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A REVIEW OF DENGUE VIRUS GENOME, STRUCTURAL AND NON-STRUCTURAL PROTEINS, AND LIFE CYCLE

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Abstract

The dengue virus-infected *Aedes* mosquito bites that cause dengue fever and propagate the potentially fatal disease. Dengue virus infection poses a risk to over 3.9 billion individuals worldwide. Its widespread incidence is currently a significant health issue. A pathogenic creature with a unique nucleotide sequence in its genome provides instructions for RNA or DNA synthesis, and protein expression, also for the organism's survival and evolution. New species or strains that are potentially more virulent than their parent strains can emerge as a result of mutations or changes in the nucleotide sequence. In this review, we have discussed the structural organization, genome, proteins, and life cycle of dengue virus. We describe in detail the structural and non-structural proteins and their functions. We describe the organization of viral RNA; it consists of one open reading frame (encodes a single polyprotein), 5' UTRs with 5' capping, and 3' UTR without poly 'A' tail. We have described in detail the life cycle of the dengue virus. This will aid in a better understanding of dengue virus organization, and life cycle.

Keywords: Dengue virus, genomics, proteomics, structural proteins, non-structural proteins, life cycle.

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Introduction

The dengue virus is the most widespread form of the arbovirus family that uses positive sense ssRNA. It belongs to the genus Flavivirus under the family Flaviviridae (WHO, 2022). This mosquito-borne virus, carried predominantly by female *Aedes aegypti* and *Aedes albopictus*, causes severe illness in animals. Mosquitoes in tropical and subtropical areas are the vectors for all of these viruses (Vogels *et al*., 2019). Over one hundred million symptomatic cases of dengue fever are recorded every year (Messina *et al*., 2014), making it a hazard to more than half the world's population. There are four distinct serotypes of the virus, designated DENV1 through DENV4, and each of these serotypes elicits a unique immune response (Thomas *et al*., 2014; Thomas *et al*., 2019).

Because each serotype has a unique antigenic composition, infection with any given serotype will only provide temporary cross-protection against other serotypes while providing lifelong immunity against that specific serotype. In high-density DENV locations, various serotypes circulate (Messina *et al*., 2014). Although this kind is more prevalent in wild areas than in cities, researchers in Sarawak, Malaysia, found a novel fifth serotype from a patient in 2007 (Normile, 2013). There may be more than 6% variation across the four DENV serotypes, although they all share at least 65% of their genetic makeup (Shrivastava et al., 2018). Because successive heterotypic infections are usually more severe after initial infection with a single serotype, it is exceedingly challenging to create vaccines against these diseases (Thomas and Yoon, 2019; Martinez *et al*., 2020; Gallichotte *et al*., 2018).

Although a lot of work has been done in this area during the past few decades. Dengvaxia is the only dengue vaccine currently on the market with regulatory approval. The 'Dengvaxia' live attenuated tetravalent chimera vaccination protects only occasionally against a single serotype. However, those who have the infection are less likely to be protected because of an imbalanced immune response (Thomas and Yoon, 2019).

Structure of dengue virus

Dengue virus is a spherical and enveloped virus (Figure 1). A smooth surface has been found on mature DENV with a diameter of 50 nm, whereas a spiky surface has been present in immature virion with a diameter of 60 nm (Perera and Kuhn, 2008; Uno and Ross, 2018). On the mature virion's surface, the membrane protein is located beneath the E protein. The mature DENV has a smooth, icosahedral

structure, while the immature form includes a prM protein that forms projecting trimers with E, giving it a "spiky" appearance (Figure 1) (Zhang *et al.*, 2003b). The dengue virus is composed of a lipid bilayer, an exterior shell with well-ordered icosahedral symmetry, and nucleocapsid proteins that are poorly organized (Kuhn *et al.*, 2002).

Above the capsid protein are the lipid bilayer and the outer protein shell. During cryo-electron microscopy imaging, it is challenging to separate the viral RNA from the capsid because it is not as well organized as the other structural proteins (Zhang *et al.*, 2003a).

The envelope glycoprotein (E), one of the three structural proteins, serves as a receptor's binding and fusion site and according to Chambers *et al.* (1990), is the primary site of neutralizing antibodies. It is a flattened class II fusion protein with 90 E dimers that is present on the surface of the virion (Kuhn et al., 2002).

A positive sense ssRNA with a length of 11,000 nucleotides (between 9.4 kb and 13 kb) makes up their genetic material. One large polyprotein is encoded by its single open reading frame (ORF) (Figure 2). The polyprotein's N and C terminals, respectively, include three structural proteins and seven structural proteins (Figure 2). The process of viral replication is controlled by non-structural proteins, whereas structural proteins help to create the DENV virion component. DENV ss-RNA has 5'UTR (untranslated region) with type I capping at the end of 5' end and 3'UTR lacks a 3' poly 'A' tail (Chambers *et al.*, 1990).

