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Viral Membranes

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Introduction

Viruses of many kinds possess lipids as integral components of their structure. Lipid-containing, or enveloped, viruses include: *Baculo-*, *Bunya-*, *Corona-*, *Filo-*, *Herpes-*, *Lenti-*, *Orthomyxo-*, *Paramyxo-*, *Pox-*, *Retro-*, *Rhabdo-*, and *Togaviridae*. Despite the great diversity of these viruses in regard to structure, replicative strategy, host range and pathogenicity, the function of the lipids in each case is the same – to form a membrane surrounding the encapsidated viral RNA or DNA genome. The lipids of the viral envelope form a continuous bilayer that functions as a permeability barrier protecting the viral nucleocapsid from the external milieu. Embedded in this bilayer are numerous copies of a limited number of virally encoded transmembrane proteins (often just one or two) that are required for virus entry into a potential host cell. These proteins mediate two essential functions: attachment of the virion to the cell surface; and fusion of the viral envelope with a cell membrane, resulting in accession of the viral nucleocapsid containing the genome to the cellular cytoplasm.

The membrane is acquired during viral assembly within an infected cell. This generally occurs by the budding of the previously assembled viral nucleocapsid through a cell membrane, incorporating host cell lipids and viral membrane proteins, but excluding virtually all cell membrane proteins. The particular cell membrane through which viral budding occurs is characteristic for each virus. Many viruses bud through the plasma membrane, but bunyaviruses bud through the Golgi apparatus, coronaviruses chiefly through the endoplasmic reticulum, and herpesviruses through the nuclear membrane. Poxviruses, which are among the largest and most complex animal viruses, are unique in acquiring two discrete membranes through a series of interactions with different cellular organelles, in a process that is not well understood.

Viral membranes have been extensively studied for many years, and for many reasons. The budded viral envelopes themselves represent isolated, readily purifiable subdomains of discrete cellular membrane bilayers. The envelope proteins that mediate entry of viruses into infectible cells are regarded as prototypes of membrane fusion machines. The initial binding of virions to potential host cells is mediated by prototypical ligand–receptor interactions in which viral proteins (ligands) bind to cell surface proteins (receptors). These properties of viral envelopes represent potential targets for antiviral therapy; they also provide models for important cellular phenomena.

Viral Bilayers

For many non-pathogenic viruses that can be readily purified in sufficient quantities in the laboratory, the bilayer arrangement of lipids in the viral envelope has been directly demonstrated using physical methods. It is assumed that the lipids in all viral envelopes are similarly arranged in a bilayer, based on those observations, and on the fact that the host cell membranes from which the viruses bud all contain bilayers, and also because it is the only physically reasonable arrangement of lipids that could supply the required protection from environmental stresses. Intact virions are impermeant to proteases and other enzymes.

Indeed, virions can swell and shrink in response to changes in osmolarity, showing that viral envelopes are impermeant to small molecules and ions as well as large proteins, and thus must consist of intact bilayers that completely surround the encapsidated viral genome.

The lipid composition of various viruses grown under different conditions, and in different cell types, has been studied in detail. These have shown that wide variations in lipid composition are tolerated in many viruses; they have provided no evidence that any substantial fraction of envelope lipids is bound to viral envelope proteins specifically, or exists in a nonbilayer conformation.

Recent studies have shown that many viruses bud from specialized regions of the plasma membrane known as 'rafts'. Rafts are regions of the plasma membrane characterized by high concentrations of sphingolipids (sphingomyelin and sphingoglycolipids) and cholesterol. These components participate in the formation of separate, partially miscible phases, distinguishable from the more fluid phase(s) which are relatively enriched in unsaturated phospholipids. Raft and non-raft phases co-exist as contiguous bilayers, but diffusion is relatively restricted within raft phases, and exchange of molecules between phases occurs more slowly than diffusion within a single phase. Although the existence of local heterogeneity in lipid and protein structure has been demonstrated in cell membranes using a variety of physical and detergent extraction techniques, a precise definition of rafts has not been achieved. There is little agreement regarding their size, or whether they are nucleated by lipids or by proteins. Despite these uncertainties, certain membrane constituents are clearly concentrated in specialized regions rich in sphingolipids and cholesterol, and these have been identified as the sites of important cellular signaling and transport functions, and of assembly and budding for many enveloped viruses. Detailed lipid analyses of purified budded virions have confirmed their origin in rafts, and have in turn helped to define the lipid composition of virus-associated rafts.

