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Review

Dengue virus receptor

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Abstract: Dengue virus is an arthropod-borne virus transmitted by *Aedes* mosquitoes. Dengue virus causes fever and hemorrhagic disorders in humans and non-human primates. Direct interaction of the virus introduced by a mosquito bite with host receptor molecule(s) is crucial for virus propagation and the pathological progression of dengue diseases. Therefore, elucidation of the molecular mechanisms underlying the interaction between dengue virus and its receptor(s) in both humans and mosquitoes is essential for an understanding of dengue pathology. In addition, understanding the molecular mechanism(s) of virus entry is crucial for the development of effective new therapies to treat dengue patients. Binding of dengue virus to its receptor molecules is mediated through a viral envelope glycoprotein, termed E protein. We present a summary and describe the structures, binding properties, and pathological relevance of dengue virus receptor molecules proposed to date. In mammalian cells, there are many candidate molecules that may act as receptors, such as sulfated glycosaminoglycans (GAGs), lectins that recognize carbohydrates, glycosphingolipid (GSL), proteins with chaperone activity, laminin-binding proteins, and other uncharacterized proteins. There are also several lines of evidence for receptor molecules such as GSLs, proteins with chaperone activity, laminin-binding proteins, and other uncharacterized proteins in mosquito cells and organs. This review focuses on several molecules involved in carbohydrate-dependent binding of the virus.
Key words: Dengue virus, Receptor, Lectin, Carbohydrate, Glycosaminoglycan

INTRODUCTION

Epidemic dengue virus (DENV) has rapidly expanded its range through tropical and subtropical regions in recent years. This pathogen causes febrile illness (dengue fever, DF) and severe bleeding disease (dengue hemorrhagic fever, DHF) in humans. DF and DHF, with an estimated annual infection rate of 100 million and approximately 500,000 deaths, are the most infectious diseases in tropical and subtropical regions. Dengue virus is transmitted between humans and the arthropod host (mosquito), forming a distinctive ring and showing that humans are not the terminal host. Infection of humans with the virus is primarily mediated by the *Aedes* mosquito. The virus grows in the mosquito gut and migrates to the salivary glands. When an infected mosquito feeds on a healthy person, the virus is inoculated subcutaneously [1–3]. Dengue virus primarily propagates in skin dendritic cells, and subsequently virus proliferation is thought to occur in target cells such as those of the monocyte/macrophage lineage [4].

There are four dengue virus serotypes, *i.e.*, types 1–4. Neutralizing antibodies are specifically induced by initial infection with each virus serotype, and lifelong immunity is established for the same type of virus. In most cases of initial infection, the host develops dengue fever, which has a mild prognosis. Cross-neutralizing antibodies against different serotypes disappear within a short period, and a virus of another serotype may cause reinfection (secondary infection). When secondary infection by a different serotypes occurs, the immune complexes of the viruses with cross-reactive antibodies produced during primary infection enhance viral infection mediated through Fcγ receptor-dependent incorporation of the virus into host cells. There is a strong possibility that such a progressive response contributes to more severe manifestations, such as DHF and dengue shock syndrome [5–10].

Dengue virus is an enveloped virus about 50 nm in diameter. The envelope glycoprotein (E protein) is present

