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SnapShot: Viral and Eukaryotic Protein Fusogens

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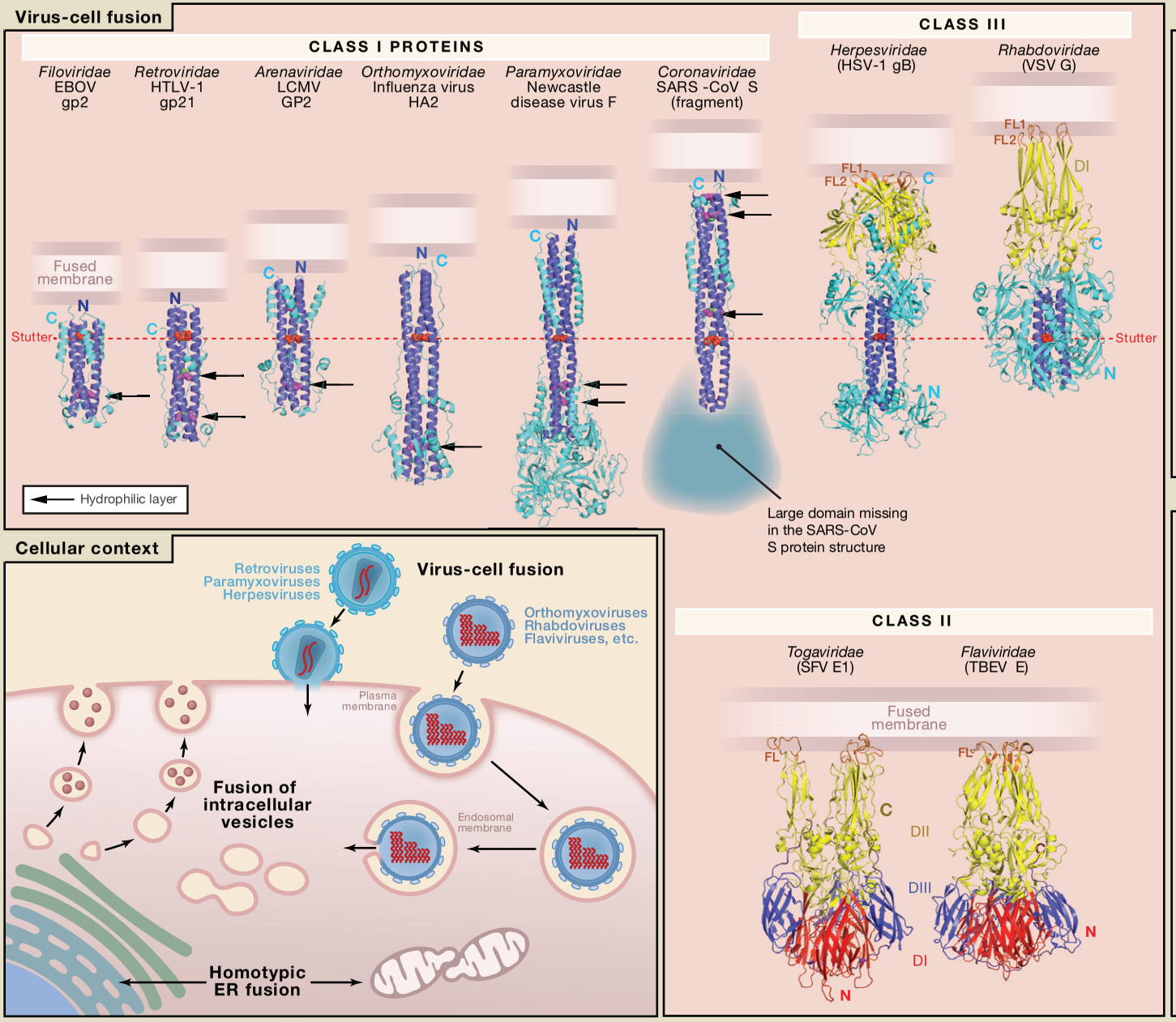

