Viral fusion proteins of classes II and III but not of class I sense the lipid composition of host membranes

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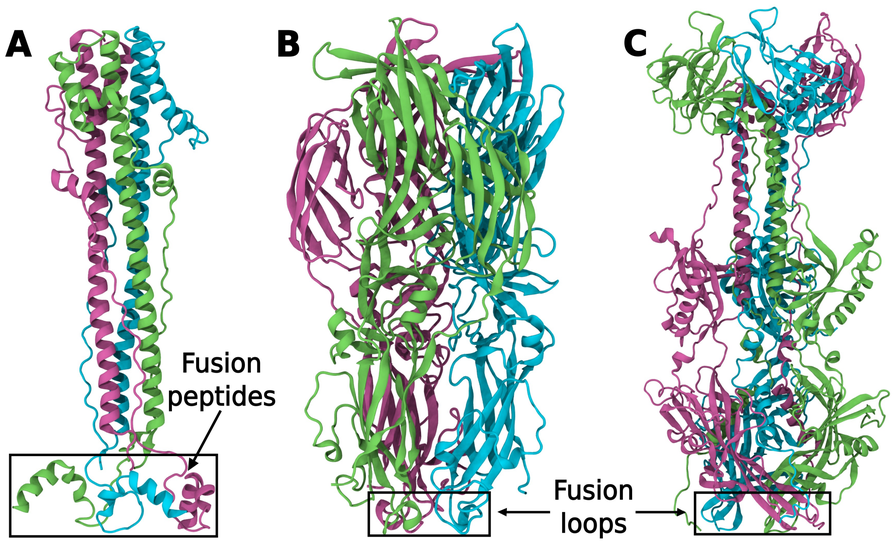
Abstract

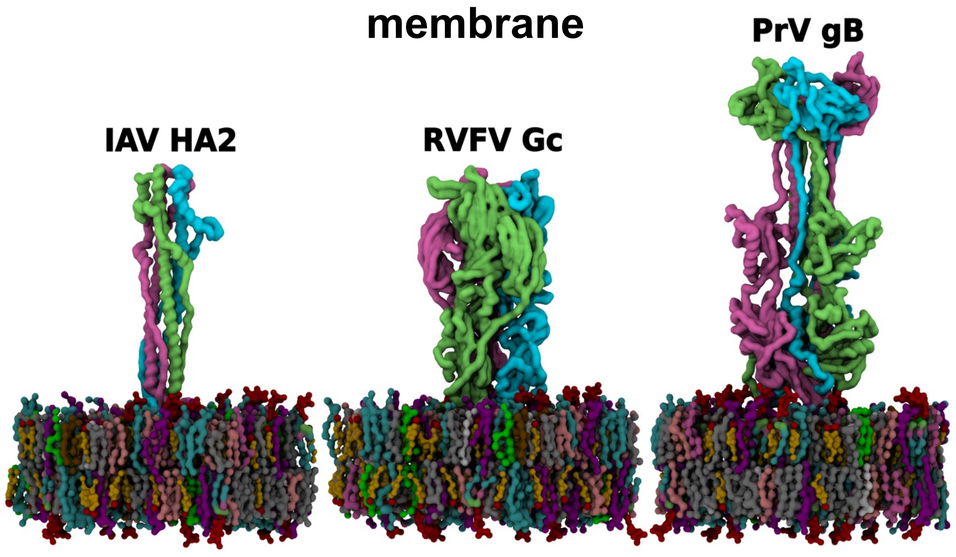
Viral infection requires stable binding of fusion proteins trimers to host membranes, which contain hundreds of lipid species. How viruses sense lipid compositions to target suitable host cells is poorly understood. Using multi-scale molecular simulations of fusion proteins from classes I-III in contact with membranes of various lipid compositions, we find that fusion proteins bind specific membranes by chemically recognizing distinct head group moieties and by sensing packing defects. Class II fusion proteins bind lipids with a pocket formed by each monomer, which enables membrane binding by monomers prior to their association to prefusion trimers. Class III fusion proteins bind with a pocket formed at the monomer-monomer interface, compatible with their preformed trimeric pre-fusion state. By computing 62 membrane binding free energies of fusion proteins, we find that membrane binding of class II and III proteins, but not of class I proteins, is greatly modulated by the content of polyunsaturated lipids, cholesterol, anionic lipids, or gangliosides. Our results show that class II and III fusion proteins selectively bind to mammalian plasma membranes or to the membranes of the endosomal compartments, albeit using distinct structural mechanisms.