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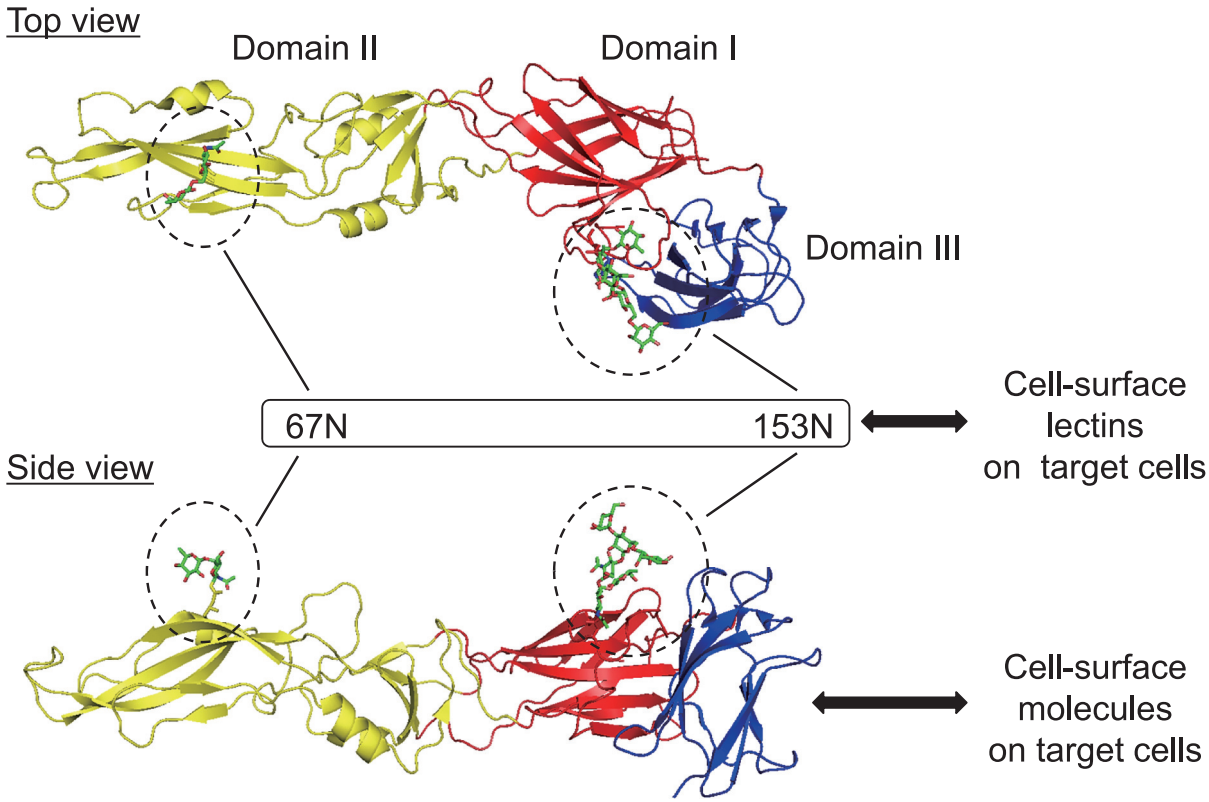

Fig. 1. DENV E protein interacts with lectin and other molecules expressed on the host cell surface. *N*-Glycan at position 67 is recognized by DC-SIGN, and *N*-glycans at positions 67 and/or 153 may be associated with host lectin proteins, such as mannose-binding protein. E protein consists of three functional domains. Domain I (red) is a flexible hinge region that contributes to the conformational change of the protein under low pH conditions in endosomes. Domain II (yellow) contains hydrophobic amino acid residues that form a fusion loop at the tip of the domain. In addition, this domain may contribute to dimerization of the protein on the mature virus membrane. Finally, domain III (blue) is thought to be responsible for the direct interaction with host receptor molecules. The structure represents E protein of DENV3, which was modeled using PyMol with PDB accession number 1UZG.

on the viral membrane (Fig. 1). E protein is a functional protein molecule that binds to receptors on the host cell membrane; it is also a major antigen against host protective immunity, which induces neutralizing antibody [11–13]. E protein is divided into three functional domains, termed domains I, II, and III. Domain I, the hinge region, is linked to the two other functional domains. The high mobility of this region is responsible for the changes in structure of E protein due to variations in external pH. Domain II has a hydrophobic-rich peptide sequence featuring the membrane fusion activity and contributes to E protein dimerization [14–16]. Domain III is thought to be involved in the binding to receptor molecules present on the host cell membrane (Fig. 1). During viral infection, the adsorption of viral particles is initiated by binding of E protein to receptor molecules present on the host cell membrane. Subsequently, the adsorbed viruses are taken into the cell by endocytosis. The pH decreases inside endosomes formed by fusion with lysosomes, and the viral membrane is fused with the endosomal membrane mediated through the action of the E protein fusion peptide. Eventually, the nucleocapsid enters the cytoplasm, and the virus genome is released into the cytoplasm.