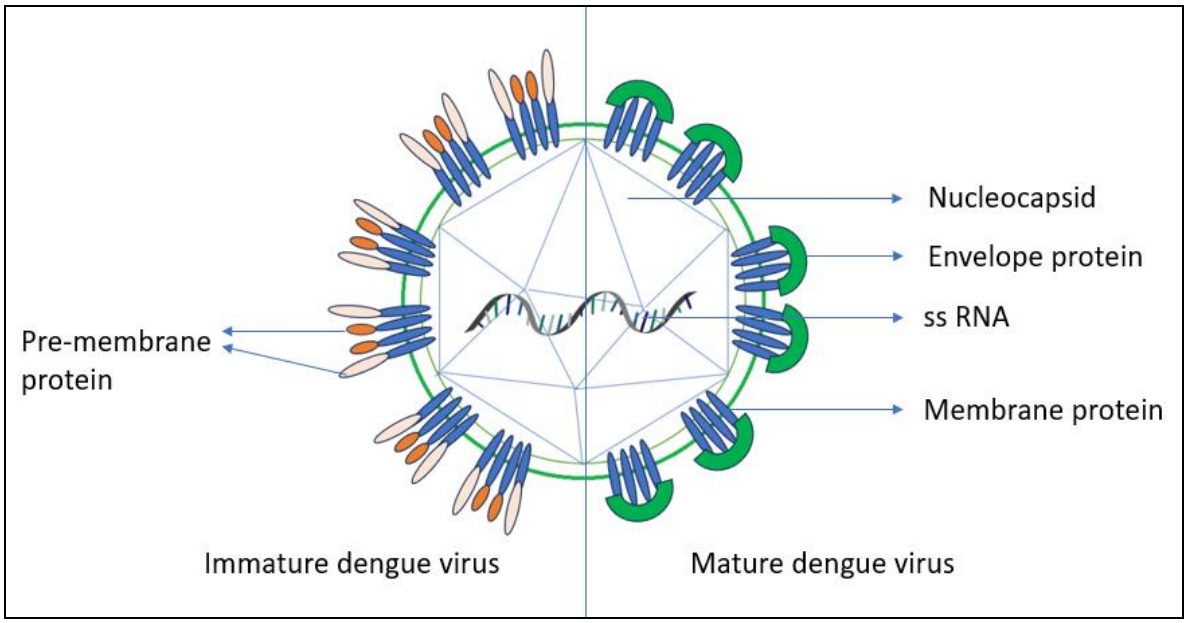

Fig. 1 : Schematic illustration showing dengue virus structure and difference between mature and immature virus portion

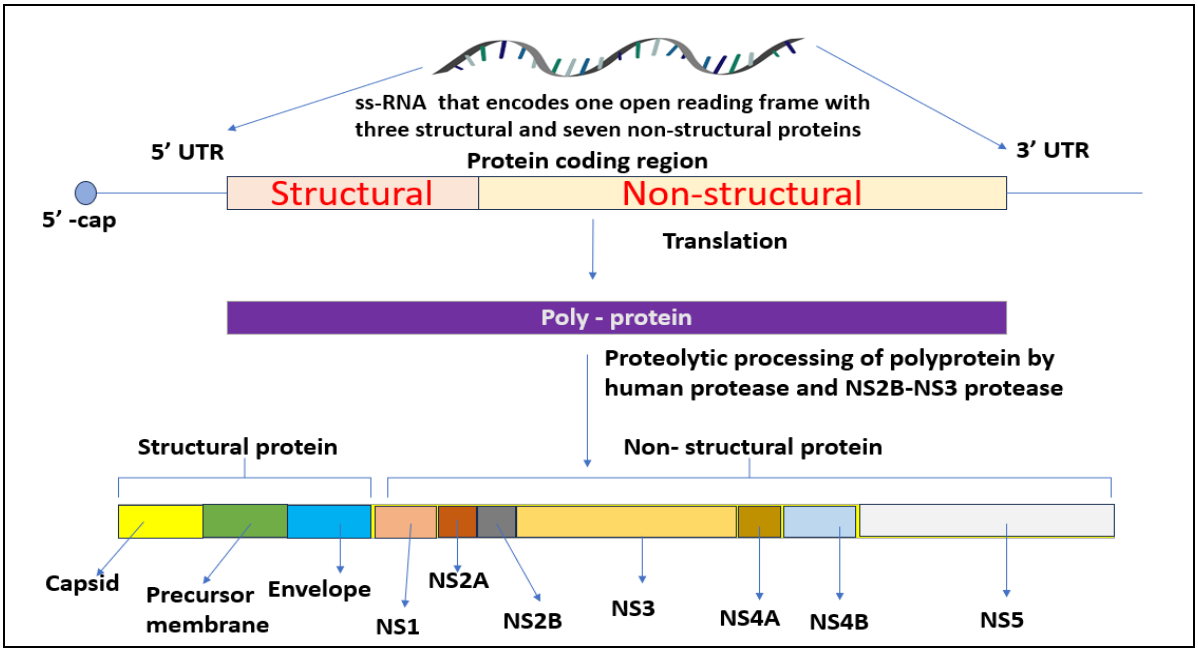

Fig. 2 : Schematic illustration showing dengue virus + ss-RNA (5' UTR with 5'capping and 3'UTR without Poly 'A' tail) and polyprotein processing by human protease and viral protease NS2B-NS3 to form three structural proteins and seven non-structural proteins. UTR- Untranslated regions.

