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REVIEW

Glycosylation of dengue virus glycoproteins and their interactions with carbohydrate receptors: possible targets for antiviral therapy

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Abstract Dengue virus, an RNA virus belonging to the genus *Flavivirus*, affects 50 million individuals annually, and approximately 500,000–1,000,000 of these infections lead to dengue hemorrhagic fever or dengue shock syndrome. With no licensed vaccine or specific antiviral treatments available to prevent dengue infection, dengue is considered a major public health problem in subtropical and tropical regions. The virus, like other enveloped viruses, uses the host's cellular enzymes to synthesize its structural (C, E, and prM/M) and nonstructural proteins (NS1–5) and, subsequently, to glycosylate these proteins to produce complete and functional glycoproteins. The structural glycoproteins, specifically the E protein, are known to interact with the host's carbohydrate receptors through the viral proteins' N-glycosylation sites and thus mediate the viral invasion of cells. This review focuses on the involvement of dengue glycoproteins in the course of infection and the virus' exploitation of the host's glycans, especially the interactions between host receptors and carbohydrate moieties. We also discuss the recent developments in antiviral therapies that target these processes and interactions, focusing specifically on the use of carbohydrate-binding agents derived from plants, commonly known as lectins, to inhibit the progression of infection.

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Introduction

Dengue virus (DENV) is a member of the family *Flaviviridae* and has four distinct serotypes, designated DENV1–4. Fifty million people are estimated to become infected with dengue virus annually, and approximately 500,000–1,000,000 of these infections lead to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), with mortality rates of 5 %–30 % [1]. With no licensed vaccine or specific antiviral treatments available to prevent dengue infection, it is considered a major public health problem in subtropical and tropical regions.

Dengue virus infection is characterized by headache, biphasic fever, prostration, rash, pain in various parts of the body, leukopenia, and lymphadenopathy [2]. In severe cases, the infection can progress to DHF, which occurs when infection with one serotype causes individuals to suffer more-severe disease after subsequent infection with a different serotype. DHF is a severe febrile disease characterized by abnormalities of hemostasis and increased vascular permeability, which in some instances results in hypovolemic shock syndrome, DSS, when immune cells are enhanced by preexisting non-neutralizing antibodies directed against dengue viral proteins, although the exact mechanism is yet to be resolved [3, 4]. However, host and viral factors, such as the genetics of the infecting viral strain, have been implicated in contributing to disease severity [5].

DENV, like other flaviviruses, has three structural proteins. These structural proteins are originally encoded as a polyprotein by a single long open reading frame (ORF), which is later cleaved co- and posttranslationally by both cellular and viral proteases to produce the C, M, and E proteins from the amino terminus of the polyprotein. The virus also expresses seven nonstructural proteins derived

Table 1 Structural and nonstructural proteins of dengue virus

Protein	Size	Subunits	Functions	References
C	100 amino acids	None	Facilitates capsid assembly	[11]
prM/M	21 kDa/8 kDa	None	prM interacts with and stabilizes the E protein.	[12]
E	53 kDa	None	Forms outer protein envelope	[12, 13]
			Receptor-binding capability	
NS1	48 kDa	None	Cleaves the NS1–NS2A junction	[14–16]
			Involved in the early steps of viral replication	
NS2	22 kDa	NS2A, NS2B	NS2A plays a role in RNA synthesis and virion maturation and as an activator of correct NS1 processing	[7, 17]
			NS2B acts as an activator of NS3, allowing its proper function	
NS3	618 amino acids	None	Acts as a protease when combined with NS2B	[18, 19]
			Functions as an RNA helicase and RTPase/NTPase	
NS4	16 kDa	NS4A, NS4B	Plays a role in membrane curvature and facilitates protein–protein interactions	[20–22]
NS5	104 kDa	None	Essential for the replication and transcription of the viral genome	[23, 24]

from the carboxyl terminal sequence of the polyprotein, NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [6, 7]. The positive-stranded RNA viral genome is packaged in a lipid bilayer [8]. The functions of the proteins are summarized in Table 1. The ORF is flanked by 5′ and the 3′ untranslated regions, which comprise the conserved *cis*-acting RNA secondary structural elements required for mRNAs translation and replication [9, 10].