Direct interaction of the virus with host receptor molecule(s) is crucial for virus propagation and the pathological progression of dengue diseases. Elucidation of the molecular mechanisms underlying interaction of dengue virus with its receptor(s) in humans and mosquitoes is essential for an understanding of dengue pathology. To date, many candidate molecules have been proposed as dengue receptors. In this review article, we present a summary and describe the structures, binding properties, and pathological relevance of dengue virus receptor molecules proposed in these previous studies.

DENGUE VIRUS RECEPTORS IN MAMMALIAN CELLS

Halstead et al. first demonstrated that dengue virus infection in human peripheral blood leukocytes was enhanced by the presence of non-neutralizing antibody [5–10]. This enhancement was mediated through Fcγ receptors expressed on leukocytes. These findings indicated that Fc receptor-mediated entry is involved in secondary infection, particularly infection with a serotype different from that involved in primary infection. With regard to primary infection and initial contact of the virus with host cells, investigations to identify receptor molecules have been performed in mammalian cells. Table 1 presents a summary of dengue virus receptors in mammalian cells proposed in previous studies. The candidate molecules can be categorized into four major groups. First, carbohydrate molecules such as sulfated glycosaminoglycans (GAGs) and glycosphingolipid (GSL) are thought to act as co-receptor molecules, which enhance the efficiency of virus entry. Among the sulfated GAGs, heparan sulfate is indispensable for virus adsorption to the host cells [17–19]. Another type of carbohydrate molecule has recently been reported to contribute to virus attachment; neolactotetraosylceramide (nLc4Cer), a GSL without sulfation, may also be a co-receptor on the host cells [20]. Native and (semi)synthetic forms of carbohydrate compounds derived from GAG and GSL structures successfully inhibited DENV infection of different cell types [17–20, 21]. These findings strongly suggest that carbohydrate molecules in the extracellular matrix are positively involved in DENV propagation in target cells. Second, carbohydrate-binding proteins, termed lectins, expressed on dendritic cells (DCs) and macrophages under the human skin are involved in initial contact of DENV introduced by mosquito bite. Among these lectins, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) has been best characterized in virus-DC interaction [22–24]. Cryoelectron microscopic analysis demonstrated that recombinant lectin protein binds directly to *N*-glycans at position of 67 of E protein expressed on viral particles (Fig. 1). DC-SIGN-mediated entry allows DENV to propagate in DC, meaning that DC is the primary target for DENV. A recent study showed that another lectin, mannose receptor, contributes to the entry of DENV into macrophages [25]. Taken together, the above observations indicate that carbohydrate recognition events are associated with DENV propagation in the human body. Third, factors related to protein folding, such as heat shock proteins [26] and chaperones [27–29], may also be involved in the interaction of DENV serotype 2 (DENV-2) and host cells. It has been reported that a single serotype, DENV-2, bound these molecules. Fourth, independent studies showed that other

Table 1. Dengue virus receptors (mammalian) proposed in the previous studies

Receptor	Properties	Cell/Tissue expression	Serotype	References
Heparan sulfate	Sulfated glycosaminoglycan	Vero cells, BHK-21 cells SW-13 cells	DENV1–4	17–19
nLc_4Cer	Glycosphingolipid	Vero cells, BHK-21 cells, K562 cells	DENV1–4	20
DC-SIGN/L-SIGN	Dendritic cell-specific lectin, CD209	Dendritic cells, Macrophage	DENV-1–4	22–24
Mannose receptor	Protein with lectin activity	Macrophage	DENV-1–4	25
HSP70/HSP90	Expression on plasma membrane Heat-shock proteins	HepG2 cells, SK-SY-5Y cells, Macrophage	DENV-2	26
GRP78	Expression on plasma membrane Chaperon	HepG2 cells	DENV-2	27–29
Laminin receptor	High-affinity laminin receptor MW: 37/67 kDa	PS Clone D cells, HepG2 cells	DENV-1–3	30, 31
CD14-associated protein	Protein associated with LPS receptor	Monocyte, Macrophage	DENV-2	32
Unknown glycoproteins	CHO-dpd binding MW: 44/74 kDa	Vero cells	DENV-4	33
Unknown protein	Trypsin-resistant MW: 29 kDa	ECV304 cells	DENV-2	34
Unknown protein	Trypsin-sensitive MW: 65 kDa	N1E-115 cells SK-N-SH cells	DENV-2	35
Unknown proteins	Serotype-specific binding MW: 78-182 kDa	HepG2 cells	DENV-2–4	36