Trimer structures of class I, II and III viral fusion proteins



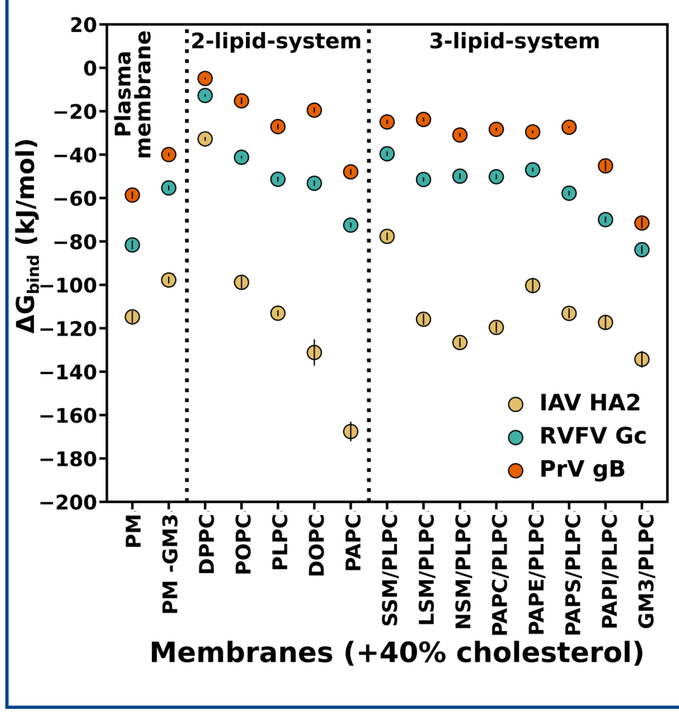
Post-fusion structures of (A) Influenza A virus hemagglutinin (PDB Ids: 1QU1, 1IBN), (B) Rift Valley Fever Virus Gc protein (PDB ID: 6EGU) and (C) Pseudorabies Virus gB protein (PDB ID: 6ESC)

MD simulations of viral fusion proteins bound to plasma membrane



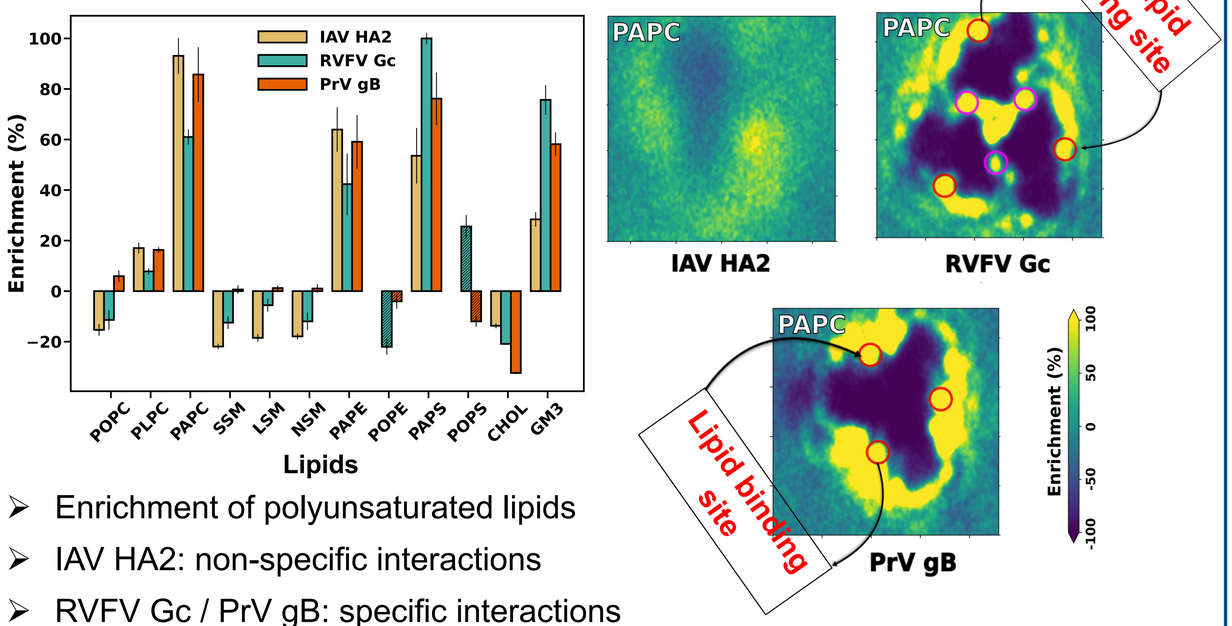
Coarse-grained models of the protein-membrane complexes

Result 1: Membrane binding affinities follow the order class I > class II > class III



