Molecular Modeling and Dynamics-Based Structural Characterization of the HTLV-1 SU Protein (gp46)

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Abstract

HTLV-1 gp46, the surface subunit of the viral envelope glycoprotein complex, is essential for receptor recognition and viral entry. Despite its importance, the structural topology and conformational dynamics remias unclear, with no full-length X-ray or cryo-EM structures available. This study investigates the structural dynamics of full-length gp46 (gp46-FL) using three-dimensional structural modeling followed by long-timescale molecular dynamics (MD) simulations. To gain domain-specific insights, a reductionist approach was employed to examine its three functional domains-Receptor Binding Domain (RBD), Proline-Rich Domain (PRD), and C-terminal Domain (CTD), individually. The RBD, responsible for binding cellular receptors such as NRP-1 and GLUT1, maintained its secondary structure and exhibited minimal RMSD and RMSF fluctuations during MD and replica-exchange MD simulations, confirming its structural stability. In contrast, the PRD exhibited significant conformational flexibility, aligning with its high disorder propensity and displayed occasional transient structures that suggest a hinge-like function during receptor-induced transitions. The CTD, containing the disulfide isomerization motif (CxxC) essential for SU-TM dissociation and membrane fusion, showed moderate disorder but retained a stable helical structure surrounding the motif throughout the trajectory, indicating a conserved functional switch. Together, these results portray gp46 as a modular protein with a rigid receptor-binding core and flexible flanking domains, providing new insights into its dynamic nature and potential therapeutic targeting during HTLV-1 entry.

Keywords: Molecular modeling, HTLV-1 gp46, RBD domain, Secondary Structure, Intrinsically disordered regions, Replica-exchange Molecular simulation

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