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Applying Computer Simulation Methods to a Molecular Understanding of Flaviviruses Proteins towards Differential Serological Diagnostics and Therapeutic Intervention

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Abstract : The flavivirus genus has several organisms responsible for generating various diseases in humans. Special in Brazil, Zika (ZIKV), Dengue (DENV) and Yellow Fever (YFV) viruses have raised great health concerns due to the high number of cases affecting the area during the last years. Diagnostic is still a difficult issue since the clinical symptoms are highly similar. The understanding of their common structural/dynamical and biomolecular interactions features and differences might suggest alternative strategies towards differential serological diagnostics and therapeutic intervention. Due to their immunogenicity, the primary focus of this study was on the ZIKV, DENV and YFV non-structural proteins 1 (NS1) protein. By means of computational studies, we calculated the main physical chemical properties of this protein from different strains that are directly responsible for the biomolecular interactions and, therefore, can be related to the differential infectivity of the strains. We also mapped the electrostatic differences at both the sequence and structural levels for the strains from Uganda to Brazil that could suggest possible molecular mechanisms for the increase of the virulence of ZIKV. It is interesting to note that despite the small changes in the protein sequence due to the high sequence identity among the studied strains, the electrostatic properties are strongly impacted by the pH which also impact on their biomolecular interactions with partners and, consequently, the molecular viral biology. African and Asian strains are distinguishable. Exploring the interfaces used by NS1 to self-associate in different oligomeric states, and to interact with membranes and the antibody, we could map the strategy used by the ZIKV during its evolutionary process. This indicates possible molecular mechanisms that can explain the different immunological response. By the comparison with the known antibody structure available for the West Nile virus, we demonstrated that the antibody would have difficulties to neutralize the NS1 from the Brazilian strain. The present study also opens up perspectives to computationally design high specificity antibodies.

Keywords : zika, biomolecular interactions, electrostatic interactions, molecular mechanisms
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