CARNEGIE MELLON UNIVERSITY BME 2023 SPRING SEMINAR SERIES

Solving the Puzzle of Coronavirus Entry and the Role of the Fusion Peptide in Breaching the Host Membrane



PRESENTED BY

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SCHEDULE

Hall of Arts (HOA) 160

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The coronavirus disease 2019 (COVID-19) necessitates developing effective therapies against the causative agent, SARS-CoV-2, and other pathogenic coronaviruses (CoV) that have yet to emerge. Focusing on the CoV replication cycle, specifically the entry steps involving membrane fusion, is an astute choice because of the conservation of the fusion machinery and mechanism across the CoV family. For coronavirus, entry into a host cell is mediated by a single glycoprotein protruding from its membrane envelope, called spike (S). Within S, the region that directly interacts with the membrane is called the fusion peptide, FP. It is the physico-chemical interactions of the FP with the host membrane that anchors it, enabling the necessary deformations of the membrane leading to the delivery of the viral genome into the cell when a fusion pore opens. Thermodynamic, kinetic, and intermolecular interactions are useful to understand molecular-level FP interactions with the host membrane. This knowledge can be leveraged to stop the spread of infection. Here, we examine the impact of calcium ions on CoV entry. Using cell infectivity, biophysical assays, and spectroscopic methods, we found that calcium ions stabilize the FP structure during conformational change that then allows its insertion into the host membrane, resulting in increased lipid ordering in the membrane. This lipid ordering precedes membrane fusion and correlates with increased fusion activity and higher levels of infection when calcium in present. As such, depletion of calcium ions leads to structure and activity changes in the fusion peptide that correlate well with in vitro experiments using calcium-chelating agents to block cell infection. We show calcium channel blockers can block virus infection in lung cells.