Glycosylation of DENV glycoproteins

DENV does not encode its own glycosyl transferase enzymes, so it requires the host cell to provide most or all of those necessary for the complete synthesis of the viral glycoproteins, including the glycosylation process. To date, N-glycosylation sites have been identified in only three of the 10 DENV proteins (prM/M, E, and NS1) [8]. The biosynthesis of these viral glycoproteins requires the transfer of a $Glc_3Man_9GlcNAc_2$ oligosaccharide precursor to the budding protein, after which the terminal glucose residues on the core unit are trimmed [25]. This involves the sequential trimming of three glucose residues attached to the oligosaccharide, which is catalyzed by the endoplasmic reticulum (ER) α-glucosidase I and II enzymes [26]. α-Glucosidase I cleaves the outer α-1,2-linked glucose residue, whereas α-glucosidase II cleaves the two inner α-1,3-linked glucose residues, leaving the proteins monoglycosylated. This action allows the glycoproteins to bind to the ER chaperones calnexin and/or calreticulin to be properly folded downstream. The reglycosylation process is initiated on the incompletely folded proteins by UDP-glucosyltransferase 1, which acts as a sensor of correct protein folding. Once correctly folded, the proteins are then released from the re- and deglycosylation cycle and transported to the Golgi complex for further processing [27].

Glycosylation of E, prM/M, and NS1 glycoproteins

The E glycoprotein monomer has three structural and functional domains. Domain I is the hinge region, which contains the amino terminus; domain II is responsible for the stabilization of the dimer and contains the fusion peptide; and domain III is an immunoglobulin (Ig)-like domain containing putative receptor-binding motifs [28, 29]. The glycoprotein has one or more potential N-linked glycosylation motifs in the form N–X–T/S, where X is any amino acid except proline [30]. Studies have shown that the numbers and locations of the motifs vary significantly among the DENV subtypes [31, 32]. Glycosylation motifs have commonly been observed in domain I at the residue asparagine 153 (N153) or N154, but the addition of a glycan to these residues is not an absolute requirement for infectivity. Although glycosylation is not essential at these residues, several studies have shown that mutations that occur at N-linked glycosylation sites in the E glycoprotein can affect virus-mediated membrane fusion and neurovirulence [33–35]. Glycosylation mutants have been described for glycoproteins E. Differences in amino acids were noted between the four wild-type DENV serotypes at amino acid 154, which is glutamic acid in both DENV 1 [36] and DENV 3 [37], and aspartic acid in both DENV 2 [38] and DENV 4 [39]. Another N-linked glycosylation motif of DENV occurs at N67, which mediates the viral infection of dendritic cells bearing DC-SIGN receptors and is essential for viral assembly and exit [40, 41]. Removal of

the N67 glycan has been shown to severely affect viral fitness and to reduce cell infectivity [42].

The glycosylation of the DENV prM/M glycoprotein has not been extensively studied. The prM protein is fused to the ectodomain of the E glycoprotein [43] with a glycosylation modification at asparagine N69. Other potential N-linked glycosylation sites have also been identified at residues 7, 31, and 52. The glycosylation of prM may allow it to act as a chaperone for E protein folding in the ER, permit its association with the membrane, and allow it to act in the assembly of the E protein [44].

The glycosylation of NS1 begins when the monomer is altered within the ER lumen by the addition of high-mannose-type glycans at both N-linked glycosylation sites and its subsequent rapid dimerization [45, 46]. Pryor and Wright [47] demonstrated that when secreted NS1 was treated with endoglycosidase H, complex glycans attached at N130 and high-mannose glycans at N207, so both N130 and N207 are N-linked glycosylation sites. Further alterations of the carbohydrate moieties in the NS1 dimer occur in the Golgi apparatus before the protein is transported to the cell surface and released from the infected cell. Interestingly, the presence of a polymannose-type sugar on the dimer may protect one of the N-glycans from further maturation in the Golgi, without which the stability of the dimer and the secretion of the glycoprotein would be reduced [48]. The glycosylation of NS1 is essential for viral processes ranging from replication to virulence, but it is unclear at this point how glycosylation affects these processes [15, 49].

