

Structures Of Langya Virus Fusion Protein Ectodomain in Pre and Post Fusion Conformation

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Langya virus (LayV) is a paramyxovirus in the Henipavirus genus, closely related to the deadly Nipah and Hendra viruses, that was identified in August 2022 through disease surveillance following animal exposure in eastern China. Here, we determine cryo-EM structures of the uncleaved LayV fusion protein (F) ectodomain in pre- and post-fusion conformations. While most previous cryo-EM structures of Henipavirus F proteins utilized pre-fusion stabilizing mutations, here we studied the F protein in the absence of engineered mutations resulting in flexibility and heterogeneity that made the processing of the cryo-EM dataset challenging. While dramatic conformational changes were visualized between the pre- and post-fusion forms of the LayV-F protein, several domains remained invariant, held together by highly conserved disulfides. Additionally, the LayV-F fusion peptide is buried within a highly conserved, hydrophobic, interprotomer pocket in the pre-fusion state and is notably less flexible than the rest of the protein, highlighting its “spring-loaded” state and suggesting that the mechanism of pre-to-post transition must involve perturbations to the pocket and release of the fusion peptide. Together, these results investigate the structural basis for how the Langya virus F protein undergoes conformational conversion and propose a mechanism for the initial step of this conversion that may apply more broadly to paramyxoviruses.