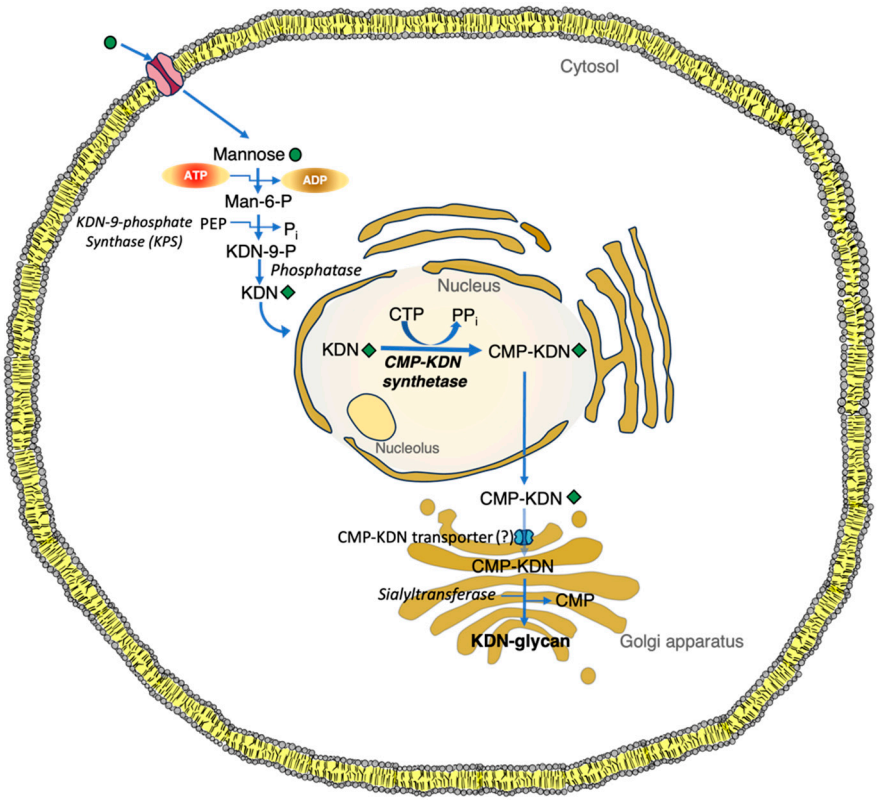

Figure 4. De novo pathways for the synthesis of KDN in animal cells. Man-6-P, a C2 epimer of glucose 6-phosphate, is a key precursor monosaccharide for KDN. The biosynthesis of KDN from Man-6-P follows comparable enzyme reaction steps to those of Neu5Ac from ManNAc-6-P. Notably, unlike other free monosaccharides, mannose is efficiently taken up by different cell types using a transporter that is unresponsive to glucose. CMP, cytidine-5′-monophosphate; CMP-KDN, cytidine 5′-(3-deoxy-D-glycero-D-galacto-2-nonulosonic phosphate); CMP-KDN-synthetase, CMP-3-deoxy-d-glycero-d-galacto-nonulosonic acid synthetase; CTP, cytidine triphosphate; KDN-9-P, KDN-9-phosphate; Man-6-P, mannose-6-phosphate; P_i, inorganic phosphate; PP_i, pyrophosphate.

A biallelic mutation in *NANS* is associated with infantile-onset severe developmental delay and skeletal dysplasia [79,85]. The *NANS* gene is responsible for encoding the synthase for Neu5Ac [79,86]. Consequently, the immediate precursor substrate builds up, so that body fluids from affected individuals will have elevated levels of N-acetyl-D-mannosamine [79]. Knockdown of *nansa*, a zebrafish ortholog for the human *NANS* gene, results in abnormal skeletal development, while exogenously added sialic acid partially rescues this skeletal phenotype. Thus, NANS-mediated synthesis of sialic acid is required for early skeletal growth [79].

The glycocalyx is central to immune recognition and checkpoint inhibition, which enables pathogen detection and activation of immune defenses [80,87]. This carbohydrate coat serves as a cellular barrier that can either facilitate or obstruct immune cell interactions. Depending on the cell type and the composition of the glycosaminoglycan layer, the immune system may identify it as representing "self". Alternatively, the sialic acid-rich layer may also potentially shield pathogens or cancerous cells from immune detection by masking their antigen-decorated surfaces with a carbohydrate-rich layer [88]. Ordinarily, for cancer cells to establish malignant lesions, they first need to evade recognition by immune cells [89,90]. They achieve this by tailoring their glycocalyx, which covers their neoantigens and other ligands, protecting them from acquired immune system cells. This alters the phagocytic efforts of myeloid cells and changes the normal immune responses [90]. This explains the upregulation of transmembrane mucins and other highly sialylated

glycoproteins in cancer cells, as a way of establishing a protective glycocalyx [80,91,92]. Accordingly, in mouse models, tumor cells with the most efficient surface glycocalyx shielding have been shown to have the highest metastatic potential [93].

The human brain grows rapidly in early life and requires adequate nutrition [94–96]. Breastfeeding significantly improves the cognitive development of infants [94,97,98]. These benefits have been attributed to human milk oligosaccharides (HMOSs), some of which are linked with sialic acids [94,97,99]. Sialic acids are recognized as essential molecules for the proper development of gangliosides, and therefore, as critical for brain development and function [95]. Dietary supplementation with sialic acid or sialylated oligosaccharides is known to enhance intelligence and cognitive performance in early and later life [95,96,100]. Similarly, exogenous supplementation of sialic acid in animal models increases its concentration in the frontal cortex and improves learning performance [101]. As a building block for neurons, dietary 3′-sialyllactose is associated with improved language development in infants [94]. Conversely, some intellectual developmental disorders are associated with genetic defects affecting the synthesis of endogenous Neu5Ac [79].

1.5. Genetic Disorders

1.5.1. UDP-GlcNAc 2-Epimerase/ManNAc Kinase (GNE) Myopathy

GNE myopathy is a hereditary myogenic disorder that results in muscle weakness due to a defect in the muscle itself. The GNE gene provides instructions for expression of the bifunctional GNE enzyme, which plays a key role in the synthesis of Neu5Ac [83,84,102]. The N-terminal epimerase domain of GNE uses UDP-GlcNAc as a substrate and epimerizes it into ManNAc by the epimerase domain, which is then subsequently phosphorylated by the kinase domain of the GNE enzyme [63,83].

Usually, GNE myopathy patients present with muscle symptoms between the ages of 15 and 35 [103]. The pathophysiology of the disease is not entirely understood, but hyposialylation of muscle glycans is thought to play an important role [84,102]. The typical presentation of bilateral foot drop in early adulthood is a consequence of weakness in the anterior tibialis muscles [102]. Over the subsequent decades, the disease gradually progresses, gradually affecting skeletal muscles throughout the body [102]. The quadriceps muscles tend to be relatively spared until the advanced stages of the disease [84,102,103].

Currently, a phase 2 clinical trial with ManNAc supplementation as a therapeutic intervention is ongoing for patients diagnosed with GNE myopathy [63,104]. Preliminary evidence of its long-term safety and biochemical efficacy, consistent with the intended mechanism of action, is reported in this cohort of patients [63]. Additionally, ManNAc supplementation restores the intracellular biosynthesis of Neu5Ac in affected subjects. Surprisingly, such an improvement is observed even in patients with homozygous GNE mutations in the kinase domain [104].

1.5.2. Free Sialic Acid Storage Disorder (FSASD)

Lysosomes are cytoplasmic organelles that contain a variety of hydrolases [105]. A genetic deficiency in one of these hydrolases can result in the accumulation of material to be degraded by the lysosome [106]. Sometimes, such lysosomal storage can be caused by the deficiency of an activator protein [107,108]. Alternatively, accumulation of lysosomal material can also occur due to a transporter deficiency, as seen in the Salla disease [105,109].

Damage to the transport mechanism of free Neu5Ac through the lysosomal membrane leads to lysosomal accumulation of Neu5Ac [110,111]. Lysosomal free sialic acid storage disorders constitute a spectrum of uncommon, autosomal recessive, neurodegenerative, and multisystemic disorders caused by defective sialic acid lysosomal membrane exporter Sialin (Figure 3) [112–114].

The biallelic pathogenic gene variants of *SLC17A5*, which encode Sialin, produce three forms of free sialic acid storage disorders: (a) Salla disease, (b) intermediate severe Salla disease, and (c) infantile free sialic acid storage disease [109,114]. Salla disease and infantile free sialic acid storage disease exemplify the mildest and the most severe manifestations of the FSASD phenotypic spectrum, respectively [109]. At six months of age, infants with Salla disease typically manifest hypotonia, ataxia, developmental delay, and, in most cases, hypomyelination [105,115]. This is followed by a gradual neurological decline in an otherwise near-normal lifespan [115]. In contrast, infantile free sialic acid storage disease is characterized by nonimmune hydrops fetalis (24%), hepatosplenomegaly, failure to thrive, severe developmental delay, cardiomegaly, club feet, increasingly coarse facial features, neurological deterioration, and premature death [112]. The recently described intermediate severe Salla disease represents individuals with an intermediate phenotype [115]. Patients usually present within the initial six months of life with severe hypotonia and developmental delay, gradually progressing to ataxia, spasticity, and epilepsy [109].