Overview of glycans: virus–glycan interactions

Carbohydrate chains, also known as glycans, are one of the four basic components of cells. They are remarkably structurally diverse [50] and usually exist as covalent linkages with saccharides that are conjugated to proteins (glycoproteins) or to lipids (glycolipids) on the cell surface. The glycans of mammals are well conserved, although species-specific variations occur. Because of these variations, glycans that are involved in pathogen–receptor interactions may determine the susceptibility of specific organisms to infectious pathogens [51]. Different types of glycans can be produced during glycosylation depending on the type of residues that are attached to the cellular proteins or lipids. The glycosylation of proteins involves N-glycans, O-glycans, and glycosaminoglycans, frequently known as proteoglycans. N-glycans are formed when they bind to a specific subset of N residues in proteins, located in the N–X–S/T motif, whereas O-glycans attach to subsets of serine and threonine residues [52, 53]. The linear glycosaminoglycans are also serine- and threonine-linked but are usually highly sulfated [54]. Lipid glycosylation is also a common modification in the secretory pathway that produces glycolipids, also known as glycosphingolipids, which include the sialic-acid-bearing gangliosides [55].

The propagation of a virus and disease progression depend on the direct interactions between the virus and the host cell receptors. Different viruses may have preferences for differ glycan moieties for their attachment. These can be charged glycan moieties, such as sialic acid, which are readily recognized by orthoreoviruses [56], rotaviruses [57], and influenza viruses [58]; heparan sulfate, recognized by herpes viruses [59] and parvoviruses [60]; or neutral glycans, such as histo-blood group antigens, which are bound by rotaviruses [61, 62] and noroviruses [63, 64]. The significant diversity in the recognition of specific glycans within a particular viral species, which arises from genetic differences, dictates the cell tropism, host specificity and adaptation, interspecies transmission, and pathogenesis of the virus.

Glycan interactions with DENV glycoproteins

Four major types of receptors in mammals are believed to be targeted by DENV. These are 1) carbohydrate molecules, 2) carbohydrate-binding proteins (also known as lectins), 3) factors related to protein folding, such as chaperones [65, 66] and heat shock proteins [67], and 4) other proteins, such as a high-affinity laminin receptor [68] and a CD14-associated protein [69]. However, in this review, we are focusing on molecules containing carbohydrate moieties (Table 2), so only carbohydrate and carbohydrate-binding protein receptors will be discussed.

Carbohydrate molecules as receptors

This group of receptors includes sulfated glycosaminoglycans (GAGs) and glycosphingolipids, which can act as coreceptor molecules, enhancing the efficiency of viral entry. Heparan sulfate is among the sulfated GAGs that are involved in the initial attachment of DENV to the cell surface, when the E glycoprotein binds to the molecule. Recently, Okamoto et al. [81] showed that a specific heparan sulfate proteoglycan, called syndecan-2, is a membrane heparan sulfate proteoglycan utilized by DENV as a receptor. Heparan sulfate is a linear repeating copolymer with variably sulfated uronic acid and glucosamine carbohydrate residues, and it is highly negatively charged [82]. It is found not only on the cell surface but also in the extracellular matrix [72].

