INFECTIVITY OF DENGUE VIRUS SEROTYPES 1 & 2 IS CORRELATED TO E-PROTEIN STRUCTURAL DYNAMICS BUT NOT TO ENVELOPE CONFORMATIONS

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ABSTRACT

Dengue is a mosquito-borne virus with dire health and economic impacts. Among its five serotypes, Dengue 2 (DENV2) is the most virulent strain responsible for an estimated ~390 million infections per year. Interestingly, it is also for strains of this serotype that large scale conformational changes, called "breathing" have been observed. Although, the structure of these morphologies have been solved to 3.5 Å resolution the dynamics of viral envelope are unknown. Here, we combine fluorescence and mass spectroscopy and computational studies to provide insights into DENV2 structural dynamics in comparison to DENV1. Using amide hydrogen/deuterium exchange mass spectrometry (HDXMS), we captured DENV2 Envelope-protein motifs that undergo either temperature or divalent-ions dependent conformational changes. While using time resolved Förster Resonance Energy Transfer (trFRET), we measured the extent of such conformational changes. Furthermore, using FRET fluctuation spectroscopy (FRET-FCS), we delineated intrinsic fluctuation dynamics of virus in ~0.9 ms and ~2.3 ms range and correlated virus dynamics to the virus infectivity. We observe unseen conformational changes and structural dynamics of DENV2 that are influenced by both, temperature and divalent ions. Our results show that the DENV structural dynamics but not the virus morphologies are correlated to virus infectivity. Both, virus structure and its related dynamics, are important determinants in viral activity and their knowledge can open new path in vaccine design.