Mw: molecular weight of interested protein.
CHO-dpd binding: carbohydrate-dependent binding.

proteins, including high-affinity laminin receptor [30, 31], CD14-associated protein [32], and uncharacterized proteins [33–36], may also be involved in DENV—host cell interaction. Some of these proteins reported to date may be identical with regard to properties, such as molecular mass. Some of the proposed receptors are commonly recognized by different serotypes of DENV, while others seem to interact specifically with a certain serotype of DENV. These findings strongly suggest that DENV binds multiple molecules that may form complexes on host cells, and that DENV uses specific combinations of receptor candidates to enter different types of cell. However, the nature of cellular receptors and molecular mechanisms for dengue virus entry has not yet been fully elucidated.

DENGUE VIRUS RECEPTORS IN MOSQUITO CELLS

Table 2 summarizes the major receptor molecules proposed in previous studies. In contrast to mammalian receptors, candidate molecules in mosquitoes are mostly proteins. Virus overlay protein binding assay demonstrated that particular proteins with certain molecular masses reacted on the membrane specifically with DENV particles or recombinant E protein in some cases. Laminin-binding protein from C6/36 cells is a possible high-affinity laminin receptor which is analogous to a molecule proposed as a receptor in mammalian HepG2 cells [37]. Several lines of evidence suggested that HSP90-related proteins may be receptor molecules in a mosquito cell line as well as organs such as the salivary glands, midgut, and ovary [38–41]. These studies also revealed receptor candidates with similar protein properties in two different species of mosquitoes, *Aedes albopictus* and *Aedes aegypti*, which can commonly transmit DENV to humans. However, the properties of the proposed proteins have not been fully determined [42–47]. Similar to mammalian receptors, a recent study showed that GSLs specifically related to mosquitoes reacted with DENV-2 particles [48]. However, previous studies demonstrated that heparin, one of the GAGs, did not bind to DENV, indicating that sulfated polysaccharides do not contribute significantly to DENV entry into mosquito cells [21, 37]. Thus, the nature of the mosquito receptors has yet to be elucidated, and further investigations are required to identify these molecules.

OTHER FLAVIVIRUS RECEPTORS

Previous studies demonstrated that two encephalitis flaviviruses, Japanese encephalitis virus (JEV) and West Nile virus (WNV), bind to sulfated GAGs, such as heparin sulfate and chondroitin sulfate E [17, 19]. These observations indicated that these sulfated polysaccharides may be commonly recognized by flaviviruses regardless of virus type in mammalian cells. Among protein candidates in mammalian cells, the best characterized is integrin $\alpha_v\beta_3$ as a receptor for WNV [49]. This heterodimer protein seems to be specifically recognized by WNV, but not DENV or JEV. In mosquito cells, there are several proteins that have been

Table 2. Dengue virus receptors (*Aedes* mosquito) proposed in the previous studies