2. Diet

In addition to their endogenous production, sialic acids can also be obtained from dietary sources, absorbed by the intestine, and transported via circulation to tissues [104,116,117]. Most of the common sialic acids are obtained through dietary sources [118], either from red meat, in the form of lamb, pork, or beef, or from a variety of milk products [119,120]. Exogenous Neu5Ac can be picked up by cells via fluid pinocytosis and a lysosomal transporter [121]. In contrast to Neu5Ac, Neu5Gc cannot be synthesized by human tissues from endogenous precursors [122]. Instead, it is metabolically incorporated in the tissues of subjects who consume red meat [123–125]. Consequently, low levels of surface expression of diet-derived Neu5Gc occur on endothelial and some epithelial cells [53,126]. Once sialic acids are internalized by cells into the cytosol [116], they are integrated with endogenous glycoconjugates, of which a relatively small fraction is retained in the body, while the rest is metabolized and excreted in urine [126,127] or feces [104].

Unlike animals, plants are known to lack sialic acids [110,128,129]. However, they are rich sources of precursors for the synthesis of sialic acids [7,60,75,129]. In fish, *O*-acetylated Neu5Ac occurs frequently on *N*-glycans, while a smaller number of Neu5Acα2-8Neu5Ac structures are also observed [130]. Neu5Gc is seen very rarely in certain marine sources (fish eggs or echinoderms) [116,131,132] and is apparently not synthesized by birds or reptiles [133,134].

The precise metabolic fates and the relative contributions of sialic acids from endogenous and dietary sources in humans remain unknown, making the inferences from current models difficult [126]. Implications of dietary uptake and the utilization of Neu5Ac and Neu5Gc deserve further investigation.

Microbiome and Sialic Acids

Plant polysaccharides include long-chain glycans, as components of plant-based fiber, which animals generally cannot digest [135]. Fiber, however, is an essential source of carbon and energy that supports the maintenance and functioning of gut microbiota [136]. These gut bacteria, which are able to utilize various types of plant glycans [136], are categorized into seven predominant divisions: *Actinobacteria*, *Bacteroidetes*, *Cyanobacteria*, *Firmicutes*, *Fusobacteria*, *Proteobacteria*, and *Verrucomicrobia*. Of these, *Bacteroidetes* and *Firmicutes* represent more than 90% of the microbiome [137]. Gut bacteria are believed to be essential to human health by (a) conferring additional energy-harvesting capacity, (b) providing niche exclusion of pathogens, (c) producing vitamins and glycans, and

(d) carrying out molecular communication activities, all of which form an integral part of human physiologic processes [136,138,139]. Thus, the quantity and quality of plant glycans consumed daily by the human host can have an impact on health [136]. Both pre-clinical and clinical studies indicate that different types of dietary plant glycans and their metabolic products contribute beneficial metabolic effects to the host [140]. For example, the fermentation of cellulose, hemicellulose, resistant starch, pectin, lignin, or various oligosaccharides can lead to the production of short-chain fatty acids (SCFAs) like acetic, propionic, or butyric acids, which, in turn, help to regulate glucose and lipid metabolism [140,141]. The release of these fatty acids can occur during digestion in the upper gastrointestinal tract but may also continue in the colon [142].

Studies of the microbiome composition in adults are mainly focused on the resulting health impacts, while the effects of dietary sialic acids in this context are largely overlooked [143]. Given the considerable dietary variation between different people, the effects of dietary sialic acids on the adult gut microbiome are often difficult to tease apart. Consequently, cohort studies focusing on particular dietary patterns, like the Adventist Health Study-2 [144] or the EPIC-OXFORD study [145], are potentially helpful in examining the impact of dietary sialic acids, like Neu5Ac or Neu5Gc, on the gut microbiome. Such information about the relationship between dietary sialic acids and the microbiome may reveal additional insights into several non-communicable diseases, like type 2 diabetes [146,147], cardiovascular disorders [148,149], or cancer [12,150–152].

Bacteria can release free sialic acids or use them as nutrient sources [153,154]. Gut microbiome symbionts, such as *Ruminococcus gnavus*, can scavenge Neu5Ac from mucins and convert it to 2,7-anhydro-Neu5Ac [1]. However, catabolism of 2,7-anhydro-Neu5Ac is not restricted to *R. gnavus*. *Escherichia coli* can also transport and catabolize sialic acids such as Neu5Ac, Neu5Gc, or KDN to satisfy its carbon and nitrogen needs. These sialic acids are transported via the transporter NanT and catabolized using the sialic acid aldolase NanA [155]. Glycosylhydrolases cleave the glycoketosidic linkages of sialic acid *O*-acceptor substrates through an exohydrolytic reaction [156]. In addition, bacterial sialidases can release Neu5Gc from red meat [153,157], helping to reduce the inflammatory effects of red meat consumption [143].

3. Interactions with Pathogens

Sialic acids act as receptors for various pathogens that produce infectious diseases [158]. Some pathogens can synthesize or appropriate sialic acids from their hosts and incorporate them into their own glycoconjugates and derivatives [159]. For example, bacteria produce adhesins or toxins that interact with sialic acids on host cells [157], viruses can use sialic acids to attach to and enter cells [160], and protozoa can use sialic acids to elude host immunity [161–163].

3.1. Sialic Acids and Bacteria

Some bacterial species can produce Neu5Ac and corresponding glycoconjugates. Others, in contrast, are merely able to use sialic acids as carbon sources. This capability to use sialic acids appears to be correlated with bacterial virulence in a range of infections, particularly in the profusely sialylated environment of the gut [143]. Bacteria obtain sialic acids in two ways: either via de novo synthesis, or from scavenging pathways using specific sialidases to cleave sialic acids from glycoconjugates [155,164]. As in eukaryotes, the de novo synthesis pathway in bacteria begins with the phosphorylation of glucose by a hexokinase [165].

In *E. coli*, in the NeuC pathway, glucose undergoes conversion into glucose-6-phosphate through the action of a hexokinase [166–170]. This is followed by the con-

version of glucose-6-phosphate to fructose-6-phosphate by glucose-6-phosphate isomerase (PGI). Four reactions take place sequentially, facilitated by three enzymes: glucosamine-6-phosphate synthase (glmS), phosphoglucosamine mutase (glmM), and the bi-functional enzyme glucosamine-1-phosphate acetyltransferase/N-acetylglucosamine-1-phosphate uridyltransferase (glmU). The result of these reaction steps is the formation of UDP-GlcNAc [166,171]. The conversion of UDP-GlcNAc to ManNAc is catalyzed by UDP-GlcNAc 2-epimerase [172] and NeuC, which is responsible for the biosynthesis of the precursor of *N*-acetyl-D-mannosamine, followed by NeuB-catalyzed conversion of *N*-acetyl-D-mannosamine with phosphoenolpyruvate to the product Neu5Ac (Figure 5) [168,171–176]. Alternatively, a shortened synthetic pathway can utilize sialyl precursors scavenged from animal hosts to produce Neu5Ac [177], particularly during cell wall synthesis [165].