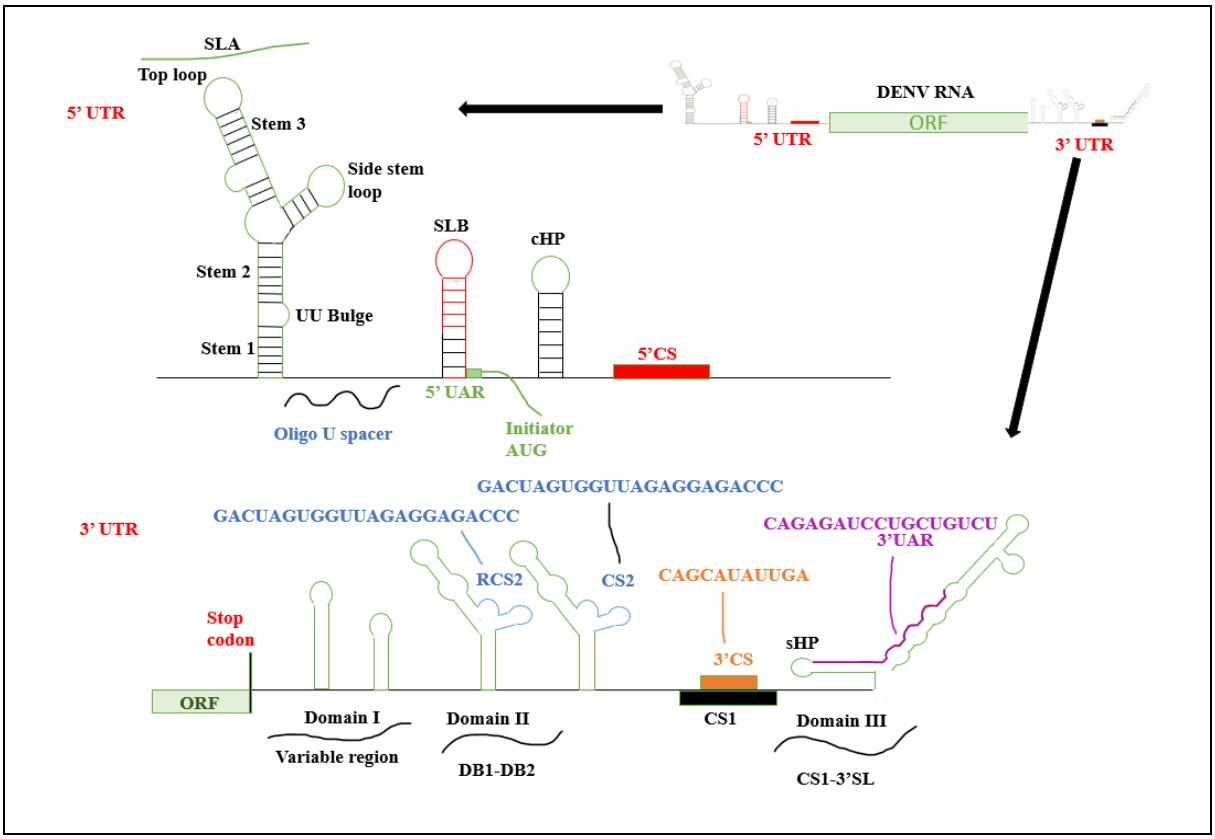

Fig. 3: Diagrammatic representation of the DENV genome 5' UTRs and 3'UTR regions(Gebhard *et al.*, 2011).

Genome

The genome of a pathogenic organism stores the information necessary for its existence and evolution, including the instructions for making RNA or DNA and expressing proteins.

Due to mutation or an alteration in the nucleotide sequence, new strains may evolve that are more virulent than the original strain. Despite their serological differences, all DENV strains have a common polyprotein that is transcribed from the same RNA genome.

DENV genome contains approximated 11 kb genome and it consists of 5' UTRs with type I capping and 3' UTRs without poly 'A' tail. The translation and replication of the DENV viral genome depend heavily on its untranslated regions (UTRs) (Gritsun *et al.*, 1997; Weaver and Vasilakis, 2009; Alcaraz-Estrada *et al.*, 2010).

The 5' UTRs of the DENV genome range in length from 95 to 101 nucleotides and are composed of two RNA domains that perform many tasks during genome construction. The initial domain of 5' UTRs folds into a large stem-loop-A (SLA) of 70 nucleotides. For the production of the non-structural protein NS5 of DENV, this SLA acts as a promotor for the RNA-dependent RNA polymerase (RdRp) (Figure 3). Nasar *et al.*, (2020) state that the NS5 protein's N-terminal region acts as a methyltransferase while the C-terminal region acts as an RNA-dependent RNA polymerase. As previously reported (Filomatori *et al.*, 2006; Yu *et al.*, 2008), RdRp interaction with SLA is required for dengue viral RNA synthesis.