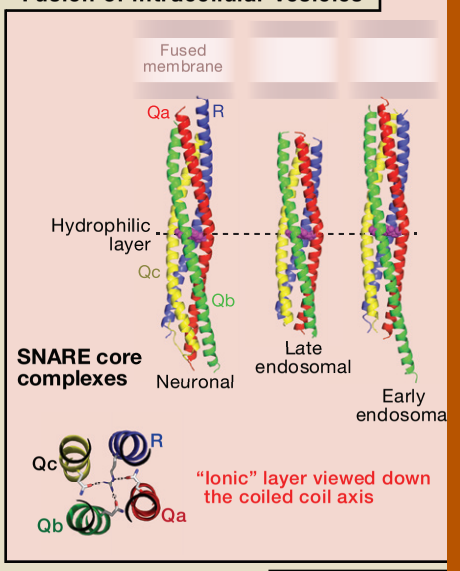

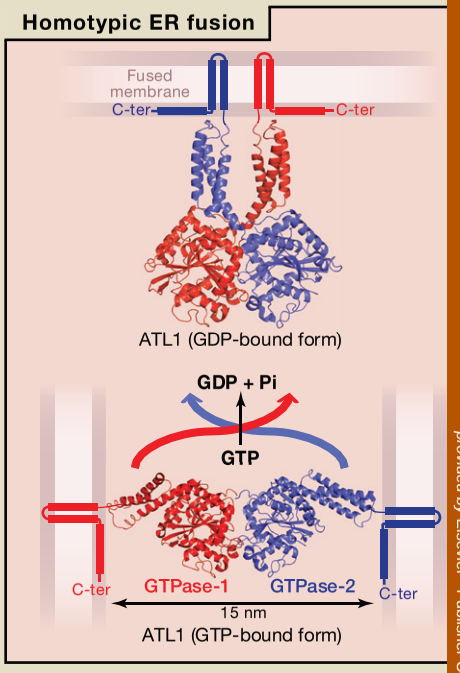

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Controlled membrane fusion is catalyzed by specific effector proteins present at the site of fusion. Fusion catalysis results from the thermodynamic coupling of protein refolding with targeted membrane perturbations. This SnapShot provides an overview of the fusion proteins that have been analyzed structurally to date, comparing common features in the conformation adopted after the membrane fusion reaction.

Viral Fusion Effectors

Viral fusogens are anchored in the viral membrane, and the initial fusogenic conformational change allows them to insert into the cell membrane. This transition is triggered by interactions of the virus particle with the host cell—either binding a cell surface receptor or protons in the acidic endosomal environment. During the fusogenic conformational change, the fusion protein initially adopts an intermediate extended conformation in which a "fusion peptide" projects away from the virus particle and inserts into the target membrane. The fusion protein subsequently collapses into a "hairpin" conformation in which the fusion peptide becomes juxtaposed to the viral transmembrane (TM) segment, thereby juxtaposing the two membranes. The structures of the postfusion hairpin conformation for a number of viruses are presented, highlighting common structural features of the observed hairpins. The overall process of virus-cell fusion and the accompanying conformational changes of the effector proteins have been reviewed, see for example Harrison (2008). The viral fusion proteins analyzed so far fall into three structural classes in which the postfusion form is a trimer of hairpins with different architectures. The predicted location of the fused membrane is outlined above the trimers.

The class I motif is characterized by a 7 residue periodicity of nonpolar amino acids (i.e.,"heptad repeats") that give rise to a central parallel trimeric α-helical coiled coil along the long axis of a rod-shaped molecule (blue in the ribbon diagrams). The N and C termini (labeled in blue and cyan) pack against each other at the membrane proximal end. A "stutter," a region where the coiled helix unwinds and alters the nonpolar repeat pattern (in red), permits the structural alignment of the various hairpin trimers (Igonet et al., 2011). The heptad repeats are also interrupted by hydrophilic layers (indicated in magenta, with horizontal arrows).