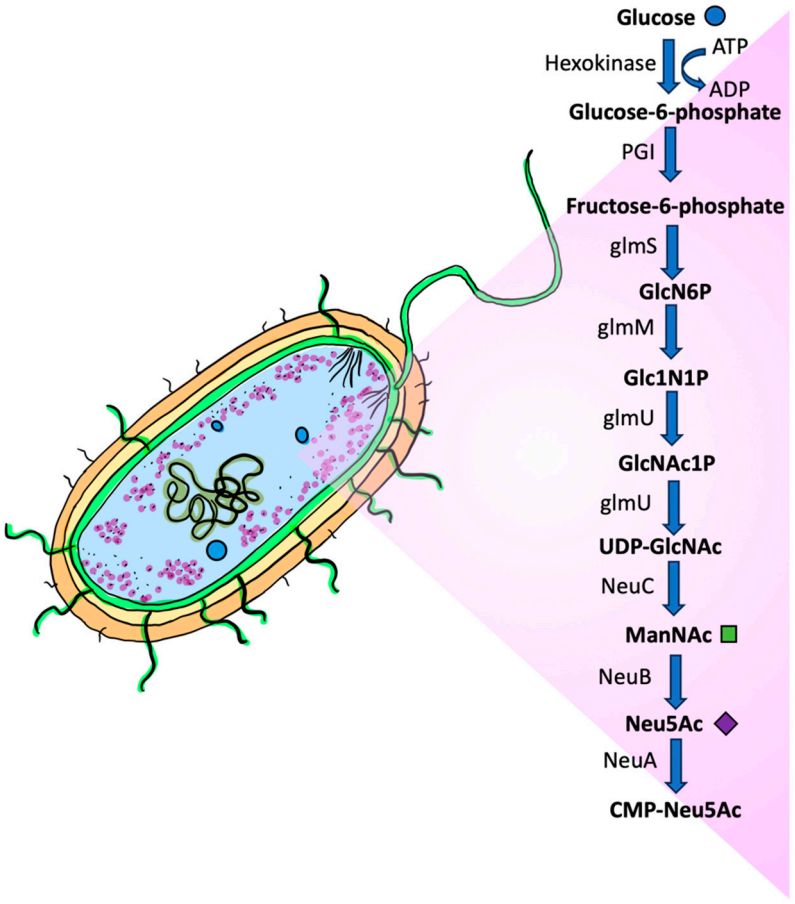

Figure 5. Biosynthesis of N-acetylneuraminic acid in prokaryotes. In the bacterium *E. coli*, glucose is metabolized through a series of enzymatic reactions. The process begins when glucose enters the cell and is phosphorylated by hexokinase to form glucose-6-phosphate. The next step involves an isomerization reaction catalyzed by the enzyme glucose-6-phosphate isomerase (PGI), which converts glucose-6-phosphate into fructose-6-phosphate by a rearrangement. The pathway proceeds through several more steps, including the cleavage of fructose-6-phosphate, followed by a series of four enzyme-catalyzed reactions to generate a nucleotide sugar called UDP-N-acetylglucosamine (UDP-GlcNAc). Then, UDP-GlcNAc is converted to ManNAc, catalyzed by NeuC, a hydrolyzing UDP-GlcNAc epimerase. Neu5Ac is produced via a condensation reaction of ManNAc with phosphoenol pyruvate (PEP), which is catalyzed by NeuB (sialic acid synthase). The Neu5Ac is primed by NeuA (Sialic acid O-acetylesterase) and CTP to form CMP-Neu5Ac. CMP: cytidine 5′-monophosphate. CTP: cytidine triphosphate; CMP-Neu5Ac: cytidine-5′-monophospho-N-acetylneuraminic acid; UDP-GlcNAc: uridine diphosphate N-acetylglucosamine.

Some bacteria may be able to synthesize additional structurally related NulOs. Such bacterial NulOs include legionaminic acid [157], pseudaminic acid [178,179], fusaminic acid [180], and acinetaminic acid [181]. In this context, the naming convention typically follows a name derivative of the microbial species first reported as its producer [178]. For example, legionaminic acid was first observed in *Legionella pneumophila*, known for the respiratory infection Legionnaires disease [182]. Similarly, acinetaminic acid was first identified in the multi-drug-resistant pathogen *Acinetobacter baumannii* [154,183].

3.1.1. *Porphyromonas gingivalis*

Periodontitis is one of the most prevalent oral diseases [184], characterized by gradual damage of the periodontal ligament and surrounding tissues, which can potentially include alveolar bone, with ultimate tooth loss [185]. These conditions are characteristically associated with poor brushing and flossing habits, allowing polymicrobial colonization on the surfaces of teeth, in the form of a sticky biofilm [186]. *Porphyromonas gingivalis* serves as a keystone pathogen in the microbial community, responsible for the occurrence and progression of periodontitis [187–189].

The survival of *P. gingivalis* next to the oral mucosa depends on its dynamic interface and its cell membrane [190], which facilitates the release of wastes and the acquisition of nutrients. Once attached to the oral cavity, *P. gingivalis* utilizes the host's amino acids and other carbon-containing molecules as energy sources and as building materials for its functions and growth [191,192]. Interestingly, this Gram-negative pathogen, although long described as asaccharolytic, can utilize sugars such as glucose for the biosynthesis of other intracellular macromolecules [193]. The cell membrane of *P. gingivalis* also contributes toward effective tissue colonization [190], by releasing vesicles with an arsenal of virulence factors, including lipopolysaccharides (LPS), fimbriae, gingipains, and others [194,195]. The host's immune system responds to these by ramping up the production and release of inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β [196]. The interplay between the destructive microorganisms and the pro-inflammatory immune responses causes periodontal tissue degradation [190,197].

In addition, *P. gingivalis* can produce and release sialidases, which can also serve as virulence factors [156]. The infection may be sustained by the action of sialidases and sialopeptidases (the *O*-sialoglycoprotease hydrolyzes the sialic acid *O*-acceptor substrate through an endohydrolytic reaction [156]), cleaving the sialic acids from the host glycoproteins [156] and contributing to disease progression [189]. In a similar manner, *P. gingivalis* virulence may be further enhanced if the sialidases also regulate the activity of gingipains (cysteine proteases) [156,198]. Conversely, the inhibition of *P. gingivalis* sialidases may be strategically helpful in treating periodontitis [189].

3.1.2. *Streptococcus pneumoniae*

Streptococcus pneumoniae, commonly known as pneumococcus, is a Gram-positive extracellular opportunistic pathogen adapted to the human upper respiratory tract [199]. This bacterium is especially predominant in pre-school-age children and those attending daycare centers [199,200]. *S. pneumoniae* is responsible for a spectrum of diseases, ranging from mild respiratory tract infections, such as sinusitis or otitis media, to severe conditions, like pneumonia, septicemia, or meningitis [181,182,184]. Pneumococcal infections pose a significant threat to global health. Globally, deaths attributed to pneumococcal disease among children under the age of five have been estimated to reach around 1.8 to 2.0 million, causing about 11% of all deaths in this age group [200–203].

The primary source of *S. pneumoniae* spread is mediated by transmission from the host nasopharyngeal airway [203]. Upon entering the human nasopharynx, *S. pneumoniae*

encounters mucus, which is rich in glycoconjugates with terminal sialic acid residues [202]. The respiratory tract is coated with mucin glycoproteins, which are rich in GlcNAc, *N*-acetylgalactosamine (GalNAc), galactose, and Neu5Ac [202,204]. These sugars are degraded by the glycan-specific metabolic machinery of *S. pneumoniae* [204], a process that includes the removal of terminal sialic acids, which also serve as carbon sources for the bacteria [204,205].

S. pneumoniae expresses up to three sialidases, including SpNanA, SpNanB, and/or SpNanC [201]. SpNanA, along with SpNanB, provides a source of sialic acids to the pathogen, and helps in host infection, nutrition, colonization, and biofilm formation [201,206,207]. SpNanC serves as a regulator of hydrolytic sialidases, such as SpNanA, catalyzing the production of the sialidase inhibitor Neu5Ac2en [201,208]. SpNanC is thought of as a potential marker of pneumococcal haemolytic uraemic syndrome in children [201], since its activity is linked to the development of this severe complication [201,209,210].

Continuing studies of these sialidases and their structure–function relationships have the potential to yield novel approaches to bacterial infections [188,192–195]. The development of selective inhibitors against sialidases opens up new perspectives for the treatment of *S. pneumoniae* [201].

3.1.3. *Haemophilus influenzae*

Haemophilus influenzae is a human pathogen that is adapted to its host [211,212]. It is classified into typeable strains, which produce a polysaccharide capsule (serotypes a to f), and nontypeable, noncapsulated strains of *H. influenzae* (NTHi) [211,213]. Healthy humans may asymptomatically carry *H. influenzae* in the upper respiratory tract [214]. Typable *H. influenzae* strains are associated with invasive forms of infection, such as sepsis or meningitis [215]. In contrast, NTHi strains are more often responsible for airway-associated inflammation, such as sinusitis, conjunctivitis, pharyngitis, otitis media, and pneumonia, in addition to possible bacteremia and meningitis [216]. Invasive NTHi, representing 43–91% of invasive isolates, is increasing in a number of countries, including Canada, the Netherlands, Portugal, Slovenia, and Sweden [217]. NTHi tends to cause severe invasive disease in neonates and in children, with significant comorbidities [216,218,219]. Approximately 10% of children from 2 to 4 years of age [220], and 17% of children in their first year, succumb to fatal NTHi infections [219–221]. The increased incidence of invasive NTHi is due to several factors, including higher vulnerability of some patients [217,220].

H. influenzae relies on its capacity to resist host defenses, including the complement system [212,222]. While evading both innate and adaptive immunity, *H. influenzae* causes recurrent and persistent infections [222]. Several factors contribute to the survival of NTHi [211,220], including the sialylation of the released lipooligosaccharide from outer membrane fragments during bacterial growth [215,220,223]. This modification protects specific epitopes of the lipooligosaccharide from bactericidal IgM in circulation [222,223]. Sialic acids, incorporated as the terminal residues on lipooligosaccharides, enable NTHi to evade antibacterial defenses, to persist within mucosal tissues, and to form a biofilm. Neither the underlying mechanisms involved in these processes, nor the role of sialic acid scavenged by NTHi during infection, are well understood yet [222,223]. However, since NTHi strains defective in sialic acid utilization are no longer virulent in animal models for otitis media, the sialic acid utilization pathway is a promising therapeutic target [223,224].

