Interaction of monomeric Ebola VP40 protein with a plasma membrane: A coarse-grained molecular dynamics (CGMD) simulation study

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Abstract

Ebola virus is a lipid-enveloped filamentous virus that affects human and non-human primates and consists of several types of protein: nucleoprotein, VP30, VP35, L protein, VP40, VP24, and transmembrane glycoprotein. Among the Ebola virus proteins, its matrix protein VP40 is abundantly expressed during infection and plays a number of critical roles in oligomerization, budding and egress from the host cell. VP40 exists predominantly as a monomer at the inner leaflet of the plasma membrane, and has been suggested to interact with negatively charged lipids such as phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidylserine (PS) via its cationic patch. The hydrophobic loop at the C-terminal domain has also been shown to be important in the interaction between the VP40 and the membrane. However, details of the molecular mechanisms underpinning their interactions are not fully understood. This study aimed at investigating the effects of mutation in the cationic patch and hydrophobic loop on the interaction between the VP40 monomer and the plasma membrane using coarse-grained molecular dynamics simulation (CGMD). Our simulations revealed that the interaction between VP40 and the plasma membrane is mediated by the cationic patch residues. This led to the clustering of PIP2 around the protein in the inner leaflet as a result of interactions between some cationic residues including R52, K127, K221, K224, K225, K256, K270, K274, K275 and K279 and PIP2 lipids via electrostatic interactions. Mutation of the cationic patch or hydrophobic loop amino acids caused the protein to bind at the inner leaflet of the plasma membrane in a different orientation, where no significant clustering of PIP2 was observed around the mutated protein. This study provides basic understanding of the interaction of the VP40 monomer and its mutants with the plasma membrane. (C) 2018 Elsevier Inc. All rights reserved.

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