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Review

The Interplay of Dengue Virus Morphological Diversity and Human Antibodies

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Dengue virus (DENV) infects ~400 million people annually, and there is no available vaccine or therapeutics. It is not clear why candidate vaccines provide only modest protection. In addition to the presence of four different dengue serotypes, there is also structural heterogeneity in DENV infectious particles, even within a strain. This severely complicates the development of vaccines and therapeutics. The currently known different morphologies of DENV are: immature, partially mature, compact mature, and expanded mature forms of the virus. In this review I describe these forms of the virus, their infectivity, and how antibodies could recognize these morphologies. I also discuss possible vaccine and antibody therapeutic formulations to protect against all morphologies.

Dengue Virus

DENV, a flavivirus, consists mainly of four serotypes: DENV1–4. Currently, there is no commercially available vaccine, or therapeutics, for DENV, and either is urgently needed. DENV infection can cause a mild fever or the more severe dengue hemorrhagic fever (DHF). Homologous infection generates lifelong protective immunity against that particular infecting serotype. However, in a secondary infection with a different serotype, the pre-existing antibodies can be non- or poorly neutralizing towards the new serotype. This can lead to an enhanced virus infection because these antibodies bind to the virus and help to concentrate the virus on monocytic cells by binding to the Fc receptor. This phenomenon is termed antibody-dependent enhancement (ADE) [1]. This suggests that a successful vaccine should elicit an equally high protective response against all serotypes at the same time. However, a recent clinical trial of a tetravalent vaccine [2] showed disappointing results, suggesting that this strategy could be too simplistic. Indeed, to date, several different morphologies of DENV (compact and expanded mature virus, fully immature virus, and partially mature virus) had been described, and they may all need to be represented in a vaccine to stimulate full protection. In this review I discuss the different DENV morphologies and how natural antibodies could bind and neutralize them.

The DENV Envelope Protein and Its Involvement in the Virus Infection Cycle

On the surface of the mature DENV particle are the envelope (E) and membrane (M) proteins anchored onto the virus bilipid layer membrane via their transmembrane region (Figure 1A) [3–5]. The capsid proteins and genomic RNA complex are inside the virus particle.

The E protein is the major surface protein of DENV targeted by antibodies. It facilitates receptor binding and fusion to the endosomal membrane during cell entry [6]. Crystal structures of the E ectodomain protein (without the stem and transmembrane region) in the prefusion [6] and postfusion [7,8] states have been solved. In the prefusion state, the E proteins exist as dimers (Figure 1B). The E protein consists of three domains: DI, DII, and DIII. The tip of DII contains the fusion loop that directly interacts with the endosomal membrane during fusion. The DI–DII hinge

Trends

Although dengue virus (DENV) infects approximately 400 million people annually, there are currently no effective therapeutics or a vaccine.

Due to the potential of causing enhancement of disease, a DENV vaccine has to stimulate equal protective responses towards all four dengue serotypes. Additionally, the presence of different dengue virus morphologies within a strain may further complicate vaccine and therapeutic design.

Antibodies may have different potencies against different DENV morphologies.

A vaccine may need to represent all DENV morphologies.

Antibody therapeutics should contain antibodies against all morphologies.