3.1.4. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a free-living, motile, and aerobic Gram-negative bacterium [225,226]. It is an opportunistic infectious pathogen, generally associated with

nosocomial infections, severe burns, chronic cystic fibrosis, cancer, AIDS, transplantation, and other immunosuppressed conditions [226].

P. aeruginosa lacks the de novo sialic acid synthetic pathway. However, it can take up monosaccharides from exogenous sources, including the glycolyl sialic acid derivative, Neu5Gc [227,228]. When sialic acids are incorporated by *P. aeruginosa*, the deposition of the complement C3b on the surface of the bacterial cell is reduced [228]. Furthermore, sialylated *P. aeruginosa* has an affinity for human CD33 receptors, including the immune cell surface receptors Siglecs 7 and 9, as a characteristic shared with other sialylated bacteria [227,229–231]. The sialylated *P. aeruginosa* also suppresses macrophage antimicrobial responses and inhibits phagosome maturation, thereby enabling its persistent viability and intracellular replication within macrophages [227]. In conclusion, acquisition of sialic acids by *P. aeruginosa* within the host contributes toward bacterial pathogenicity and further host infection by reducing complement deposition and by mimicking Siglec-dependent recognition.

3.1.5. *Clostridium perfringens*

Clostridium perfringens is the primary pathogen in intestinal and histotoxic infections, producing conditions such as gas gangrene and clostridial myonecrosis [232,233]. *C. perfringens* is also frequently associated with cases of food poisoning [234]. *C. perfringens* is known to be able to utilize sialic acids as carbon sources [232,235]. In addition to a variety of toxins [233], this Gram-positive anaerobic bacterium also produces a number of sialidases. Of these, NanH has a cytoplasmic location during the culture log-growth phase. In contrast, NanJ and NanI are secreted exosialidases [232,233,236]. Most *C. perfringens* strains produce all three sialidases. However, some *C. perfringens* strains produce only one or two of them. For strains that produce all three, NanI is typically responsible for 70% of total exosialidase activity [236]. When present, NanI enhances the colonization of *C. perfringens* in the intestinal tract [237] and increases the cytotoxic activity and interaction of several toxins with host cells [232].

The role of sialidases in histotoxic infections remains unclear [233]. Sialidases could enhance *C. perfringens* adherence to host cells through both nonspecific and specific mechanisms [233]. The nonspecific mechanisms include disruptions of physiologic host cell interactions. Terminal sialic acids promote endothelial barrier integrity and cellular interactions in epithelial monolayers [238]. Sialidases mediate the removal of terminal sialic groups, leading to barrier disruption and increasing access for *C. perfringens* [238,239]. Therefore, nonspecific effects of secreted NanI on both surface charges and epithelial barrier integrity could help to increase toxin binding and *C. perfringens* colonization [238].

The specific mechanisms of sialidase-mediated enhancement of *C. perfringens* infectivity include modifications to host cell surface receptors. Some strains, such as *C. perfringens* CN3718, display significantly enhanced adhesion to specific mammalian cells, including Caco-2 and HT-29 intestinal cell lines [240]. Similarly, toxins involved in *C. perfringens* intestinal infections bind to and affect only certain cells. These observations suggest that NanI sialidase modifies host cell surface adhesins and toxin receptors and trims adjacent molecules to enhance the accessibility of the adhesin or toxin receptors [233].

C. perfringens infections pose significant challenges, in spite of antibiotic treatments, due to the persistence of previously synthesized toxins [233,241]. Similarly, altered surface antigens in certain *C. perfringens* strains make it difficult to prepare comprehensively effective vaccines or neutralizing antibodies [234]. As a result, development of effective sialidase inhibitors represents novel treatment options for *C. perfringens* infections.

3.1.6. *Neisseria gonorrhoeae*

Gonorrhea poses a significant global health challenge, due to escalating infection rates, the emergence of antibiotic resistance, and evasion of defensive immune responses [242–244]. The exact mechanisms of *N. gonorrhoeae*-mediated disruptions of host immune responses are not well understood. It is known, however, that *N. gonorrhoeae* sialyltransferase attaches sialic acids, scavenged from the host, to its own abundant surface lipooligosaccharide [243]. The length and composition of these glycolipids are regulated by genes encoding the lipooligosaccharide glycosyltransferases [245,246]. The expression of these genes constitutes a primary mechanism of bacterial adaptation to challenging environments by altering their surface oligosaccharide composition [233,235]. *N. gonorrhoeae*, isolated from urethral infection, predominantly produces lipooligosaccharides, which can be sialylated by sialyltransferases for optimal genital tract infection [247,248]. In this context, CMP-sialic acid from the host can be used by *N. gonorrhoeae* sialyltransferases to attach sialic acid to its own acceptor hydroxyl groups [243]. Many aspects of the *N. gonorrhoeae* virulence mechanism, and its association with sialic acids, remain to be worked out.

3.2. Sialic Acids and Viral Interactions

The initial step in the viral life cycle is the attachment of virus particles to the cell surface [249]. This adherence is facilitated by the interaction of the virus with a specific receptor [250]. Receptor molecules are integral components of the cell membrane. The receptor determinant, which serves as the binding site for the virus, may consist of either a protein epitope or the carbohydrate molecule of a glycoprotein or glycolipid [160]. Soluble proteins in body fluids and mucus on respiratory and enteric epithelia may also contain carbohydrates and interfere with virus binding to the cell surface [251]. Attachment is attained by the virus binding to a cell surface receptor, usually via electrostatic interactions. Sometimes, co-receptors are also involved, which might promote post-attachment events in the entry process. Early contact between the viral attachment protein and a receptor is weak and reversible. However, as multiple viral attachment proteins interact with multiple receptor molecules, the binding becomes stronger and irreversible [252]. Thus, cells with a higher density or a higher number of receptors are more readily infected [253].

3.2.1. Influenza Virus

As members of *Orthomyxoviridae*, influenza viruses contain segmented, single-stranded, negative-sense RNAs packaged as ribonucleoproteins in enveloped virions [254,255]. Based on the antigenic diversity of the virion proteins, such as the matrix protein and the nucleocapsid protein, influenza viruses are further classified into three genera: A, B, and C [256–258]. Additional classification is based on the haemagglutinin and sialidase glycoproteins expressed on the viral envelope of influenza A and B viruses [258]. Avian influenza A viruses exhibit a strong affinity for α2,3-linked sialic acid as a receptor [258]. As a result, avian viruses tend to bind to Neu5Ac when linked to galactose by an α2,3 bond, while human viruses bind largely to Neu5Ac, linked to galactose via an α2,6 bond [259–261].

Usually characterized by annual seasonal epidemics, sporadic pandemic outbreaks involve influenza A virus strains of zoonotic origin [262]. The World Health Organization estimates that annual epidemics of influenza result in approximately 1 billion infections, 3–5 million cases of severe illness, and 300,000–500,000 fatalities [263]. Approximately 10% of the global population is affected by influenza annually, resulting in approximately half a million fatalities annually [264].

Influenza viruses enter cells via endocytosis, by both clathrin-independent and clathrin-dependent pathways [265]. The viral phospholipid bilayer, originating from the host membrane, includes hemagglutinin, which is expressed in the form of spikes on

the virion surface [266,267]. Through the clathrin-dependent endocytosis pathway, hemagglutinin binds to sialic acids of host cell surface glycoproteins or glycolipids and mediates virus–host membrane fusion [266,268–270]. However, alternative endocytic pathways, such as macropinocytosis, may also be employed [265,271,272].

Furthermore, sialidases are also inserted into the viral phospholipid bilayer as spikes [266,267]. These sialidases are of crucial importance during viral invasion of the ciliated epithelium in human airways [273], specifically, in the removal of decoy receptors on mucins, cilia, and cellular glycocalyx [266,274]. Moreover, sialidase contributes to the pathogenicity of influenza through several additional mechanisms, all which stem from its ability to cleave the α-ketosidic linkage between the terminal sialic acid and the adjacent sugar residue [275]. Notably, influenza sialidase facilitates the release of sialic acid, which can serve as a carbon source for bacteria [273], explaining the frequent superinfection by bacteria following influenza viral infection [276,277].

It is anticipated that influenza vaccines will be introduced in the near future that simultaneously target both the viral hemagglutinin and the viral sialidase [278].

3.2.2. SARS-CoV-2

In response to the rapid global spread of Coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) declared a public health emergency of international interest on 30 January 2020 [279]. This infectious disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has resulted in many deaths worldwide. By October 31, 2020, over 45 million confirmed COVID-19 cases and 1.2 million deaths had been reported globally [280]. While all coronaviruses infect the respiratory tract, SARS-CoV-2 also damages other organs, like the heart, gastrointestinal tract, liver, kidneys, and central nervous system. This can potentially lead to multi-organ failure [281,282].

