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Insights into the mode of recognition of DIII of dengue E protein with GRP78: A molecular dynamics approach

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Abstract

Dengue virus (DENV), a single stranded RNA positive-strand virus belongs to Flaviviridae causes Dengue in several parts of South-East Asia. During infection, dengue virus proteins interact with host cellular constituents, thus promotes the remodeling of the cell to facilitate virus production. Recent studies have shown that DENV E protein interact the cellular chaperone GRP78. GRP78 that plays a dual role in virus life cycle i.e., virus entry and virus replication, is a novel host factor that could be a potential therapeutic target. Currently, the three-dimensional interaction between GRP78 and DENV E protein remains largely unknown. It is assumed that DENV E protein interacts with the C-terminus of GRP78, and the C-terminus of GRP78 is believed to be the predominant protein interacting domain, while the N-terminus is believed to contain regulatory domains that mediate C-terminal binding. Although the exact E protein domain mediating binding to GRP78 is not known, it has been proposed that GRP78 and DENV E protein interact through the immunoglobulin like structure in the DENV E protein that resides in domain III (DIII). So, the present study was undertaken to unravel molecular basis of GRP78 and DENV E protein interaction through molecular modeling, protein-protein docking and Molecular dynamics simulations. The three-dimensional structures of DIII of E protein from DENVI was modelled and docked against crystal structure of GRP78 (PDB ID: 3LDL) using ClusPro. The top ranked pose from ClusPro was again refined using HADDOCK. Molecular dynamics simulation was performed to understand mode of recognition and dynamics stability of the refined DIII-GRP78 complex in aqueous solution for 10 ns. The critical residues i.e., Thr303/Lys46, Lys295/ Lys152 and Lys399/Asn239 identified in this study are indispensable for DIII mediated interaction of dengue virus with host protein GRP78. The results from this study is expected shed deep insights into the crucial host factors that could be targeted to cripple virus infection and ultimately lead to development of effective anti-viral therapy for DENV in near future.

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