Another type of carbohydrate molecule that has been reported recently is neolactotetraosylceramide (nLc4Cer), a glycosphingolipid with no sulfation. This carbohydrate

Table 2 Carbohydrate receptors targeted by DENV on mammalian and insect cells

Molecule	Type	Cell type	Serotype	References
DC-SIGN	C-type lectin	Monocyte-derived dendritic cells	DENV 1, 2, 3, and 4	[71]
Heparan sulfate	Glycosaminoglycans	Vero	DENV 2	[72]
		CHO K1		
nLc4Cer	Glycosphingolipid	K562	DENV 2	[73, 74]
		BHK-21		
		LLC-MK2		
Mannose receptor	Protein	NIH3T3	DENV 1, 2, 3, and 4	[75]
		Monocytes		
		Macrophages		
High-affinity laminin receptor	Protein	HepG2	DENV 1, 2 and 3	[68, 76]
		PS clone D		
CLEC5A	C-type lectin	Macrophages	DENV 1, 2, 3, and 4	[77]
L-3	Glycosphingolipid	AP-61	DENV 2	[74]
40- and 45-kDa glycoproteins	Glycoprotein	C6/36 cells	DENV 4	[78–80]

molecule may be a coreceptor of DENV and assist in the attachment of the virus to the host cell [73]. DENV interacts with this glycosphingolipid at the nonreducing terminus of Galβ1-4GlcNAcβ, which is expressed on the surface of susceptible cells, such as human erythroleukemia K562 and baby hamster kidney BHK-21 cells.

Carbohydrate-binding proteins

These proteins are commonly grouped with the C-lectins, which are expressed on dendritic cells and macrophages located under human skin. They are known to play an important role in the initial contact with DENV, after it is introduced by a mosquito bite. The best-characterized lectin involved in the interaction between the virus and dendritic cells is dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN). DC-SIGN is classified as a member of the calcium-dependent C-type lectin family and has affinity for the high-mannose glycans found on different pathogens, including Ebola virus [83], hepatitis C virus [84], human immunodeficiency virus (HIV) [85], and several parasites, yeasts, and bacteria [86]. The interaction between DC-SIGN and DENV occurs through the high-mannose N-linked glycans found on the E glycoprotein [40, 87]. This interaction has been confirmed in studies by Navarro-Sanchez et al. [70] and Tassaneetrithep et al. [71] in which both groups successfully inhibited DENV infection by introducing soluble DC-SIGN and antibodies directed against DC-SIGN. However, the internalization of DC-SIGN is not essential for DENV infection [88], so the lectin may not function as a specific receptor but may allow the attachment and concentration of the virus on the cell surface.

This phenomenon can be explained by studying the attachment of the E glycoprotein to the carbohydrate moiety of DC-SIGN. When the E glycoprotein binds to the carbohydrate-recognition domain of DC-SIGN, there is no conformational change in the E glycoprotein of the mature virus, even though such changes are observed when full-length DC-SIGN molecules bind to the glycoprotein. However, this binding leaves a single E glycoprotein in the asymmetric unit vacant, and the putative receptor-binding domain III present in each E glycoprotein is free to bind the receptor at the icosahedral fivefold and threefold axes [40]. Because DC-SIGN is in an oligomeric state on the surface of the cell, occurring as a tetramer when interacting with the virus, the binding of DC-SIGN could promote viral clustering on the cell surface and facilitate its binding to the receptor. It has been proposed that the interaction of carbohydrate moieties with DC-SIGN mimics normal cellular processes and therefore protects the receptor-binding domain of the E protein from the host's immune surveillance and neutralization.

Lectin receptors on macrophages

Macrophages bear other C-type lectin receptors, the mannose receptor and C-type lectin domain family 5 member A (CLEC5A). The mannose receptor has been shown to bind DENV, Japanese encephalitis virus, and tick-borne meningoencephalitis virus by a mechanism similar to the mechanism of DC-SIGN binding. However, the ligand specificity of the mannose receptor differs from that of DC-SIGN in that its ligands are terminal mannose, fucose, and N-acetyl glucosamine rather than high-mannose oligosaccharides and fucosylated glycans. It has been hypothesized

that the mannose receptor is more than just an attachment molecule for DENV because it is internalized into cells during infection and is found mainly in the endocytic pathway, unlike DC-SIGN, which is mainly restricted to the plasma membrane [75].

