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Development of Peptide Inhibitors against Dengue Virus Infection by in Silico Design

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Abstract : Dengue virus (DENV) infection is a global public health problem with approximately 100 million infected cases a year. Presently, there is no approved vaccine or effective drug available; therefore, the development of anti-DENV drug is urgently needed. The clinical reports revealing the positive association between the disease severity and viral titer has been reported previously suggesting that the anti-DENV drug therapy can possibly ameliorate the disease severity. Although several anti-DENV agents showed inhibitory activities against DENV infection, to date none of them accomplishes clinical use in the patients. The surface envelope (E) protein of DENV is critical for the viral entry step, which includes attachment and membrane fusion; thus, the blocking of envelope protein is an attractive strategy for anti-DENV drug development. To search the safe anti-DENV agent, this study aimed to search for novel peptide inhibitors to counter DENV infection through the targeting of E protein using a structure-based in silico design. Two selected strategies has been used including to identify the peptide inhibitor which interfere the membrane fusion process whereby the hydrophobic pocket on the E protein was the target, the destabilization of virion structure organization through the disruption of the interaction between the envelope and membrane proteins, respectively. The molecular docking technique has been used in the first strategy to search for the peptide inhibitors that specifically bind to the hydrophobic pocket. The second strategy, the peptide inhibitor has been designed to mimic the ectodomain portion of membrane protein to disrupt the protein-protein interaction. The designed peptides were tested for the effects on cell viability to measure the toxic to peptide to the cells and their inhibitory assay to inhibit the DENV infection in Vero cells. Furthermore, their antiviral effects on viral replication, intracellular protein level and viral production have been observed by using the qPCR, cell-based flavivirus immunodetection and immunofluorescence assay. None of tested peptides showed the significant effect on cell viability. The small peptide inhibitors achieved from molecular docking, Glu-Phe (EF), effectively inhibited DENV infection in cell culture system. Its most potential effect was observed for DENV2 with a half maximal inhibition concentration (IC50) of 96 μM, but it partially inhibited other serotypes. Treatment of EF at 200 μM on infected cells also significantly reduced the viral genome and protein to 83.47% and 84.15%, respectively, corresponding to the reduction of infected cell numbers. An additional approach was carried out by using peptide mimicking membrane (M) protein, namely MLH40. Treatment of MLH40 caused the reduction of foci formation in four individual DENV serotype (DENV1-4) with IC50 of 24-31 μM. Further characterization suggested that the MLH40 specifically blocked viral attachment to host membrane, and treatment with 100 μM could diminish 80% of viral attachment. In summary, targeting the hydrophobic pocket and M-binding site on the E protein by using the peptide inhibitors could inhibit DENV infection. The results provide proof of-concept for the development of antiviral therapeutic peptide inhibitors to counter DENV infection through the use of a structure-based design targeting conserved viral protein.

Keywords : dengue virus, dengue virus infection, drug design, peptide inhibitor
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