

## Viral Membrane Fusion and Its Inhibition

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The fusion of lipid bilayers is central to a number of diverse processes, such as fertilization, synaptic transmission, muscle development, and viral infection. Studies of enveloped viruses have advanced our knowledge of the mechanism of membrane fusion. Infection of a host cell by an enveloped virus requires that the two membranes fuse, so that the contents of the virus can be transferred to the host.

A general mechanism emerges for enveloped-virus membrane fusion, based on insights from studies of several viruses, but particularly two viral proteins: (i) influenza hemagglutinin and (ii) human immunodeficiency virus type-1 (HIV-1) glycoprotein envelope. In this mechanism, newly synthesized fusion proteins fold into a thermodynamically stable conformation that is inactive. Subsequently, the protein is proteolytically processed. No longer free to sample all conformational space, the processed protein is trapped in a metastable conformation, primed for fusion. When an appropriate activation signal arrives, whether low pH or receptor binding, the protein unleashes its fusion potential. No additional energy, such as ATP hydrolysis, is required for fusion. Through a spring-loaded mechanism, the fusion-peptide regions are propelled out of the protein and inserted into the target membrane. The transient, prehairpin intermediate spans both membranes and is vulnerable to inhibition. Subsequently, the protein adopts its most stable fold, the trimer-of-hairpins, which brings the two membranes together.

Dissection of the membrane-fusion process has led to a new strategy in HIV-1 therapy development – targeting viral entry – and may have implications for the development of an effective HIV vaccine. Because many enveloped viruses likely use the same mechanism of entry, similar strategies may be effective against a wide range of viral diseases.

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