The SARS-CoV-2 virus particle is a spherical, enveloped RNA virus containing a single-stranded genome. The viral envelope has an average diameter between 65 and 97 nanometers [281]. Like other coronaviruses, SARS-CoV-2 contains spike S protein trimers protruding from its envelope. The S protein is made up of 1273 amino acids comprising two subunits, S1 and S2. Binding of the S1 subunit to host cell receptors mediates viral entry and infection. The S1 subunit contains two distinct domains: an N-terminal domain and a C-terminal domain [283,284]. The glycan-binding domain located in the N-terminal domain interacts with glycolipids and glycoproteins on the host cell surface [285]. The C-terminal domain contains the receptor-binding domain that attaches to the ACE2 receptor, the primary entry point for SARS-CoV-2 and other coronaviruses [286].

Some coronaviruses are known to bind sialic acids, and SARS-CoV infection might also involve sialic acid interactions [287,288]. Computational predictions, modeling studies, and microscopic analyses indicate that SARS-CoV-2 may bind to sialic acids [289,290]. This binding capacity may explain the extremely high transmissibility of SARS-CoV-2, compared with other human coronaviruses [287,291]. Although gold nanoparticles conjugated with sialic acids have high avidity for the SARS-CoV-2 S1 protein (containing both the N-terminal domain and receptor-binding domain), their binding to model sialylated molecules appears to be relatively weak [292,293]. While numerous reports and reviews [294,295] discuss the potential role of sialic acids as co-receptors for SARS-CoV-2, the specific sialyl structure that is targeted by the spike protein remains unclear [296]. The receptor-binding domain of the SARS-CoV-2 spike protein is known to bind oligosaccharides containing sialic acids. Nonetheless, the preferential interactions seem to be with lipids that enable the virus to enter host cells [293]. Additionally, direct binding between sialic acid-containing oligosaccharides (α2,3 and α2,6 sialyl *N*-acetyllactosamine) and the N-terminal domain of the SARS-CoV-2 spike glycoprotein has been verified through saturation transfer difference nuclear magnetic

resonance spectroscopy [297]. However, the relevance of this interaction for cellular entry still needs to be confirmed. More work is needed for an improved understanding of the infection mechanism and spread of SARS-CoV-2.

3.3. Sialic Acids and Fungi

Fungi are effective degraders of dead organic matter [298] and may impact the human ecosystem [20,299]. Occasionally, fungi may become pathogenic, leading to the development of disease, exploiting the host living tissue for survival [300]. Before that can happen, however, fungal cells must somehow withstand the human immune system defenses. Hence, fungal infections tend to occur in immunocompromised individuals. Despite this, fungi with polysaccharide capsules tend to be more infectious.

3.3.1. *Cryptococcus neoformans*

Cryptococcus neoformans is used as a model organism illustrating how sialic acids might contribute to the evasion of the human immune response [20,301]. This pathogenic fungus has a true polysaccharide capsule on the outside of its cell wall [302], serving as its major virulence factor [301,303]. Protection from the immune system is aided by sialic acids, and their 9-*O*-acetylated derivatives, which are a part of the fungal capsular polysaccharides [20,304]. These sialic acids appear to reduce the likelihood of phagocytosis by alveolar macrophages during the initial stages of infection, as the basidiospores are inhaled and gain entry to alveolar spaces [302,305].

3.3.2. *Histoplasma capsulatum*

Infection with *Histoplasma capsulatum* results in substantial global morbidity and mortality [306]. As a dimorphic ascomycete, this fungus grows in its hyphal form in the soil and bird and bat droppings [307]. Upon entry into the host, in the form of microconidia or hyphal fragments, *H. capsulatum* travels through the respiratory system inside phagocytes until it reaches the alveoli [308]. There, the yeast, inside or outside of host phagocytes, is transformed into the pathogenic phase, producing histoplasmosis [296,297]. While invading the host respiratory system, the yeast must evade immune-mediated and intracellular defenses [306]. Meanwhile, these yeast cells need to survive or evade the hostile anti-microbial environment within phagocytes [309,310], including potential exposure to reactive oxygen, such as hydrogen peroxide, and reactive nitrogen species [309,311]. Yeast cells actively inhibit phago-lysosomal fusion, thereby preventing exposure to the acidic hydrolytic enzymes of the lysosomes [308,312]. Moreover, *H. capsulatum* impedes the accumulation of vacuolar ATPase, which is ordinarily needed for proton accumulation in phagosomes, allowing the fungus to alkalinize the phagosomal pH to 6.5 [309,311,312]. If a suitable environment for growth and reproduction is located, the yeast may also disseminate and develop granulomas [313]. Subsequently, the pathogen is disseminated to the lymph nodes, and then to various organs, by phagocytes as its carriers [306,308,314].

Interactions between carbohydrates and lectins are considered to be pivotal to the recognition of target particles by phagocytes [311,315]. The expression of lectins by pathogenic microorganisms has been correlated to the organisms' attachment and invasion of host tissues [311,316,317]. *H. capsulatum* expresses a 50 kDa lectin that recognizes sialic acid residues on laminin, a key protein of the basement membrane, potentially mediating surface interactions [318–320].

The identification and isolation of sialic acid-specific lectins from pathogenic fungi, particularly airborne species that cause severe infections, is highly desirable. It represents an opportunity to intervene at the initial stages of infection, as the microconidia interact with lung epithelial cells. If this initial stage is dependent on specific lectin structures, then several options for diagnosis and therapy could become available [320].

3.3.3. *Candida albicans*

Candida albicans commonly colonizes the skin, the oropharyngeal cavity, the gastrointestinal system, and the vaginal tract [321]. Infections by *Candida* species are widespread and are increasing in frequency [321–323], particularly during infancy or in old age [324,325]. A diverse array of conditions, encompassing environmental, local, and systemic factors, as well as hereditary predispositions, may alter *Candida's* normally dormant state [321,325,326]. The signs and symptoms may correspond with a range of morbidities, from localized superficial mucocutaneous disorders to invasive diseases involving multiple organ systems [309,315]. The transition in pathophysiology from the onset through the progression of infection is also influenced by the particular virulence traits that ultimately lead to the development of candidiasis [321,327].

Three types of monosaccharides form carbohydrate chains, or glycans, within the *Candida* cell wall: d-glucose (Glc), *N*-acetyl-d-glucosamine (GlcNAc), and d-mannose (Man) [328]. Several reports document sialic acids as constituents of the *Candida* cell wall [20,304,329]. Sialic acids contribute to the negative charge of fungal cells and have a role in their specific interaction with the host tissue, including a potential role in pathogenicity [329]. Although several microorganisms infecting animals or humans produce sialidases for adhesion or invasion, *C. albicans* does not, implying that fungal sialidase is likely of no relevance in cutaneous or mucosal candidiasis [330]. Consequently, this implies that sialic acids are likely acquired by *C. albicans* from the host environment via sialyltransferases. Further investigations are needed into the role of surface sialylation of *C. albicans*, particularly as it relates to the infectivity of this organism.

3.4. Sialic Acids and Parasites

Parasites are significant contributors to human disease worldwide, particularly in less-developed nations. The clinical severity and outcomes of parasitic diseases are often strongly affected by the host's immune status [331]. For example, helminths tend to elicit a protective helper T-lymphocyte type 2 host response, with production of IgE, eosinophilia, and mastocytosis [332], whereas protozoa induce a humoral and/or cellular immune response that is not usually associated with eosinophilia [333]. To overcome the immune defenses, parasites employ a variety of mechanisms. These may include (a) becoming "invisible" to the immune system by invading immune-privileged organs or cells, such as the central nervous system, eyes, or blood cells, or (b) decorating surface glycoconjugates with sialic acids, which may be directly synthesized or appropriated from the host [334]. Consequently, the T-cells and antibodies of the vertebrate's immune system either cannot access the parasite, or do not easily recognize the parasite's specific antigenic surfaces [335] for effective detection, attack, and subsequent elimination. Such evasive mechanisms are crucial for the parasite's survival inside the host [159].

3.4.1. *Trypanosoma cruzi*

Trypanosoma cruzi is a protozoan parasite that causes Chagas disease [336]. In Latin America, nearly 30% of chronically infected people with Chagas disease manifest an intense systemic response that is frequently associated with damage to essential organs, such as the heart or the gastrointestinal tract. This suggests that a wide range of host–parasite interactions affect the course of the infection [163,337].