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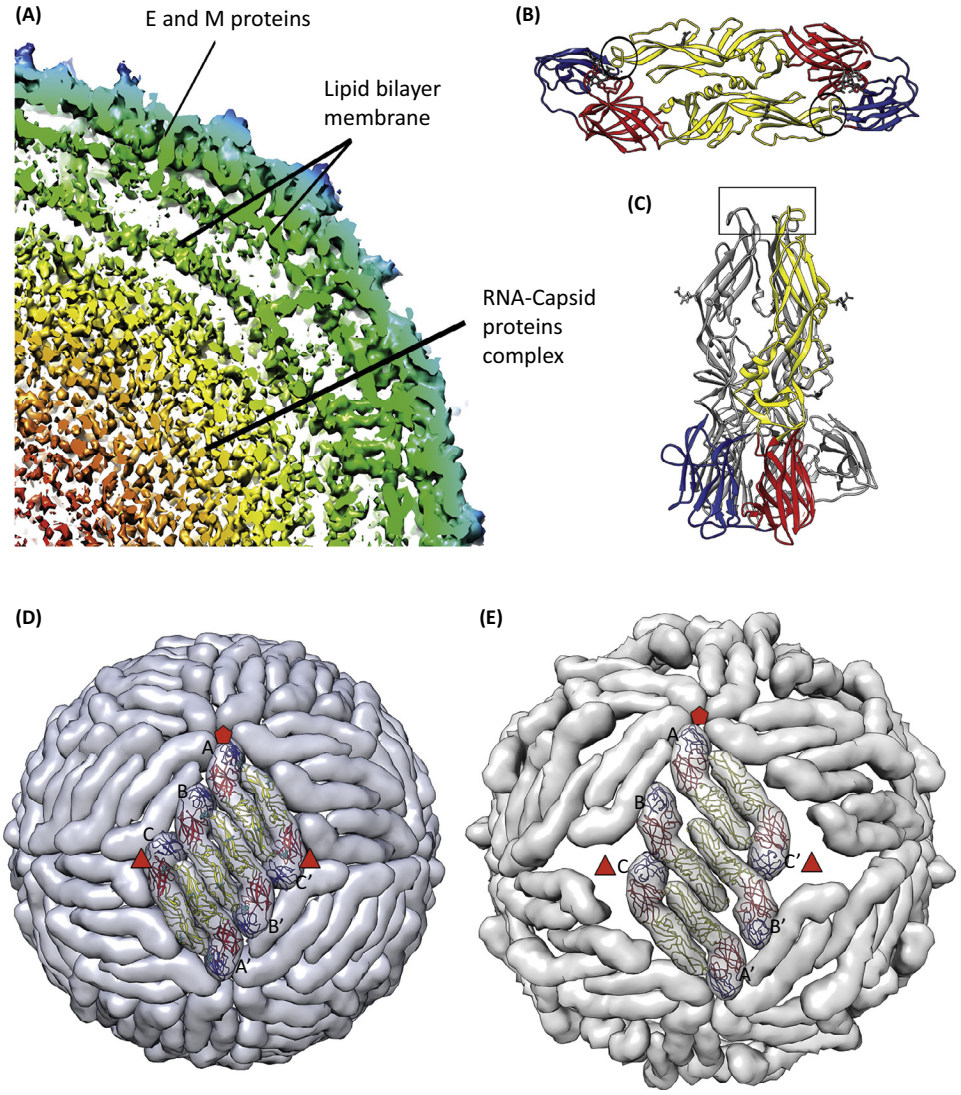

Figure 1. Mature Dengue Virus (DENV) Structures. (A) A quarter of the central cross-section of a cryoEM map of DENV. The map is colored radially: red (1–130 Å), yellow (131–200 Å), green (201–234 Å), cyan (235–249 Å), and blue (>250 Å). The part of the DENV structure colored in red and yellow indicates the approximate radius that contains the RNA–capsid proteins complex. In green, the lipid bilayer membrane is shown with the E and M transmembrane regions; cyan indicates the E and M ectodomains, and blue indicates the glycosylation sites of E and M proteins. (B) Crystal structure of the prefusion dimeric E protein [Protein data bank (PDB) 1OAN]. DI, DII, and DIII are colored in red, yellow, and blue, respectively. The fusion loop on each E protein is circled in black. (C) Crystal structure of the postfusion trimeric E proteins (PDB 1OK8). One E protein is colored as indicated in (B), the other two are shown in gray. Fusion loops are assembled at one end (enclosed in the black box) and likely interact with the endosomal membrane. (D) Organization of E proteins on the compact mature DENV at 28°C (PDB 3J27). Ribbon representation of an E protein raft is shown. One asymmetric unit contains three individual E proteins: mols A, B, and C. The neighboring symmetry-related E proteins within a raft are labeled as A′, B′, and C′. All E proteins on the virus surface are also shown as gray surfaces. The 5- and 3-fold vertices are indicated by red pentagon and triangle shapes, respectively. (E) The cryoEM structure of the DENV2 class III particles at 37°C (PDB 3ZKO). All of the E proteins have moved to higher radius. The E protein dimer near the 5-fold vertex (mols A–C′) has undergone rotation. The B and B′ dimer dissociate from each other.