The second 5' UTRs RNA domain folded into a short stem-loop (SLB). Alvarez *et al.* (2005a), Clyde *et al.* (2008), Polacek *et al.* (2009a), and Gamarnik (2010) all point to specific nucleotide sequences in this region as being essential for RNA duplication and long-range RNA-RNA interaction.

The length of the DENV 3' UTRs is roughly 450 nucleotides (Figure 3), and it is divided into three distinct domains. Domain I (Figure 3) immediately follows the termination codon and is the most dynamic part of the 3' UTRs (Alvarez *et al.*, 2005b). Sizes range from >120 nucleotides to 50 nucleotides with considerable variation between DENV serotypes (Shurtleff *et al.*, 2001; Clyde *et al.*, 2008).

According to several studies, the second domain (Domain II, Figure 3) of DENV 3' UTRs contains a unique dumbbell (DB) structure with tandem duplications (Shurtleff *et al.*, 2001; Zhou *et al.*, 2006; Silva *et al.*, 2008). All vector-borne flaviviruses share the conserved sequences CS2 and RCS2 (repeated CS2) found in the DB structure (Hahn *et al.*, 1987; Olsthoorn and Bol, 2001; Gritsun and Gould, 2006-2007; Romero *et al.*, 2006).

Domain III (Figure 3) contains the terminal stem-loop structure (3' SL) and the CS1 element which are the most conserved parts of the DENV 3' UTRs. DENV's CS1 has crucial sequence motifs for long-range RNA-RNA interaction (Hahn *et al.*, 1987; Gebhard *et al.*, 2011). The data presented here will be useful in deciphering the DNA editing virus's (DENV) genomic structure.

Structural and non-structural proteins

Structural proteins

1. Capsid Protein (C)

Capsid protein is a homodimer with a molecular weight of 12 kDa and a total of 100 amino acids, as stated by both Uno and Ross (2018) and Byk and Gamarnik (2016). Four-helical segments and a disorganized N-terminal region make

up the structure. The C proteins, a 20 amino acid long membrane bridging domain that is hydrophobic in nature, facilitate the attachment of C protein to the endoplasmic reticulum. The lipid droplets which are negatively charged interact with the positively charged N terminal domain to facilitate virion assembly, as stated by Perera and Kuhn (2008). Synthesis of nucleocapsids, an early step in dengue virion assembly, requires the C protein. Vaccines and antivirals preferentially target it since it does not induce an adverse drug-enhancing response (ADE) and is hence essential for prM development (Figure 2-4) (Pujar *et al.*, 2021; Nasar *et al.*, 2020).

2. PrM/Membrane Protein (M)

The PrM/M protein is composed of two transmembrane helices, the stem region, the N-terminal region, and the M domain, which together contain a total of 175 amino acids. The prM protein was cleaved by the cellular protease furin, which resulted in the release of 91 amino acids at the N-terminus but left 180 copies of the core protein with 75 residues. (*Nasar et al.*, 2020). According to research carried out by Uno and Ross *et al.*, (2018) and Dwivedi *et al.*, (2017), the M protein has a major impact on both the assembly and maturation of DENV. PrM is degraded into M-protein as a result of a break that occurs at the interface region of the Golgi apparatus between the N and M domains. This, in turn, leads to the maturation of the virus. Keelapang *et al.*, (2004) state that the PrM and E proteins have been reorganized (Figure 2-4).

3. Envelope protein (E)

Structural protein (E) is approximately 493-495 amino acids long with a 53 kDa molecular weight. During the primary infection, when the DENV E proteins interact with host cell surface molecules or receptors. The host cell clathrin proteins help in the internalization of the virus into the host cell via clathrin-mediated endocytosis (Figure 2-4). Several studies on the envelope protein have revealed its atomic structure. The envelope protein of each monomer contains three individual domains (I-III). Domain I (DI) may be found towards the N-terminus; however, it is structurally equivalent to other core domains. Domain II has a hydrophobic fusion peptide, an extended finger-like structure. At the end of a loop in Domain II is a hydrophobic pocket (dengue type 2, residues 98-109). The opening and closing of this hydrophobic pocket depend on the conformational change in the beta-hairpin (at the interface of the two domains). Out of the three domains of E protein monomers, domain III is thought to be a possible receptor-binding domain.

Because of the acidic environment in the endosome, the homodimers disintegrate and once inside the cell, they construct a junction between the virus and the host (Behnam *et al.*, 2016; Alen and Schols, 2012). The E protein's primary role is to fuse with and bind to the membrane of the host cell. Early stages of infection are prevented by the E protein inhibitors from being attacked by DENV. Because there isn't a putative active site suitable for viral proteases and polymerases, the creation of antivirals that target envelope proteins is greatly impeded (Naresh *et al.*, 2020). The stem domain, the soluble ectodomain, and the C-terminal transmembrane anchor domain are all parts of each monomer that are linked together by a common link.