CLEC5A, also called myeloid DAPI2-associating lectin (MDL-1), is classified as a type II transmembrane receptor and is found on the surface of macrophages and monocytes [89]. The receptor contains a C-type lectin-like domain in its C-terminal extracellular region and has only four amino acids in its predicted N-terminal cytoplasmic region. The receptor is recognized as a potential DENV receptor. The binding of DENV to CLEC5A contributes significantly to the mortality associated with DENV infection by triggering excessive macrophage activation. Chen et al. [77] demonstrated that the survival rate in mice increased when CLEC5A was blocked. Both human and mouse CLEC5A are reported to bind DENV and the interaction is inhibited by mannose and fucose in vitro.

Viral glycosylation processes as therapeutic targets

Understanding the mechanisms that contribute to the invasion of host cells, as discussed above, may clarify how specific agents that interrupt or modify viral replication or expression can be used to limit the damage caused during infection. The synthesis of N-glycans may be interrupted at several stages by the inhibition of specific enzymes. In the rough ER, tunicamycin inhibits the transfer of the trimannose core to asparagine residues. The removal of terminal glucose residues may be blocked by nojirimycin or castanospermine [90], and the phosphatase-mediated conversion of the dolichylpyrophosphate released by glycosidic cleavage is inhibited by bacitracin. Brefeldin A inhibits the transport of the resultant high-mannose N-glycans to the Golgi apparatus, and further processing by mannosidase enzymes may be affected by deoxymannojirimycin or swainsonine [91, 92]. Deoxynojirimycin is an inhibitor of ER α-glucosidase and disrupts the trimming of

Table 3 Properties and specificities of carbohydrate-binding agents derived from plants used to target viruses

Acronym	Source of lectin	Common name	Major specificity	Virus	References
HHA	*Hippeastrum* hybrid	Amaryllis bulbs	α1,3-mannose and/or α1,6-mannose	SIV, HCV, DENV1–4	[94–96]
GNA	*Galanthus nivalis*	Snowdrop	High-mannose structures, multiple terminal mannose α1,3-mannose	HCV, HIV-1, DENV1–4	[94, 96]
ConA	*Canavalia ensiformis*	Jack bean	Terminal mannosyl residues	DENV2	[97]
NTL	*Narcissus tazetta* var. *chinensis*	Chinese daffodil	Similar to GNA	RSV, various strains of influenza virus A and B	[98, 99]
NPA	*Narcissus pseudonarcissus*	Daffodil or Lent lily	α-D-mannose	HIV-1	[100]
CA	*Cymbidium* hybrid	Cymbidium (orchid)	Mannose-specific, D-mannose	HIV-1 and 2, CMV, influenza A, HCV	[94, 101]
EHA	*Epipactis helleborine*	Broad-leaved helleborine	Mannose-specific, D-mannose	HIV-1 and 2, CMV, influenza A	[101]
TDL	*Typhonium divaricatum* (L.) Decne	Rodent tuber	Mannose-specific	HSV-2	[102]
SGM2	*Smilax glabra*	Sarsaparilla	Mannose and/or mannan	HSV-1, RSV	[103]
PpeL	*Parkia pendula*	Acacia (male)	Terminal mannosyl residues, glucose	CMV, herpes virus 6	[104]
PCL	*Polygonatum cyrtonema*	Giant Chinese Solomon's seal	Mannose and sialic acid	HIV-1 and HIV-2	[105]
BanLec	*Musa acuminate*	Banana	High-mannose structures	HIV-1	[106]
WGA	*Triticum vulgaris*	Wheatgerm	GlcNAc oligomers, N-acetyl lactosamine, some sialic acid residues	DENV2	[107]
UDA	*Urtica dioica*	Stinging nettle root	GlcNAc oligomers, Galβ1,4-GlcNAcβ1	CMV, coronaviruses, SIV, DENV1–4	[95, 96, 101, 107]
JFL	*Artocarpus heterophyllus*	Jackfruit	*N*-acetyl-α-D-galactosamine	HSV-2, VZV, CMV	[108]

SIV = simian immunodeficiency virus; CMV = cytomegalovirus; DENV = dengue virus; HIV = human immunodeficiency virus; RSV = respiratory syncytial virus; HSV = herpes simplex virus; VZV = varicella-zoster virus

terminal glucose, thus affecting the subsequent folding pathways of DENV glycoproteins prM and E [44, 93].