The protozoan parasite is carried by a triatomine insect [338]. After the infected insect has a blood meal, *T. cruzi* metacyclic trypomastigotes are discharged via the insect's feces or urine. Then, the trypomastigotes can infect the mammalian host by penetrating the mucosa, or via discontinuous regions in the epithelium. Once inside the host, the protozoan parasite rapidly infects a variety of nucleated mammalian cells. The attachment to and invasion

of host cells, and the formation of the parasitophorous vacuoles with *T. cruzi*, involves a collection of polymorphic glycosylphosphatidylinositol-anchored surface proteins, including mucins and trans-sialidases [339]. Using its arsenal, the parasite destabilizes both the host's innate and adaptive immunity [340,341]. Though unable to synthesize sialic acids de novo, *T. cruzi* uses a unique trans-sialidase enzyme that cleaves terminal sialic acid residues from host cell surface glycoconjugates and transfers them onto parasite surface mucins, generating a protective/adhesive covering [342]. The sialylation of parasite-derived mucins has inhibitory effects on CD4 T cells [341], inducing suppression of their responses. Additionally, *T. cruzi* sheds trans-sialidase into circulation, as a mechanism of modifying the host's surface sialic acid signature, exploiting the signaling and functional properties of mammalian host target cells [22]. After lysosomes merge with parasitophorous vacuoles, a complex network of antioxidant enzymes, including superoxide dismutase, shield the microorganism from reactive oxygen and nitrogen species [343]. The acidification associated with the lysosomal contents activates certain critical steps that allow the parasite to escape from the phagosome to the cytoplasm, where it differentiates into the replicative amastigote form. Following numerous duplications and rupture of the host cell membrane, the amastigotes differentiate into infective trypomastigotes that are capable of infecting adjacent cells and being transported by them to distant areas via circulation [343,344]. Based on screening studies, ciprofloxacin binds trans-sialidases, which are essential for *T. cruzi* survival [345]. This suggests that the antiparasitic effects of quinolones are, at least in part, caused by trans-sialidase inhibition [346].

3.4.2. *Plasmodium* spp.

Malaria can be caused by several Plasmodium species [347]. According to the most recent World Malaria Report, in 2023, there were 263 million cases, a slight increase from 252 million cases the year before. In 2023, malaria-related deaths were estimated to reach 597,000 [348]. The escalation in malaria cases is primarily attributed to (a) the developing resistance of the parasite to antimalarial medications, and (b) the rapid population growth in the most severely affected regions [347,349,350].

Infection is initiated during a blood meal by an infected *Anopheles* mosquito, when, along with anticoagulant saliva, 10–100 sporozoites are injected into the host circulation [351,352]. The parasites invade hepatocytes in the liver [353], where they undergo their first replication cycle, producing thousands of merozoites. These merozoites are released into the bloodstream [354], where they infect erythrocytes. The parasite encases itself within a parasitophorous vacuolar membrane and commences remodeling the host cell [355]. These processes entail both internal and external alterations that facilitate the parasite's survival and proliferation within the red blood cell [356]. During the blood stage, the parasites replicate asexually, maturing into schizonts that undergo multiple rounds of nuclear division to produce merozoites [354,357]. Since red blood cells are not targeted by cytotoxic cells, the parasite is protected from the immune system [354,358]. While digesting host hemoglobin and replicating within the red blood cell, the parasite undergoes expansion and modifies the red blood cell membrane [162,354,358]. Red blood cells infected by *P. falciparum* become more rigid, whereas those infected by *P. vivax* become more flexible [352]. At this stage, a fraction of parasites differentiate into sexually competent gametocytes, which can then be transmitted via the mosquito vector [359].

The malaria pathogen has a relatively high selectivity for its respective host [360]. Of the five *Plasmodium* species that infect humans, *P. falciparum* and *P. vivax* are by far the most common and most lethal [361]. Both rely on sialic acids for the establishment of infection, the invasion of red blood cells, and the evasion of the immune system [354,357,362,363]. Reticulocyte invasion by *P. vivax, however,* is primarily dependent on the reticulocyte Duffy

antigen/receptor for chemokines (DARC) [364]. *P. falciparum*, on the other hand, employs a more direct and critical dependence on erythrocyte sialic acid residues, mediated in part by two distinct sialic acid-binding protein ligands, expressed on the parasite surface and used during red blood cell invasion. These are (a) cysteine-rich protective antigen (PfCyRPA) [365], and (b) antigen 175 (EBA-175) [366,367]. The merozoite surface receptor EBA175 binds to the sialic acid residues of erythrocyte glycophorin A [162,362]. The binding activity of EBA175 is primarily restricted to Region II of the protein. Consequently, this domain is thought to present a potential target for the development of a malaria vaccine [368]. The expression of different forms of EBA and Rh proteins in field parasite isolates, including EBA175, EBA140, EBA181, Rh1, and Rh2, makes such efforts more challenging. Therefore, targeting EBA175 alone by a vaccine against *P. falciparum* is likely to be insufficient. Developing a multivalent vaccine, incorporating several key blood-stage proteins, should be more promising [368].

4. Inflammatory Processes

Several pathological conditions are characteristically associated with structural and functional changes in sialic acid expression [77]. Such alterations in sialylated glycans can readily be detected in histological sections using plant lectins or antiglycan antibodies [369]. Increased levels of both total and free sialic acid forms in almost any severe condition or inflammatory process are consistent with their potential role as markers of inflammatory disorders [49,56,370,371]. While the rationale supporting the prognostic value of sialic acids in pathological conditions is unclear, some potential explanations have been proposed. These include (a) activation of the hepatocyte-based synthesis and secretion of acute-phase proteins, including several sialoglycoproteins, (b) impaired membrane integrity due to cell damage, and (c) upregulated activities of sialidases and sialyltransferases [371]. These circumstances could lead to measurable changes in sialic acid levels or sialylation patterns, correlating with disease progression.

4.1. Cardiovascular Disease

Cardiovascular disease (CVD), with its behavioral, environmental, cardiometabolic, and social risk factors, represents the leading cause of global morbidity and premature mortality in Western developed countries [372]. Some of the risk factors that could be modified to help prevent or reduce CVD include a lack of adequate physical activity, a sedentary lifestyle, hyperlipidemia, obesity, hypertension, diabetes, and tobacco smoking [373].

Arterial walls comprise several cell types and a specialized extracellular matrix, all of which provide adjustable vascular elasticity and strength [374]. Vascular luminal surfaces are lined with a layer of endothelial cells, which themselves are covered with a dense, heavily sialylated glycocalyx [375]. These sialylated glycoconjugates participate in the regulation of cell–cell interactions for (a) cellular junctions between endothelial cells, and (b) contact between endothelial and circulating blood cells. They also play a role as vascular receptors that modulate the binding of soluble ligands and their signaling [376]. Additionally, sialic acids provide net negative surface charges to vascular endothelial cells and low-density lipoprotein (LDL) receptors. Thus, sialylation, or the covalent addition of sialic acids to the termini of glycoconjugates, and desialylation, or the removal of sialic acid from glycoconjugates, represent a pivotal part of sialic acid metabolism in a variety of physiological and pathological processes [89,377].

Since sialic acids coat all cell surfaces, many circulatory molecules and most molecular complexes, their alteration could have varied effects, potentially including a role in the pathogenesis of CVD [26,148,378]. Desialylation, for example, is recognized as one of the most important steps in the pro-atherogenic pathological cascade [379]. The deposition

of cholesterol in cultured human aortic intimal cells is significantly increased when LDLs are treated with sialidase before addition to the culture [379]. The diminished sialic acid content of LDLs leads to increased formation of aggregates, which are readily taken up by smooth muscle cells. Moreover, some free sialic acids, such as the nonhuman Neu5Gc, could also be potential risk factors for CVD [380], or serve as biomarkers for it, as does Neu5Ac [381–383]. Neu5Gc accumulates on endothelial surfaces and in atherosclerotic plaques, where anti-Neu5Gc antibodies can trigger endothelial activation and induction of vascular inflammation [384]. Despite such in vitro studies, however, the clinical correlation between serum sialic acids, anti-Neu5Gc antibodies, and their relationship to CVD remains unclear (Table 1).

Comparing the content of sialic acids in the adipose tissue among individuals following habitually vegetarian or non-vegetarian dietary patterns, significantly higher levels of Neu5Ac were found in vegans and lacto-ovo-vegetarians relative to non-vegetarians [39]. These findings could be comparable with other studies reporting intrinsically protective cardiometabolic effects of Neu5Ac or ManNAc supplementation [380,385,386]. Despite this, the beneficial effects of dietary Neu5Ac in vegetarian subjects have not yet been established. However, the positive effects are frequently inferred, given the low risk of cardiovascular disease mortality among these individuals [387].