Each monomer of envelop proteins contain n-octyl-D-glucoside (hydrophobic pocket) and a receptor binding domain III. After internalization into host cells, alternation in envelop protein is influenced by lower pH in the endosome, as a result, the envelop protein is converted into trimer from dimer. This facilitated the fusion of DENV envelop protein with the endosomal membrane of the host and then RNA release into the cytoplasm. Researchers have focused mainly on the envelope protein in their efforts to develop effective vaccines (Wang *et al.*, 2009).

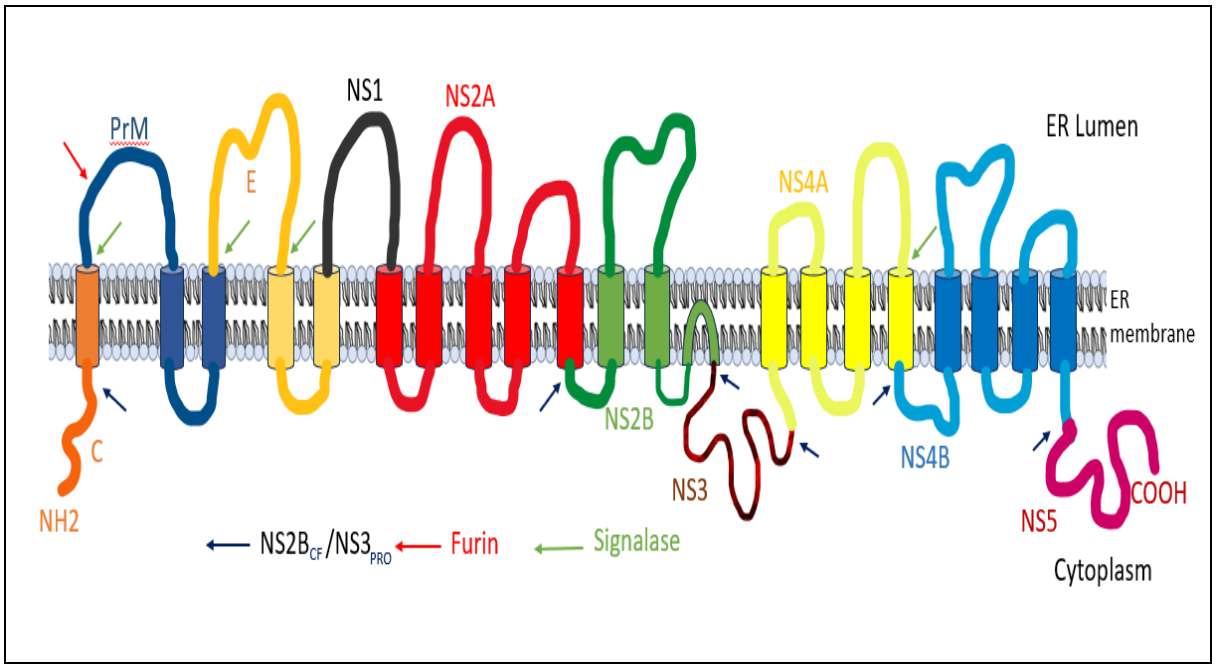

Fig. 4 : Schematic illustration showing the structure of polyprotein with three Structural proteins and seven non-structural proteins. The arrow (Blue, Red, and Green) is the point of cleavages in polyprotein by the host protease and viral protease.

Non-structural proteins

At the C′ terminus of the viral polyprotein is seven non-structural proteins that play a major role in the viral replication process (Table 1).

Table 1 : Non-structural proteins with their structural feature and functions.

Non-structural protein	M.W. (kDa)	Structural features	Functions
NS1	43-48	A multifunctional protein having an exposed hydrophobic region.	Role in the early stages of RNA replication, helping to construct the RNA replication complex (Uno and Ross, 2018; Dwivedi *et al.*, 2017). Since the bloodstream detects the produced NS1 protein on the first day of acute infection symptoms, it is employed as a diagnostic biomarker. Most conserved protein, which makes it a perfect target for a vaccine (Nasar *et al.*, 2020; Modhiran *et al.*, 2015).
NS2A	42	It is a hydrophobic protein. The C terminal is found in the cytoplasm, while the N terminal is found inside the ER lumen (Nasar *et al.*, 2020).	The transfer of viral RNA in vesicles, which aids in viral assembly. The assembly and secretion of viruses are mediated by C terminal residues, whereas cytopathogenic activity is mediated by N terminal residues (Shrivastava *et al.*, 2017). Xie *et al*. (2019) and Gopala *et al*. (2018) both report that DENV NS2A has been exploited as a target in very few drugs discovery research.
NS2B	15	Cytoplasmic hydrophobic protein with both N and C terminals.	Function as a cofactor for NS3 proteolytic activity. While NS2A itself is not a direct target for antivirals, interaction with NS3 can be a potential target for dengue inhibitors. (Dighe *et al.*, 2019).
NS3	70	Multipurpose protein. serve as an RNA helicase, serine protease, ATPase, and RNA triphosphatase (RTPase). All kinds of DENV share 77% of the same amino acids, making it the best candidate for vaccine development. It is difficult to develop effective inhibitors because of its planer nature (Perera and Kuhn, 2008; Yildiz *et al.*, 2013).	In host-immune response invasion, RNA genome replication, and viral assembly. The DENV NS2B/NS3 protease is a key target for rational drug development. its union is essential for immune suppression and proper folding protease activity (Phoo *et al.*, 2020). For substrate identification and efficient proteolysis, the closed conformation state of the NS2B in solution is required.
NS4A	16	Transmembrane ER protein is extremely hydrophobic. The cytoplasm contains the N terminal domain, whereas the ER lumen contains the C terminal domain (Gopala *et al.*, 2018). The six helices of the protein are split into three transmembrane helices at the C-terminus and three amphipathic helices at the N-terminus. (Xie *et al.*, 2015).	The continuation of viral multiplication depends on it.
NS4B	27	Hydrophobic protein. The N terminal cleavage of polyprotein precursors by the NS2B/NS3 serine protease results in the production of NS4B, while the C terminal cleavage produces a cellular signalase. There isn't much information known about the crystal structure or NMR structure of the NS4B protein, according to Xie et al. (2015) and Miller et al. (2006).	NS4B is thought to play a role in innate host immunity as well as protein-protein interactions with other viral proteins, while its precise role in viral replication is unclear.