Viral Membrane Proteins

The proteins of viral membranes, like those of other membranes, may be classified as either integral or peripheral. Integral proteins are those that cross the membrane bilayer at least once, and thus cannot be solubilized without disrupting the bilayer, that is, without using detergents. Peripheral proteins are also membrane associated, but they do not cross the membrane and they can be removed from it by treatment with aqueous salts, high pH or chaotropic agents, which leave intact the hydrophobic interactions that stabilize the bilayer.

Most integral membrane proteins of enveloped viruses span the bilayer only once, although exceptions exist. Each transmembrane (anchoring) domain is a sequence of 18–27 predominantly hydrophobic amino acid residues. Because transmembrane sequences are inherently insoluble in water, integral membrane proteins require detergents for extraction from the bilayer and solubilization. When detergents and lipids are both removed from purified viral proteins, they tend to aggregate into rosettes, forming a kind of protein micelle, with the transmembrane sequences clustered together at their centers in order to maximize hydrophobic interactions and minimize contact with water. Purified viral membrane proteins can be reinserted into lipid bilayers of defined composition by mixing the detergent-solubilized protein with lipids, then removing the detergent by dialysis. These reconstituted viral membranes ('virosomes') often possess the native receptor binding and fusion activities.

The functions of the major integral viral membrane proteins are: first, to attach the virus to the uninfected host cell; and second, to effect penetration of the genome into the host cell cytoplasm through membrane fusion of the viral envelope with a host cell membrane. As much as 90% of each viral receptor binding/fusion protein is external to the viral membrane and thus accessible to removal and/or degradation by added proteases. Viral membrane proteins are often morphologically identifiable in electron micrographs as 'spikes' on the outer surface of membrane particles. Under favorable conditions, nearly the entire external domain may be rendered soluble and recovered intact and correctly folded after proteolytic removal from the virion, facilitating crystallization and structural analysis. These domains possess oligosaccharide side chains identical to those of cellular integral proteins in structure and attachment sites, and often possess disulfide bonds as well, reflecting the viral proteins' normal procession through the cell's endoplasmic reticulum–Golgi system (**Figure 3**).

While these proteins constitute the major fraction (>95%) of viral integral membrane proteins, there is an additional class of small integral proteins that oligomerize within the bilayer to form channels that facilitate the transport of ions or small molecules. These proteins have been called 'viroporins'. They include the M2 protein of influenza, the 6K protein of alphaviruses, and Vpu of HIV-1. They are thought to function in various ways to facilitate the assembly and release of new viral particles from the infected cell.

Peripheral membrane proteins are attached to the viral membrane by a combination of hydrophobic and electrostatic interactions. They may penetrate the bilayer to some extent, but they do not cross it as integral proteins do. Viral peripheral membrane proteins include M1 of influenza, M of paramyxoviruses, and MA of retroviruses. All enveloped viruses except the togaviruses encode an M-like peripheral protein that functions to bring together the envelope and nucleocapsid components during viral assembly.

Cellular Virus Receptors: Virus Membranes as Ligands

The first step in infection, attachment of the virus to the outer surface of the host cell, is performed by specific membrane proteins of enveloped viruses. One or more unique cellular 'receptors' are recognized by each species or strain of virus. The presence of a specific cellular receptor is often the major factor determining the susceptibility of a particular species to infection; it also determines the infectibility of different tissues or cells within infected individuals.

