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Flavivirus capsid assembly and dynamics: evidence of a structure-driven regulation of protein interaction with intracellular hydrophobic interfaces.

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Dengue (DENV) and Zika (ZIKV) are major arthropod-borne human viral disease, for which no specific treatment is available. They are a worldwide important health concern, which causes neurological disorders and hemorrhagic syndrome. Although the structure of ZIKV and DENV virion has been determined, information on the nucleocapsid is lacking. The most accepted hypothesis is of a disorganized nucleocapsid. Using NMR, we solved the structure and dynamics of full length ZIKV capsid protein (ZIKVC) and the dynamics of DENV capsid protein (DENVC). We showed that the addition of oligonucleotides can form an organized nucleocapsid-like particles (NC-like). The binding to intracellular hydrophobic interfaces, such as endoplasmic reticulum and/or lipid droplets is essential for virus replication. The hydrophobic cleft is the binding site, along with the intrinsically disordered region, and an open-close dynamic of the globular domain that are species-specific. For ZIKVC, α-helix 1 is smaller and partially occludes protein hydrophobic cleft. Measurements of the dynamics of α-helix 1, surface exposure and thermal susceptibility of each backbone amide hydrogen in protein structure revealed the occlusion of the hydrophobic cleft by α1/α1´ and supported a α-helix 1 position uncertainty. Based on the findings, we propose that the dynamics of flaviviruses structural elements responds for a structure-driven regulation of protein interaction with intracellular hydrophobic interfaces, which would impact in the switches necessary for nucleocapsid assembly. Subtle differences in the sequence of helix 1 impact on its size and orientation and on the degree of exposure of the hydrophobic cleft, suggesting that α-helix 1 is a hotspot for evolutionary adaptation of flaviviruses' capsid proteins.
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