NS5	103	The viral protein with the highest degree of conservation. According to Nasar *et al.* (2020), the most efficient enzymes for making viral RNA are RNA-dependent RNA polymerase (C terminal region) and methyltransferase (N terminal region). The ER houses the NS5 protein in an oligomeric state together with the NS2B and NS3 proteins. It can change structural confirmations while keeping its active domains the same.	It is required for the replication of the RNA genome. It serves as a target for the development of vaccines and therapeutics.

Dengue virus life cycle

Dengue fever is spread by the bite of an infected mosquito, specifically those of the *Aedes* genus, including the *Aedes aegypti* and *Aedes albopictus.* It is also unknown whether types of human cells or binding receptors interact with DENV. GAG (Heparan sulfate), phosphatidylserine families (TIM/TAM), glycosphingolipid nLc4Cer, DC-SIGN, mannose, antibody-dependent enhancement (FCR), and heat shock proteins (HSP70/90) are all probable receptors (Figure 5) (Cruz-Oliveira *et al.*, 2015).

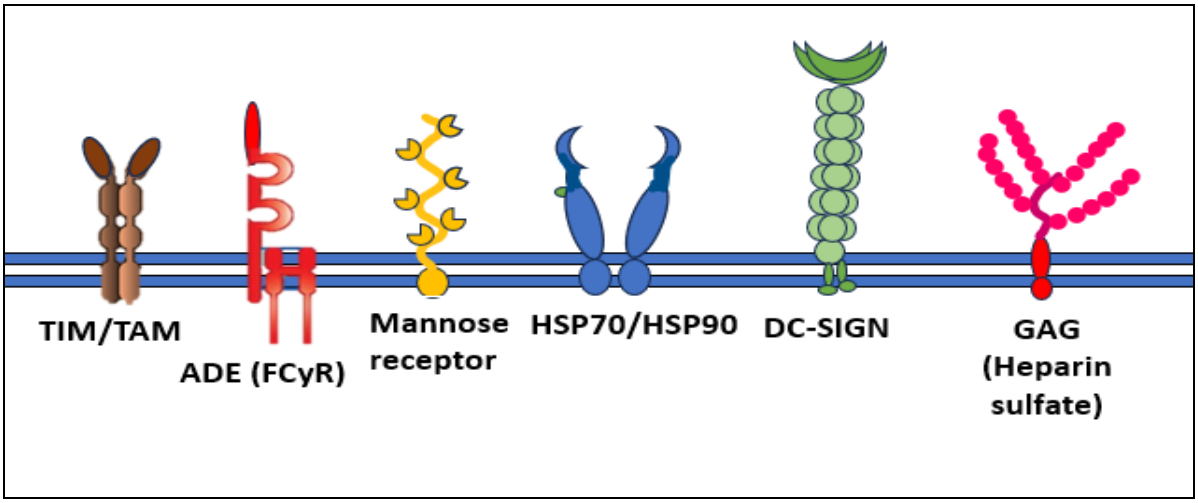

Fig. 5 : Schematic illustration showing cell surface components involve in DENV recognition/ attachment/ binding and internalization.

Cells such as dendritic cells (DCs), fibroblasts, endothelial cells, keratinocytes, mast cells, macrophages, and monocytes are susceptible to infection by DENV (Garcia *et al.*, 2017).

Clathrin-mediated endocytosis allows DENV to enter cells once the virus has attached to a receptor on the E glycoprotein (Figure 6). Conformational changes in the virus caused by a decrease in endosomal pH cause the membrane to fuse, releasing viral RNA into the cytoplasm (Heinz and Allison, 2000).