Receptor	Properties	Cell/Tissue expression	Serotype	References
Laminin-binding protein	Possible high-affinity laminin receptor Mw: 50 kDa	C6/36 cells (*A. albopictus*)	DENV-3,4	37
Unknown glycoprotein	Cell-surface protein, CHO-indp binding HSP90-related protein Mw: 40, 45 and 74 kDa	C6/36 cells (*A. albopictus*) Salivary glands, midgut, ovary, malpighian tubules (*A. aegypti*)	DENV-2,4	38–41
Ar_3Cer nLc_4Cer	Neutral glycosphingolipids	C6/36 cells (*A. albopictus*)	DENV-2	42
Prohibitin	Membrane-associated protein Mw: 35 kDa	C6/36 cells (*A. albopictus*) CCL-125 cells (*A. aegypti*) Mosquito whole body (*A. aegypti*)	DENV-2	43
Tublin-like protein	Cytosolic protein Mw: 48 kDa	C6/36 cells (*A. albopictus*)	DENV-2	44
Unknown proteins	Cell-surface proteins Mw: 67 and 80 kDa	C6/36 cells (*A. albopictus*) Midgut (*A. aegypti*)	DENV-1–4	45, 46
Unknown protein	Cell-surface protein Marker of vector competence Mw: 67 kDa	Midgut (*A. aegypti*)	DENV-2	47
Unknown proteins	Several detergent-soluble proteins Mw: 35–80 kDa	Salivary glands (*A. aegypti*, *A. polynesiensis*)	DENV-1–4	48

Mw: molecular weight of interested protein.
CHO-indp binding: carbohydrate-independent binding.

Table 3. Other flavivirus receptors proposed in the previous studies

Receptor	Properties	Cell/Tissue expression	Virus	References
Heparan sulfate	Sulfated glycosaminoglycan	Vero cells, BHK-21 cells	JEV	17
Chondroitin sulfate E	Sulfated glycosaminoglycan	Vero cells, BHK-21 cells	JEV	19
Integrin $\alpha_v\beta_3$	Cell-surface proteins, Protease sensitive Mw: 105 kDa	Vero cells, BHK-21 cells	WNV	49
Unknown proteins	Membrane-associated proteins, Mw: 50–150 kDa	C6/36 cells (*A. albopictus*)	JEV	50
CqOR7	Odorant receptor	Olfactory tissues (*Culex quinquefasciatus*)	WNV	51
Unknown glycoprotein	Plasma membrane-associated protein Mw: 70 and 95 kDa	C6/36 cells (*A. albopictus*)	WNV JEV DENV-2	52

Mw: molecular weight of interested protein.

proposed as receptors for WNV [50–52]. However, the nature of these proteins in mosquito cells is yet to be fully elucidated. These other flavivirus receptors proposed are listed in Table 3.

CONCLUSION

Dengue virus is transmitted from human to human by mosquitoes. Thus, this virus can efficiently infect and proliferate in both humans and mosquitoes as hosts. Over the past 30 years, many studies have been performed to identify and characterize host receptor(s) for dengue virus. Several molecules have been proposed as possible receptors in human and mosquito cells and tissues.

In mammalian cells, sulfated glycosaminoglycans (GAGs), lectins that recognize carbohydrates, glycosphingolipid (GSL), laminin-binding proteins, GSLs, chaperone proteins, and undefined proteins have been reported as candidates. Independent studies by different groups strongly suggested that heparan sulfate and DC-SIGN are indispensable for dengue virus infection in humans. Heparan sulfate is thought to be a co-receptor, which associates with other molecules to form functional complexes and enhances the efficiency of virus infection into host cells. DENV infects dendritic cells mediated through DC-SIGN specifically expressed on the cells. As virus-infected dendritic cells move to the peripheral lymph nodes where the virus is propagated and disseminated into blood, this molecule acts as the primary receptor for the virus. Several studies supported the suggestion that carbohydrate molecules in extracellular matrix are strongly related to DENV receptors.

One of the major differences from the case of mammalian cells is the fact that GAGs are not significantly involved in viral infection of mosquito cells. To date, laminin-binding proteins, GSLs, and other undefined proteins have been proposed in mosquito cells and organs. These findings suggested that molecules distinct from those in mammals contribute to interaction between the virus and host cells in mosquitoes.

Elucidation of the molecular mechanisms underlying the interaction of dengue virus with receptor(s) in humans and mosquitoes is essential for an understanding of dengue pathology. In addition, understanding the molecular mechanism(s) of virus entry is crucial for the development of effective new therapies to treat dengue patients. Further investigations to elucidate the nature of the molecular complex of DENV receptor are required.

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