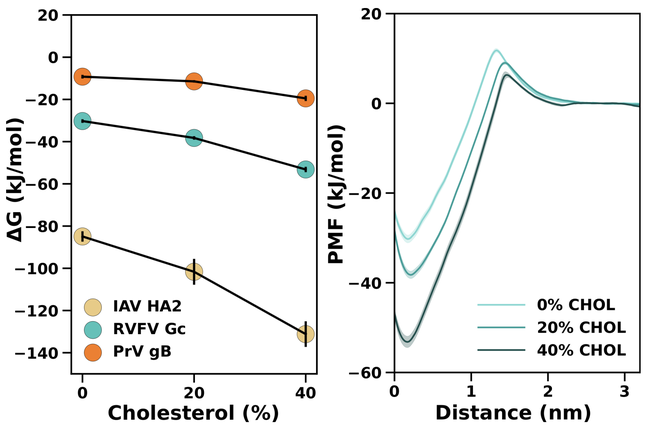
- Class I binds strongly
- Class II, III sensitive to lipid composition
- Polyunsaturated lipids enhance binding
- Saturated SM reduces binding, unsaturated SM does not interfere with binding
- Anionic lipids enhance or recover binding
- GM3 acts as co-receptor

Result 2: Polyunsaturated lipids bind to specific interaction sites



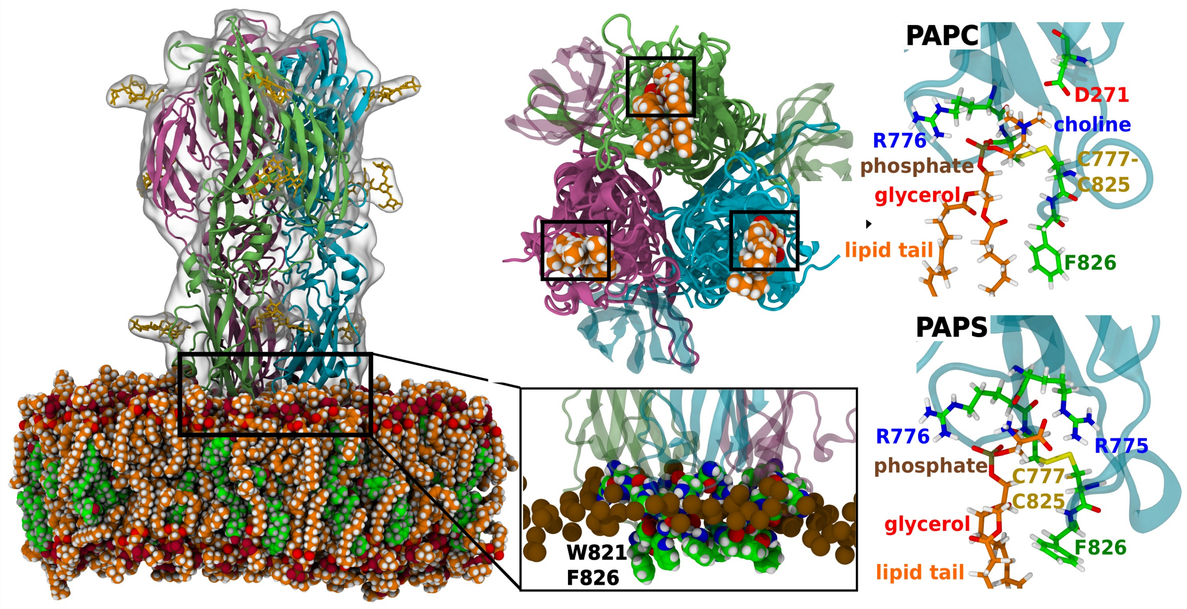
- Enrichment of polyunsaturated lipids
- IAV HA2: non-specific interactions
- RVFV Gc / PrV gB: specific interactions
- RVFV Gc: PC, PE, PS lipids bind to experimental binding site

Result 3: RVFV Gc and PrV gB are sensitive to cholesterol but not IAV HA2



- Binding increases with cholesterol conc.
- Strict cholesterol requirement for binding of RVFV Gc / PrV gB
- Cholesterol acts as a spacer between lipids
- Direct interactions between cholesterol and fusion loop residues

Result 4: Atomistic model of RVFV Gc interactions with PAPC and PAPS lipids



- Polyunsaturated PC, PE, PS find their way to exp. binding site
- Binding site lipid is anchored via PO4-ARG interactions
- Lipid binding on each monomer corroborates with monomeric prefusion state

Conclusions : (1) Sequence conservation analysis across 74 fusion proteins from 12 viral families indicate observed binding affinities follow class I > class II > class III. (2) Class I and class II/III fusion proteins utilize different mechanisms of binding to host membranes. (3) Binding of lipids to RVFV Gc and PrV gB is compatible with their prefusion state. (4) Enrichment of polyunsaturated lipids serves as a platform to stabilize the stalk-like fusion intermediate.

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