Targeting virus–carbohydrate receptor interactions with plant lectins

Plant lectins, also known as carbohydrate-binding agents (CBAs), have recently emerged as potent agents for treatment of DENV infection, targeting the initial attachment of the virus to cells. Several CBAs with unique properties and specificities (Table 3) have been identified and used to block viruses. Most of these lectins bind specifically to mannose moieties, ranging from terminal mannosyl residues to high-mannose glycans, which are targeted by a wide range of viruses [94–106].

The antiviral activities of these CBAs against DENV have recently been explored, particularly the lectins of *Hippeastrum* hybrid (HHA), *Galanthus nivalis* (GNA), and *Urtica dioica* (UDA), which were initially found to inhibit the interaction between HIV and DC-SIGN-expressing cells [100]. The same CBAs have also been shown to dose-dependently inhibit the interaction between all four serotypes of DENV and DC-SIGN in Raji/DC-SIGN+ cells and monocyte-derived dendritic cells [96]. Binding assays have shown that these CBAs do not interact with cellular membrane proteins but instead interact directly with the viral glycosylated envelope proteins [109]. Concanavalin A (ConA) and wheat-germ agglutinin reduce the development of plaque induced by DENV in BHK cells [97]. A competition assay using mannose showed that the inhibitory effect of ConA results from its binding to α-mannose residues on the viral protein. However, these lectins do not completely inhibit DENV when introduced individually to infected cells. Therefore, further studies of the effects of combinations of CBAs are required.

Concluding remarks

The importance of DENV glycosylation and its interaction with carbohydrate receptors warrants further investigation to develop an efficient treatment for DENV-related diseases. Available drugs that disrupt protein glycosylation will result in the incomplete maturation of DENV. In cases of severe dengue infection, where DENV replication can be enhanced by an antibody-dependent enhancement mechanism [110], these drugs are anticipated to be effective in limiting viral replication, thus reducing the viral load, which may lessen the severity of the disease. The aforementioned drugs are designed to inhibit human glycosylation enzymes, but whether the same drugs can elicit similar effects on the glycosylation enzymes of DENV vectors must be explored further. To date, no studies have specifically explored the DENV protein glycosylation processes in mosquitoes. However, Mason [111] demonstrated the ability of mosquito cell lines to release the mature and glycosylated E glycoprotein and NS1 of Japanese encephalitis virus, another member of the family *Flaviviridae*, Therefore, it is predicted that DENV also undergoes glycosylation in the mosquito, and glycosylation inhibitors are anticipated to be effective to some degree.

Although drugs that disturb the glycosylation process during the formation of viral glycoproteins may seem useful in this context, the same drugs may also disturb the glycosylation of cellular glycoproteins. However, CBAs or lectins act directly on the viral interaction at the cell surface and need not fuse with the cell to exert their antiviral activities. Therefore, it is anticipated that CBAs will not interfere with the synthesis of glycans on cell-surface glycoproteins. The potential utility of lectins as antiviral agents seems promising. The antiviral potency of lectins against each virus may differ because their three-dimensional conformations differ, or because the availability of glycan conformations with the proper carbohydrate moieties differs across viral proteins. Several challenges must still be addressed, such as the high cost of the purification and mass production of lectins, their storage and stability, bioavailability, and cellular toxicity. However, these issues may be resolved by designing synthetic CBAs that are structurally similar to the natural molecules but stable and nontoxic. Several synthetic molecules are already available [112, 113], providing a basis for the further exploration of potentially therapeutic CBAs. Drug delivery using especially designed capsules or nanocarriers may also be a useful strategy to combat bioavailability problems. Based on these factors, CBAs should be considered a valuable class of antiviral agents that warrants further investigation and eventual application in the clinical setting.

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