Different viruses may bind to any of a large number of different cell surface proteins, carbohydrates, or lipids. Binding serves several purposes. Most generally, it attaches the virus to the uninfected cell, maintaining proximity, and increasing effective viral concentration on the cell surface. More specifically, interaction of viral spikes with specific cell surface proteins may initiate conformational changes that activate the viral proteins for fusion. Binding to certain cell surface proteins may also promote endocytosis of the virus, by any of several cellular pathways. Endocytosis introduces the viral envelope into the lower pH of the endosome, which is required for activation of some viral fusion proteins. Activation of certain cell surface receptors by virus binding may also initiate specific signaling cascades within the cell, which may be useful to the virus during subsequent steps of infection.

Each enveloped virus exhibits unique binding specificities of its membrane proteins with particular cell surface features, resulting in a unique combination of these effects. For example, the HIV-1 recognition protein gp120 exhibits a near total specificity for binding to the CD4 receptor on immune cells. Further activation of the virus' fusion protein gp40 occurs by interaction with a coreceptor, either the chemokine receptor CCR5 or CXCR4. In contrast, orthomyxo- and many paramyxoviruses have much broader specificity. Their recognition proteins (HA or HN, respectively) bind to sialic acid residues attached to various cell surface proteins or lipids. Different strains show preference for sialic acid in different covalent linkages. Rhabdoviruses such as vesicular stomatitis or rabies virus are still less specific, binding indiscriminately to negative charge clusters, whether created by lipids, proteins, oligosaccharides, or surface-bound polyanions. This nonspecific binding property helps to account for the broad host range of these viruses, although some have also been reported to bind specifically to acetylcholine receptors, which may explain their neurotropism.

Viral Fusion

Fusion of the viral envelope with a cell membrane is facilitated by integral viral membrane proteins. The best studied viruses (HIV-1, orthomyxo-, paramyxo-, retro-, toga-, and rhabdoviruses) each possess a single fusogenic glycoprotein, but herpes- and poxviruses may possess several that work together. Virosomes consisting only of a purified viral fusion protein reconstituted into a lipid bilayer vesicle fuse readily with protein-free lipid bilayers, suggesting that the fusion proteins can act on host cell lipids and do not require participation by host cell proteins.

Because of their ready availability and ease of purification, viral fusion proteins have served as prototypes for understanding biological fusion reactions. Several general principles have emerged, which have been found to apply to at least one major class of cellular fusion reactions (those mediated by proteins called SNAREs) as well as all characterized viral fusions.

First, both viral and cellular fusion proteins act directly on the lipid bilayer to facilitate rearrangements identical to those that occur during protein-free lipid bilayer fusion. Fusion is thought to occur through a series of steps, constituting the so-called 'stalk–pore' pathway (**Figure 1**). The two closely apposed bilayers (**Figure 1(a)**) dimple