In order for the virus to replicate and translate, DENV RNA is released into the cytoplasm. Virus RNA acts in a manner analogous to host mRNA. Unlike host mRNA, viral RNA does not have a poly-A tail, which is the most obvious difference. Host mRNA translation differs from viral mRNA translation. Thus, the ribosomes in the ER are where the viral mRNA is translated into a polypeptide chain (polyprotein). The viral serine protease and the host proteases each cleave the polypeptide chain into three distinct structural and non-structural fragments (Perera and Kuhn, 2008).

Several changes occur in the host cell during the transformation process. In response to these changes, the host cell actively promoted viral RNA replication.

One instance of these changes to the cell is the building of a replication complex (RC), a microenvironment that is membrane-bound. Morphogenesis and amplification of viral RNA have been observed in RC (TuiskunenBack and Lundkvist, 2013). Deleting NS1 limits viral RNA replication, despite the fact that the NS1 dimer is on the lumen side of the ER (Lindenbach *et al.*, 1999). By connecting with the NS4A and NS4B transmembrane, NS1 aids in the production of viral replication complex (RC) vesicles (Lindenbach *et al.*, 1999; Watterson *et al.*, 2016). NS1 is also associated with dsRNA. The replication complex (RC) is a change in membrane structure that occurs concurrently with replication and is produced by viruses. The host ribosome can initiate the translation of a polyprotein from a positive-sensed RNA genome right immediately (Polacek *et al.*, 2009b).

NS3 and NS5 exhibit the enzymatic activity required for viral propagation. Protease and helicase activities in viruses are catalyzed by NS3. Splitting the viral polypeptide

into structural and non-structural proteins requires the N-terminal domain of NS3 to function as a protease (Falgout *et al.,* 1991). For RNA duplex unwinding to occur during replication, the NS3 protein must have a helicase domain at its C-terminal end (Umareddy *et al.,* 2006). The protease activity of NS3 relies on the presence of the cofactor NS2B. DENV NS5 protein is the largest and most resilient protein. A methyltransferase, found in the protein's N-terminus of NS5, is responsible for capping the 5′ ends of newly synthesized viral genomes and it also acts as "RNA-dependent RNA-polymerase" (C-terminal)(Issur *et al.,* 2009).

A viral genome replicates in two distinct phases. At this early stage, viral RNA with a positive polarity is in the process of being transformed into RNA with a negative polarity. The second phase makes advantage of these defective RNA strands to increase the production of functional ones. The translation may involve some of the positive strands. To create a protective nucleocapsid around the genome, newly replicated positive sense ssRNA encapsulated in C protein on the membrane of the endoplasmic reticulum (TuiskunenBack and Lundkvist, 2013).

The structural prM and E proteins are generated in the lumen of the endoplasmic reticulum following proteolysis of the polyprotein by viral and host enzymes, whereas the NS proteins are localized in membrane vesicles produced by the virus for RNA synthesis (Welsch *et al.,* 2009).

The nucleocapsid bud penetrates the endoplasmic reticulum (ER) and gains access to the E and PrM proteins during an important period in viral growth. A virus's immature particles are transported to the Golgi apparatus, where they are glycosylated and the PrM is broken down into M-protein by cellular endo-proteases. (Uno and Ross, 2018; TuiskunenBack and Lundkvist, 2013; Byk and Gamarnik, 2016). The infectious, mature virion is released by exocytosis. However, if PrM cleavage is not effective, immature and partially mature virions are also released (Junihon *et al.,* 2010). The infection spread to new cells by the infected cell releasing mature virus particles (Lim, 2019; Nasar *et al.,* 2020).