Class II proteins are folded essentially as β sheets with no long coiled α helix, and the trimer of hairpins is formed by the parallel interactions of domains I and II (red and yellow). The trimer is further clamped in place by the lateral interactions of domain III (in blue), which stabilizes the hairpin conformation. A stem region (only partially present in the available structures) connects to the TM segment. The fusion peptide is internal, situated in the loop between two β strands, and is therefore termed "fusion loop" (FL).

Class III proteins appear to be intermediate between classes I and II: they have a central parallel coiled coil (blue), but they have an elongated, β-sheet-rich fusion domain N terminal to it (yellow) instead of a fusion peptide as in class I. Although this fusion domain is superficially similar to its counterpart in class II proteins, the topological β-strand organization is unrelated, suggesting convergent rather than divergent evolution. The central parallel coiled coil also has a stutter, allowing a close alignment to the class I fusion proteins. The fusion domain of class III proteins has two fusion loops labeled FL1 and FL2.

Although there is no amino acid sequence conservation across virus families, the structures show clear homology within classes II and III. However, the simple heptad repeat pattern of class I fusogens is in several cases not sufficient to distinguish between divergent or convergent evolution and therefore, only for a subset of families displayed in the figure do the fusion proteins appear as clearly homologous.

Fusion of Intracellular Vesicles

A variety of different proteins control the fusion of intracellular vesicles, but the actual fusion effectors are believed to be the SNARE proteins, as reviewed by Südhof and Rothman (2009). The prefusion form of the SNAREs appears to be largely unstructured, and the postfusion form consists of a hetero-oligomeric complex formed by SNARE subunits that were anchored in the two opposing membranes before their fusion. The SNAREs in their postfusion conformation share with viral proteins of classes I and III an elongated, α-helical, parallel oligomeric coiled-coil organization in which the C-terminal TM segments are juxtaposed at the same end, making a stable protein rod termed "SNAREpin" by analogy to the viral hairpin. The SNAREpin organization differs from the viral proteins because it is a four-stranded coiled coil in which the amino acid sequence of each α helix is different. At the center, there is a hydrophilic, or "ionic," layer consisting of a central arginine (R) and three glutamine (Q) residues that hydrogen bond the guanidinium group of the arginine. This feature has allowed the classification of the SNAREs into four different categories—R-SNAREs and Qa-, Qb-, and Qc-SNAREs—with one representative of each being necessary for formation of a functional SNAREpin, as displayed in the figure.

Homotypic ER Fusion

ER tubule fusion is mediated by the atlastins (Hu et al., 2009; Orso et al., 2009). The crystal structures of atlastin 1 in two conformations, interpreted as pre- and postfusion (Bian et al., 2011; Byrnes and Sondermann, 2011), revealed an N-terminal globular GTPase domain followed by a three-helix bundle. The polypeptide chain then crosses the ER membrane twice, bringing the C-terminal end, which contains an amphipathic α helix, back to the cytosolic side of the ER membrane. GTP binding triggers the dimerization of the N-terminal GTPase domain, resulting in a conformation that physically bridges the two membranes to be fused, analogous to the extended (or "prehairpin") intermediate of viral fusion. GTP hydrolysis with the concomitant release of inorganic phosphate (Pi) triggers a repositioning of the three-helix bundle with respect to the GTPase domain. This motion—reminiscent of the myosin power stroke—projects the C-terminal ends of the subunits toward each other (red toward blue and vice versa, as shown), thereby forcing the apposition of the two membranes (Bian et al., 2011).

Abbreviations

ATL1, Atlastin 1; EBOV gp2, Ebola virus glycoprotein 2; ER, endoplasmic reticulum; HSV-1 gB, herpes simplex virus type 1 glycoprotein B; HA2, hemagglutinin subunit 2; HTLV-1 gp21, human T cell leukemia virus protein gp21; LCMV GP2, lymphocytic choriomeningitis virus glycoprotein 2; SARS-CoV S, severe acute respiratory syndrome coronavirus spike protein; SFV E1, Semliki forest virus envelope protein E1; SNARE, *N*-ethylmaleimide-sensitive factor attachment protein receptor; TBEV E, tick-borne encephalitis virus envelope protein E; TM, transmembrane; VSV G, vesicular stomatitis virus glycoprotein.

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