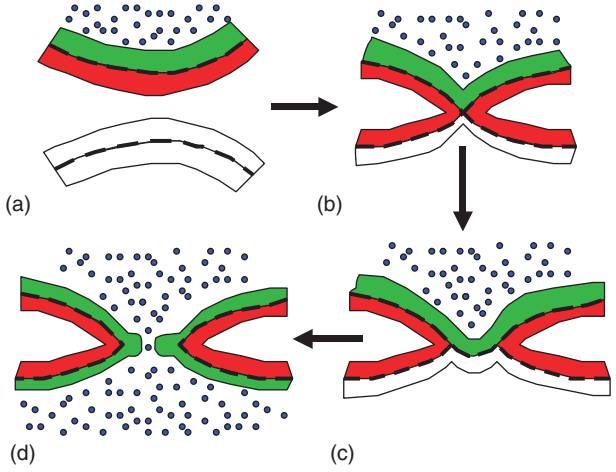

Figure 1 The stalk–pore mechanism of membrane bilayer fusion. (a) Initial pre-fusion state. The two leaflets of the cell membrane bilayer are colored green and red. The cytoplasm is indicated by blue dots. The viral membrane is colorless. (b) The stalk structure. In this state, continuity is established between the outer leaflets of the two membrane bilayers, allowing lipid mixing. (c) The fusion diaphragm constitutes a single bilayer separating the two aqueous compartments, comprising the inner leaflets of the cellular and viral membrane bilayers. The outer leaflets have already fused, and their lipids have mixed. (d) The fusion pore arises from rearrangement of the limited-area fusion diaphragm, perhaps facilitated by fusion proteins. Expansion of the fusion pore allows complete mixing of aqueous compartments and completes fusion. Fusion can occur even between protein-free lipid bilayers under certain conditions, but fusion proteins increase efficiency, probably by acting at each step in this pathway. Reproduced from Chernomordik LVand Kozlov MM (2005) Membrane hemifusion: Crossing a charm in two leaps. *Cell* 123: 375–382.

towards each other to form the 'stalk' (**Figure 1(b)**). This thins to form a 'hemifusion diaphragm' (**Figure 1(c)**), which now separates the two aqueous compartments by a single membrane bilayer in place of the two that separated them in the pre-fusion state. The hemifusion bilayer consists of the inner leaflets of the two original bilayers, the outer leaflets having already fused with consequent mixing of their lipid components. The hemifusion diaphragm can then rearrange to form a 'fusion pore' (**Figure 1(d)**), which must stabilize and widen to allow aqueous mixing, and thus complete the fusion reaction.

Precisely how viral membrane proteins promote fusion via the stalk–pore mechanism remains a subject of active research. Several properties of viral fusion proteins are known to be essential for activity, however. All viral and cellular fusion proteins are oligomeric, usually trimeric for virus fusion proteins. In most cases, several (probably 5–7) trimers must act cooperatively in order to complete the fusion reaction. One attractive idea is that the several fusion protein trimers encircle a limited area of bilayer, into which the fusion proteins can then transfer the energy released by their ensuing conformational transitions (**Figure 2**) in order to effect the lipid rearrangements required for fusion. Viral fusion proteins might potentiate any or all of the fusion steps: initial stalk formation, hemifusion diaphragm formation from the stalk, fusion pore formation from the hemifusion diaphragm, expansion of the initial fusion pore to complete fusion.