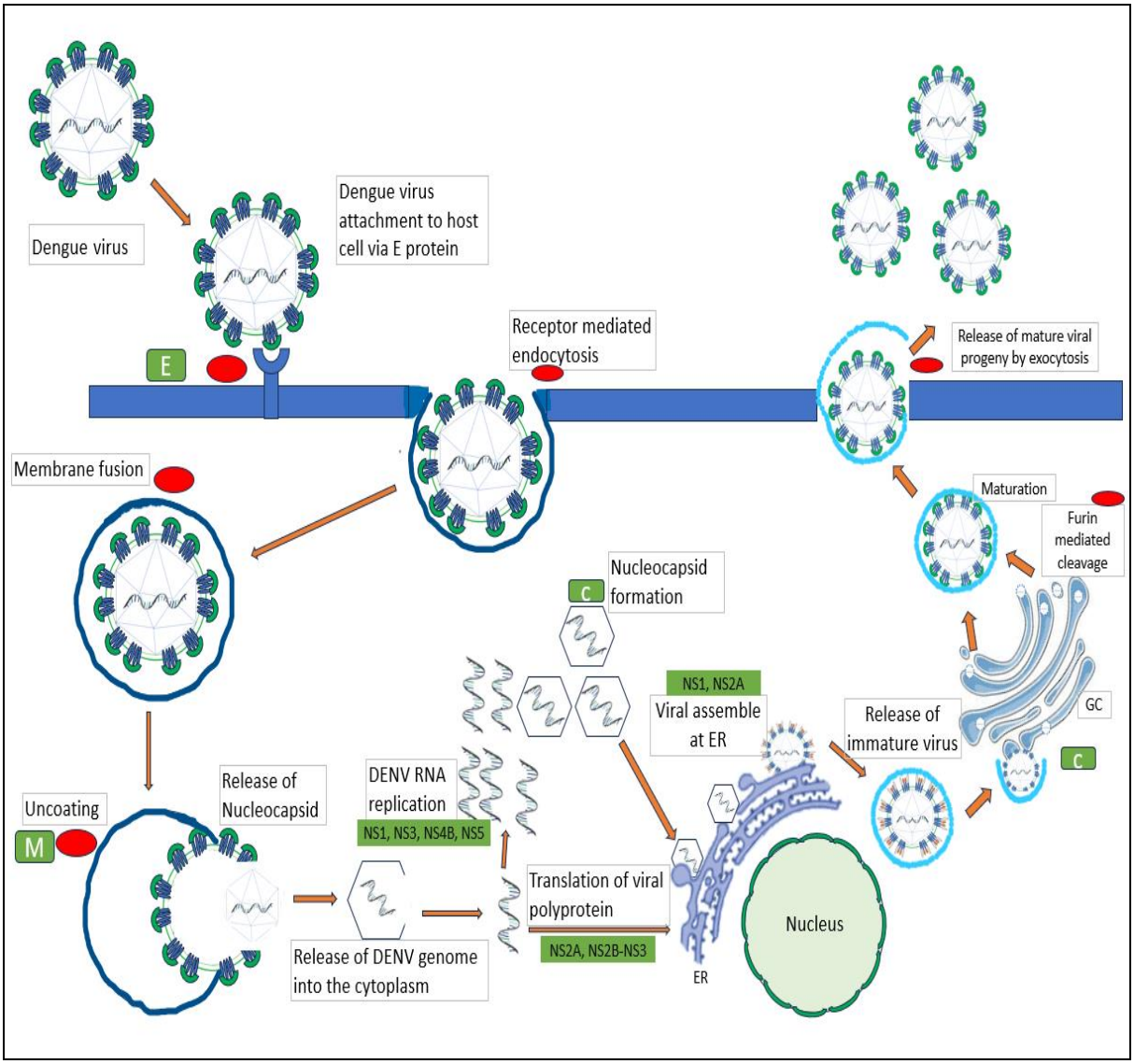

Fig. 6 : Schematic illustration showing the life cycle events of dengue virus in a host cell. (Green dot- Viral targets, Red dot- Host targets)

Conclusion remark

A life-threatening medical condition known as dengue fever is brought on by the dengue virus (DENV). Dengue virus has been reported as having a total of five distinct serotypes (DENV 1-5). However, only DENV (1-4) genomic sequencing data is available.

Each DENV RNA genome contains 5' and 3' UTRs regions, which play a significant role in virion genome replication and translation. The first domain of 5' UTRs contains 70 nucleotide secondary structure SLA; this serves as a promotor for RdRp and is essential for dengue virus RNA synthesis. The second domain of 5' UTRs contains the secondary structure SLB, which helps in RNA duplication and long-range RNA-RNA binding. DENV RNA 450 nucleotide long 3' UTRs divided into 3 domains (DI, DII and DIII). DI contains a variable region, it varies greatly in DENV serotypes, DII includes conserved sequences CS2 and RCS2 and DII includes the most conserved sequence (CS1 and 3'SL). A single large precursor polyprotein encoded by 11 kb single stand positive RNA of DENV that is subsequently processed by viral (NS2B-NS3) and host cell protease at a specific site. This results in the production of three structural proteins and seven non-structural proteins.

Structural capsid protein plays a significant role in the first stage assembly of dengue virion and in the maturation of precursor membrane protein (PrM). The PrM protein is processed into M protein by the cellular protease Furin in the Golgi apparatus, which in turn causes the virus to mature. The envelop protein (E) interacts with the host cell membrane and helps in virions penetration into host cells via clathrin-medicated endocytosis. During infection, lower endosomal pH dissolves the homodimer, and the E protein experiences structural changes that cause it to change from a dimeric to a trimeric orientation, as a result DENV E protein merges with the endosomal membrane, releasing the RNA into the cytoplasm.

Non-structural proteins; NS1 help in replication complex formation and replication. NS2A protein help in viral assembly, NS2B protein serves as a cofactor for NS3 proteolytic action, NS3 protein is a multipurpose protein, it acts as RNA helicase and serine protease, NS4A protein helps in viral multiplication, NS4B protein is thought to play a role in innate host immunity and the most significant and largest non-structural protein, NS5, serves as an RNA-dependent RNA polymerase (RdRp) that replicate the viral RNA and an RNA methyltransferase enzyme (MTase) that caps the viral genome to protect it and speed up the translation of polyproteins. The most "powerful therapeutic target" for the development of potent drugs against all serotypes of DENV is NS2B-NS3 protease, NS3, and NS5.

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