An excessive accumulation of abdominal adipose tissue is strongly associated with a prognosis of atherosclerosis [388]. Interestingly, it seems that diet could also indirectly affect sialic acids through alterations in BMI or adiposity. For example, KDN levels are lower with increasing BMI, independent of diet, even when comparing individuals following habitually vegetarian or non-vegetarian dietary patterns [39]. These findings are consistent with previous reports of lower sialic acids in obese individuals [386], suggesting that obesity is associated with a higher inflammatory tone. Moreover, in contrast to non-vegetarians, vegetarians have been reported to have a lower BMI and smaller waist circumference [389], which are risk factors for metabolic syndrome, diabetes [390], and cardiovascular disease [387,391]. Therefore, the effects of diet on sialic acids could be related, at least in part, to adiposity. Either way, a plant-based diet promotes a lower BMI and an anti-inflammatory state, both of which appear to be associated with higher sialic acids in adipose tissue. The sialic acids, in turn, could help to regulate or prevent the development of cardiovascular and other chronic diseases. Nevertheless, more detailed epidemiological and clinical studies are necessary to better elucidate the relationships between diet, BMI, and sialic acid levels.

4.2. Cancer

The immune system can be directed in various ways to identify and attack tumors [392]. Sialic acids shield host surfaces by resisting inappropriate immune reactions against self-antigens. This effectively suppresses the immune response. In this context, glycans, including terminal sialic acids, represent self-associated molecular patterns (SAMPs), which are recognized by self-pattern recognition receptors [393]. As a result, sialic acids play a pivotal role in modulating immune reactivity by serving as a self-recognition signal in several ways, including (a) via complement interactions, (b) via alteration of antibody-mediated clearance of pathogens, or (c) via sialic acid-binding immunoglobulin-like lectins (Siglecs) [394]. Consequently, strategies that disrupt sialic acid-mediated immune evasion, such as targeting Siglec interactions or modulating sialoglycan expression, hold promise for enhancing immune recognition and improving cancer therapies.

Table 1. Sialic acids and cardiometabolic diseases.

Title	Approach		Year	Findings	Reference
	Animal	Human			
Relation of serum sialic acid to blood coagulation activity in type 2 diabetes		x	2002	Serum sialic acid level is positive correlated with (a) blood coagulation activity and (b) circulatory fibrinogen levels.	[147]
High fat diet-induced inflammation and oxidative stress are attenuated by N-acetylneuraminic acid in rats	x		2005	Neu5Ac could be useful for preventing inflammation and oxidative stress associated with hyperlipidemia.	[395]
Relationship between Sialic acid and metabolic variables in Indian type 2 diabetic patients		x	2005	Among Indian patients with type 2 diabetes, elevated levels of serum and urinary sialic acid, as well as microalbumin, are strongly associated with microvascular complications.	[396]
Percentage of body fat and plasma glucose predict plasma sialic acid concentration in type 2 diabetes mellitus		x	2006	Percentage of body fat correlates with plasma sialic acid levels and contributes to elevated sialic acid concentrations in patients with type 2 diabetes mellitus.	[146]
Sialic acid and oxidizability of lipid and proteins and antioxidant status in patients with coronary artery disease		x	2007	Patients with CAD show significant increases in total sialic acid levels and markers of oxidative stress. Furthermore, higher TSA levels correlate with greater CAD severity.	[370]
N-Acetylneuraminic Acid Supplementation Prevents High Fat Diet-Induced Insulin Resistance in Rats through Transcriptional and Nontranscriptional Mechanisms	x		2015	Administering a low dose of sialic acids prevents insulin resistance in rats fed a high-fat diet.	[397]
N-Acetylneuraminic acid attenuates hypercoagulation on high fat diet-induced hyperlipidemic rats	x		2015	Data show that Neu5Ac prevents high-fat diet-induced high blood lipid levels and associated increased blood clotting in rats.	[385]
Sialidase downregulation reduces non-HDL cholesterol, inhibits leukocyte transmigration, and attenuates atherosclerosis in ApoE knockout mice	x		2018	Decreasing Neu1 expression or function reduces atherosclerosis in mice by substantially impacting lipid metabolism and inflammation.	[398]
Supplementation with the Sialic Acid Precursor N-Acetyl-D-Mannosamine Breaks the Link between Obesity and Hypertension	x	x	2019	Interventions targeting hyposialylated IgG and FcγRIIB, such as ManNAc supplementation, could potentially break link between obesity and hypertension and provide novel therapeutic approaches.	[386]
Neuraminidases 1 and 3 trigger atherosclerosis by desialylating low-density lipoproteins and increasing their uptake by macrophages	x	x	2021	Neuraminidases 1 and 3 initiate atherosclerosis and formation of aortic fatty streaks.	[149]
Sialic acid metabolism as a potential therapeutic target of atherosclerosis Sialic acids Neu5Ac and KDN in adipose tissue samples from individuals following habitual vegetarian or non-vegetarian dietary patterns		x	2023	Concentrations of Neu5Ac are significantly higher in vegans and lacto-ovo-vegetarians compared to non-vegetarians. Significant inverse association observed between KDN levels and body mass index.	[39]

CAD, coronary artery disease; FcγRIIB, Fc gamma receptor IIB; KDN, 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid; ManNAc, *N*-acetylmannosamine; Neu1, neuraminidase 1; Neu5Ac, *N*-acetylneuraminic acid; TSA, total sialic acids; x, report is based on animal study, human study or both, as indicated.

Lectins represent a family of immunomodulatory receptors located on the surfaces of granulocytes, monocytes, antigen-presenting cells, and natural killer cells. Commonly, Siglecs contain an immunoreceptor tyrosine-based inhibitory motif (ITIM) within the cytoplasmic domain [152,399,400]. A subset of these, Siglecs 14–16, do not possess an ITIM, but instead contain within their transmembrane region a lysine residue, which facilitates interactions with immunoreceptor tyrosine-based activatory motif (ITAM)-containing adaptor proteins [401].

The role of the immune system is unclear during tumor formation and progression, or in the development of resistance to and eradication of emerging neoplasias, late-stage tumors, and micrometastases [402]. The theory of immune surveillance holds that cells and tissues are constantly scanned by the immune system, and that such ever-alert immune surveillance is responsible for recognizing and eliminating most early cancer cells and nascent tumors [403]. The detection of abnormal cells may occur when aberrant surface expression of the sialylated glycans SLeA, SLeX, STn, or GM2 takes place (Figure 6) [91,399,404–406]. This can be a result of upregulated activity of sialyltransferases, leading to various surface sialic acids (Table 2) [92,407]. However, once Siglecs are bound to sialylated glycans on cancer cells, immunosuppressive signaling may also be promoted [408–410]. For instance, natural killer (NK) cell-mediated tumor cell death is inhibited by interactions between NK-expressed Siglec-7 or Siglec-9, and sialylated glycans, which serve as Siglec ligands on tumor cells [268].

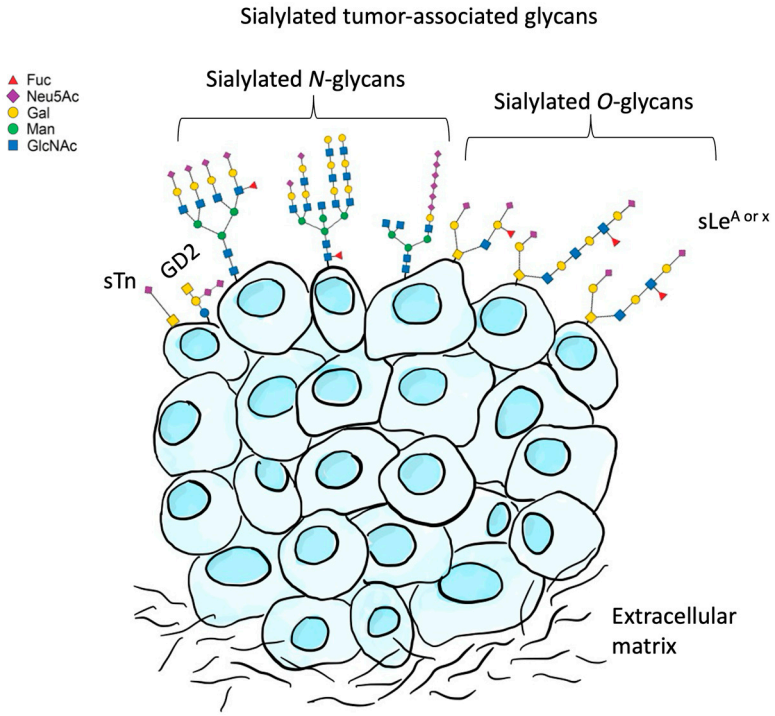

Figure 6. Sialylated glycans in cancer. Tumor cells have increased levels of sialylated glycans on their cell surface, including sialyl Lewis^{A} (SLe^{A}), sialyl Lewis^{X} (SLe^{X}), and sialyl-Tn (sTn). GD2, di-sialoganglioside.

