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Quaternary epitope landscape of Zika virus antibody complexes

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Abstract

Zika virus (ZIKV), a mosquito-borne human flavivirus is closely related to dengue virus, yellow fever virus, West Nile virus and Japanese encephalitis virus. ZIKV can cause congenital Zika syndrome in infants and Guillain-Barré syndrome in adults. Neutralizing antibodies (nAbs) are amongst the preferred antiviral therapeutic strategies against infection by flaviviruses. Successful vaccines exist against YFV, JEV and TBEV. However, vaccine development against other flaviviruses like dengue virus is not straightforward. This is partly because of the high sequence conservation and immunological cross-reactivity among flavivirus envelope glycoproteins leading to antibody mediated enhancement of disease (ADE). Thus, understanding the immune response in consecutive flavivirus infections and virus neutralization mechanisms by various classes of nAbs may help to prevent disease severities leading to ADE, which is a major risk factor for vaccine development.

The structures of the mature[1-3] (Figure 1A) and the immature[4] ZIKV and its complexes with nAbs, unfolded structural components important for infection and the binding epitopes for diverse nAbs. In summary, the nucleocapsid core formed by the capsid protein-RNA complex in a mature virus is protected by the heterodimeric arrangement of the glycoproteins, E-M, embedded in a host-derived lipid envelope. The E protein, in addition to its role in virus assembly contains putative receptor binding sites and mediates virus entry by pH mediated fusion with the host membrane. The E ectodomain (E_e) accessible to nAbs, consists of three domains: a central ß-barrel domain I (DI), which connects to the dimerization domain II (DII), and an Ig-like receptor binding domain III (DIII) (Figure 1A). E protein DII harbors a conserved hydrophobic sequence, called the fusion loop (FL), a feature of type-II fusion proteins. The FL inserts into the host cell membrane during pH-induced conformational changes leading to virus-host membrane fusion during infection. Several ZIKV-nAb complexes have been structurally and functionally characterized[5,6]. The nAbs against E might inhibit several processes during infection including receptor binding, blocking conformational changes and exposure of the FL. Among these, the primary focus will be on structural aspects of ZIKV nAbs utilizing novel quaternary epitopes on the virus surface (Figure 1B and 1C). Quaternary epitopes span over multiple E proteins decorating the surface of the virus or multiple domains (DI-II-III) of more than one E protein. The nAbs that will be discussed here were identified either in individuals with subsequent flavivirus infections or discovered as a result of a sprint program to deploy protective antibody treatments against viral outbreaks. The binding stoichiometry and neutralization mechanisms conferring high potency and virus specificity of the nAbs with quaternary epitopes will be discussed and the landscape of the quaternary epitopes among diverse flaviviruses will be compared.

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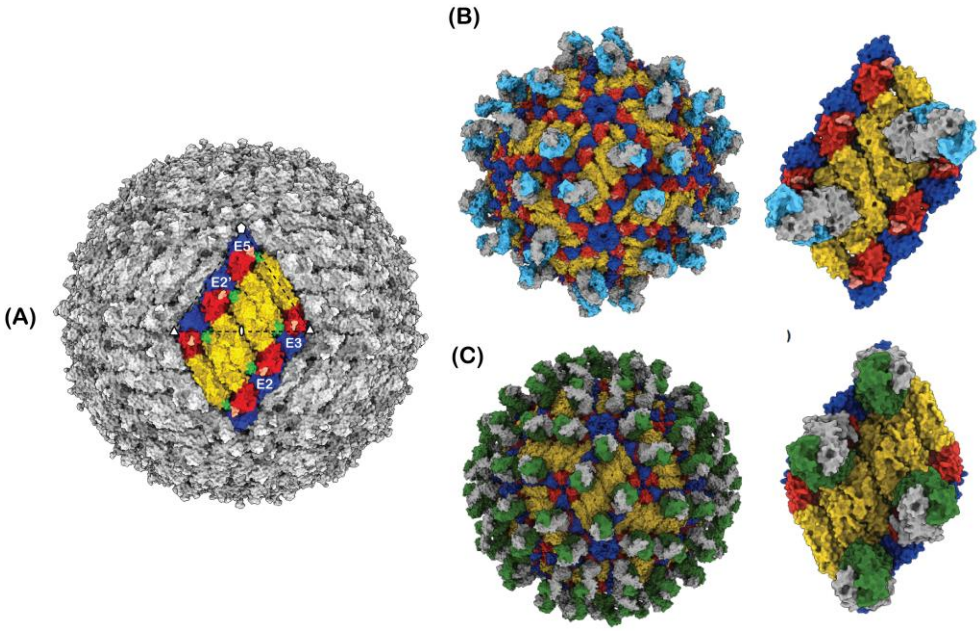

Figure 1. (A) ZIKV structure showing the herringbone pattern formed by 6 E–M heterodimers. One icosahedral asymmetric unit is identified by a black triangle. For clarity only the ectodomain of the E protein (from residues 1–400) has been shown. The E proteins near the two-fold, three-fold and five-fold axes of symmetry are labelled E2, E3 and E5, respectively. Domains E-DI, E-DII and E-DIII are colored red, yellow and blue, respectively. (B-C) Representative structures of ZIKV-nAb complexes with quaternary epitope. (B) E-protein Domain-II specific antibody and (C) ZIKV in complex with envelope protein Domain-I-II specific antibody.

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