

Structure of the dengue virus envelope protein after membrane fusion.

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Abstract

Dengue virus enters a host cell when the viral envelope glycoprotein, E, binds to a receptor and responds by conformational rearrangement to the reduced pH of an endosome. The conformational change induces fusion of viral and host-cell membranes. A three-dimensional structure of the soluble E ectodomain (sE) in its trimeric, postfusion state reveals striking differences from the dimeric, prefusion form. The elongated trimer bears three 'fusion loops' at one end, to insert into the host-cell membrane. Their structure allows us to model directly how these fusion loops interact with a lipid bilayer. The protein folds back on itself, directing its carboxy terminus towards the fusion loops. We propose a fusion mechanism driven by essentially irreversible conformational changes in E and facilitated by fusion-loop insertion into the outer bilayer leaflet. Specific features of the folded-back structure suggest strategies for inhibiting flavivirus entry.