Through a process of immunoediting [403], tumor cells are selected that mimic the glycosylation patterns of healthy cells using "self"-surface-sialylated glycan signals, as part of evasive strategies [416,417]. This mechanism might represent a potential immune checkpoint for cancer, since immune cells make aberrant sialoglycans prime ligands for Siglecs [418,419]. Thus, it is feasible to target the sialoglycan–Siglec glyco-immune checkpoint by employing Siglec-blocking antibodies. An alternative approach could be to reduce the ligand density by targeting sialoglycans [420]. It has been demonstrated, for example,

that when the glyco-profile of a cancer cell is altered by hypersialylation (an increment in sialic acid residues of up to 40–60%) [416], occurring either by the upregulation of sialyltransferases, the downregulation of neuraminidases, or a combination of both, the tumor becomes more aggressive, leading to metastasis and chemoresistance [6,416]. This suggests that downregulation of the surface sialylation of cancer cells may render them less aggressive and more accessible to the immune system.

Table 2. Sialic acid concentrations in human cancer, in different tumor cells.

Cancer	Neu5Ac		Neu5Gc		KDN	Reference
Endometrial cancer (μg/g)	$6.99 \times 10^5 \pm 3.05 \times 10^2$		$1.3 \times 10^4 \pm 5 \times 10^3$		-	[411]
Osteosarcoma cells (μg/mL)	53.6		17.5		0.36	[412]
Prostate cancer (μg/100 μg protein)	3.09×10^{-5}–6.04×10^{-2}		-		-	[413]
Pancreatic cancer (μg/L)	9.27×10^{-3}–3.7×10^{-3}		-		-	[151]
Throat cancer (μg/g)	85		0.03		2	[36]
Malignant mesothelioma (μg per 10^6 cells)	Culture media	Cell membrane extracts	Culture media	Cell membrane extracts	-	[414]
STAV-FCS	5.05	Traces	35.77	20.37		
STAV-AB	10.85	ND	13.66	19.23		
Wester	11.53	ND	18.65	25.3		
Adenocarcinoma cells (μg per 10^6 cells)						
Wart	6	Traces	16.51	21.12		
Osteosarcoma cells (μg per 106 cells)	3.97	-	2.75	4.48	-	[415]

KDN, 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid; Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid; ND, not detected; STAV-AB, cancer cell line, specifically, malignant mesothelioma; STAV-FCS, cancer cell sub-line, specifically, the sarcomatoid phenotype of mesothelioma.

Colorectal Cancer

Colorectal cancer (CRC) is among the most common cancers and is associated with one of the highest worldwide mortality rates [421]. It is the third most commonly diagnosed cancer among men, and the second most common cancer among women [422]. Numerous studies report associations between dietary factors and total cancer risk [387,423–427]. Diet and nutrition are estimated to explain as much as 30–50% of the worldwide incidence of CRC [428]. Dietary approaches to cancer prevention are of high interest [387], because of their impact as risk modifiers within the multistep process of colorectal tumorigenesis [428]. In this context, vegetarian diets are associated with an overall lower incidence of colorectal cancer [387]. Conversely, consumption of red and processed meats is associated with an increased risk of colon and rectal cancers [429–432].

Multiple mechanisms explain the potential cancer-promoting effects associated with the consumption of red or processed meats. These include (a) DNA damage due to toxic and mutagenic effects of *N*-nitroso compounds produced during high-temperature grilling [433], (b) high dietary intake of salt and saturated fats [434], (c) pro-oxidant effects of heme and iron [435], (d) production of trimethylamine (TMA) by the gut microbiome, which is subsequently oxidized by hepatic enzymes to form trimethylamine N-oxide (TMAO) [150,436], (e) altered human gut microbiome composition [153], and (f) increased levels of contaminating cancer-causing viruses [437].

The hypothesis of xenosialitis as an aspect of chronic inflammation is being increasingly discussed [50]. The human body synthetizes its own sialic acids, in addition to exogenously obtained dietary sugars [55,72]. Such dietary sources can include Neu5Gc,

especially from foods like red meat, milk, or dairy products [120,438,439]. It has been suggested that Neu5Gc could be a potential aggravating risk factor for carcinoma [436]. The proposed likely mechanism is based on mouse model studies [122,131,432]. The two principal contributors are (a) the fact that humans have a mutation in the gene CMAH, encoding cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase (Cmah), which converts Neu5Ac to Neu5Gc [122,125,131,440], and (b) the fact that humans can metabolize dietary Neu5Gc and incorporate it during the formation of native human glycans in the place of the usually employed Neu5Ac [131,441]. Thus, multiple instances of potentially immunogenic Neu5Gc-containing glycan neoantigens can be expressed on the colon's epithelial surfaces [131]. As a result, two different mechanisms may be activated: (a) the canonical NF-κB signaling pathway, which regulates the transcription of inflammatory factors, and (b) the in situ formation of antigen–antibody immunocomplexes [122]. Both processes promote systemic inflammation and subsequent tissue damage [442]. Consequently, each of these could explain the link between a red meat-rich diet and colon carcinoma.

This xenosialitis hypothesis was tested, with some mixed results. Since polyclonal rabbit anti-T cell IgG (ATG) is known to elicit an immune response in humans toward Neu5Gc [443], allograft recipients treated with animal-derived IgG were tested. Yet, in one study, no evidence was found that exposure to higher anti-Neu5Gc levels is associated with a higher incidence of colon carcinoma [53], possibly due to low cohort numbers. In contrast, in another study of 71 subjects, a positive association between total anti-Neu5Gc and CRC risk was reported [150]. However, a significant association between anti-Neu5Gc IgG and dietary red meat intake has not yet been demonstrated [150]. Interestingly, a different study reported a clear link between the levels and repertoire of serum anti-Neu5Gc IgG and the Neu5Gc from dietary red meat and dairy consumption [131]. Further, adequately powered investigations are needed to elucidate the links between diet, Neu5Gc, anti-Neu5Gc, and the risks of chronic diseases.

5. Conclusions

Sialic acids are versatile nine-carbon carbohydrates that play essential roles in human health and disease. Given their abundance on cell surfaces and secreted proteins, they mediate critical processes, such as facilitating cell–cell interactions, signaling mechanisms, immune responses, and developmental processes. Pathogens frequently exploit sialic acids to mimic host surfaces and evade immune responses. Conversely, changes in host sialylation patterns are known to be associated with inflammation, cardiovascular diseases, and cancers. Advances in analytical techniques, particularly mass spectrometry, have expanded understanding of sialic acid biology. Further investigations are needed to elucidate the diverse roles of sialic acids in physiologic and pathologic processes, in order to enable targeted therapeutic interventions.

Author Contributions: Conceptualization, D.S.B., G.N.G.-F. and F.J.P.; methodology, D.S.B. and G.N.G.-F.; writing original draft and preparation, D.S.B., G.N.G.-F. and F.J.P.; writing review and editing, D.S.B., G.N.G.-F., F.J.P., F.M.B., G.Z. and V.L.M.M.; visualization, G.N.G.-F. and D.S.B.; supervision, D.S.B. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by: (a) Grant for Research and School Partnerships (GRASP), Loma Linda University (#2170258), California, USA; (b) Doctoral scholarship to GNGF, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Ministry of Science and Technology, Argentina (RESOL-2018-2704-APN-DIR#CONICET); (c) Research grant, School of Medicine, Adventist University of River Plate, Entre Rios, Argentina.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ADP	adenosine diphosphate
ATP	adenosine triphosphate
CMAS	CMP-*N*-acetylneuraminate synthetase
Cmah	cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase; CMP
CMP	cytidine monophosphate
CTP	cytidine triphosphate
GalNAc	*N*-acetylgalactosamine
GlcNAc	*N*-acetylglucosamine
GNE	UDP-GlcNAc 2-epimerase/ManNAc kinase
GD2	disialoganglioside
GM2	ganglioside-mono sialic acid 2
GlmM	phosphoglucosamine mutase
GlmS	glucosamine-6-phosphate synthase
GlmU	glucosamine-1-phosphate acetyltransferase/*N*-acetylglucosamine-1-phosphate uridyltransferase
HBP	hexosamine biosynthesis pathway
ITAM	immunoreceptor tyrosine-based activatory motif
ITIM	immunoreceptor tyrosine-based inhibitory motif
KDN	2-keto-3-deoxy-D-glycero-D-galacto-nononic acid
LC-MS/MS	liquid chromatography with tandem mass spectrometry
Man	mannose
ManNAc	*N*-acetylmannosamine
MS	mass spectrometry
NANP	*N*-acetylneuraminic acid phosphatase
NANS	*N*-acetylneuraminic acid 9-phosphate synthase
Neu	neuraminic acid
Neu5Ac	*N*-acetylneuraminic acid
Neu5Gc	*N*-glycolylneuraminic acid
NeuA	sialic acid synthase A
NeuB	sialic acid synthase B
NeuC	sialic acid synthase C
NulO	nonulosonic acid
PEP	phosphoenolpyruvate
PGI	glucose-6-phosphate isomerase
ROS	reactive oxygen species
SLeA	sialyl-Lewis A
SLeX	sialyl-Lewis X
STn	sialyl-Tn
SCFAs	short-chain fatty acids
UDP	uridine diphosphate
SARS-CoV-2	severe-acute-respiratory-syndrome-related coronavirus 2.

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