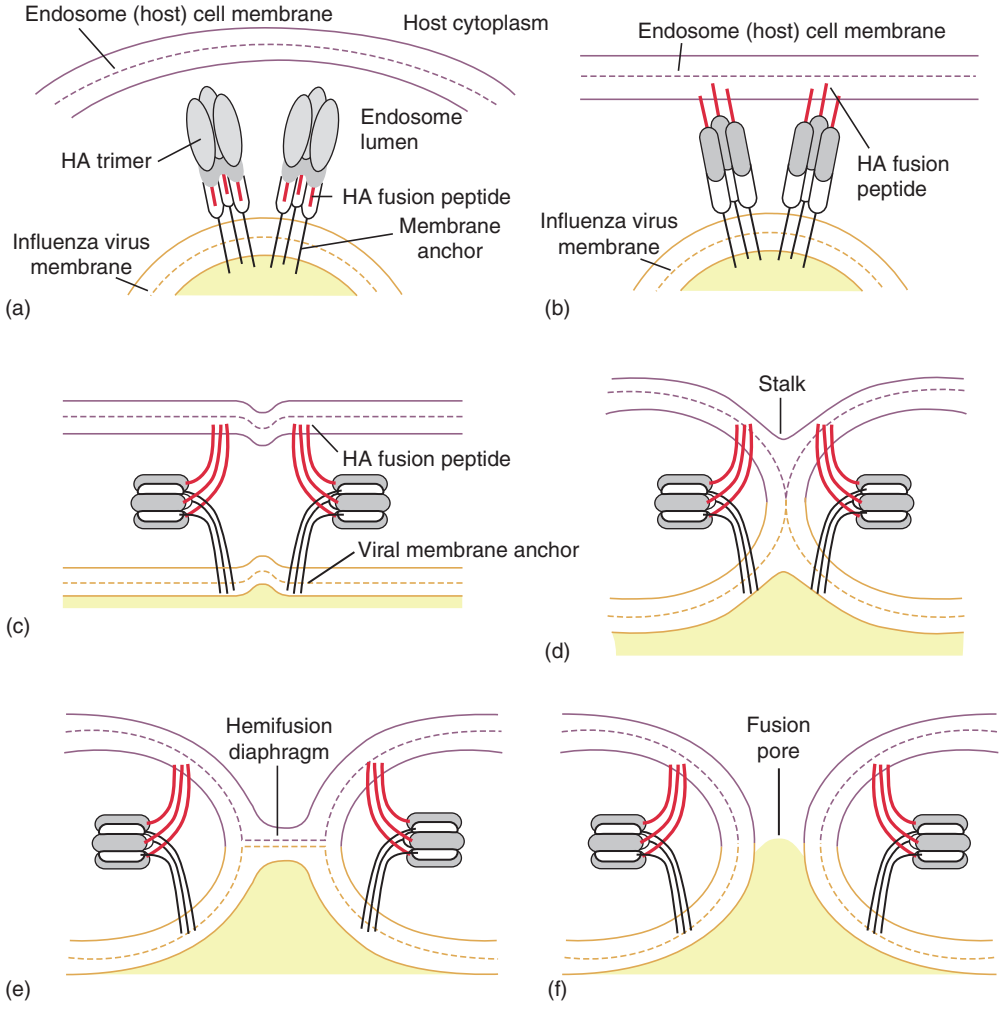

Figure 2 Proposed stalk–pore mechanism for membrane fusion mediated by a class I virus fusion protein, influenza hemagglutinin, HA. (a) The influenza virus has been internalized into the host cell endosome by receptor-mediated endocytosis (not shown). (b) Acidification of the endosome causes a conformational change in HA, which causes the fusion peptide (red) to become exposed; it subsequently inserts into the endosomal membrane. (c) Further refolding and clustering of HA trimers leads to bending of the two membranes toward each other. The resulting stalk (d) rearranges into the hemifusion diaphragm (e), where the virus interior is separated from the cytoplasm by a single bilayer, composed of the internal leaflets of the original membranes. This eventually rearranges, resulting in the formation of the fusion pore (f), which initially flickers and then dilates to complete the fusion reaction (not shown). Intra-leaflet lipid mixing, illustrated in **Figure 1**, is not shown. From Cross KJ, Burleigh LM, and Steinhauer DA (2001) Mechanism of cell entry by influenza virus. *Expert Reviews in Molecular Medicine* 6: 1–18, Cambridge University Press.

Within these general principles two distinct classes of viral fusion proteins have been recognized, possessing radically different architecture. Type I viruses include orthomyxo-, paramyxo-, retro-, and coronaviruses. Type II viruses include toga- and flaviviruses. Despite their different structures, these two classes of proteins facilitate the same lipid modifications during fusion.

All virus fusion proteins must remain inactive during biosynthesis and assembly so as to prevent premature, indiscriminate, counterproductive fusion within the infected cell. Both type I and type II fusion proteins are activated by a two-step process potentiated by interactions with a host cell. The inactive type I precursor protein is first cleaved at a specific site by limited proteolysis during assembly, generating a metastable, active form (**Figure 2(a)**). This then undergoes a conformational change mediated either by interaction with a specific cellular co-receptor (HIV-1), or by interaction with viral recognition proteins (paramyxoviruses) or by the low pH inside an endosome (orthomyxoviruses). Type II viral fusion proteins acquire their active conformation by an incompletely understood rearrangement of viral envelope proteins to form fusion protein trimers followed by interactions with specific lipids, notably cholesterol.

Activated fusion proteins of either type possess the following three structural features, which are required for complete fusion (**Figure 2**):

1. *Transmembrane domain.* This is the helical hydrophobic sequence (around 20 residues) that defines the fusion protein as an integral protein, and fixes it irreversibly in the viral bilayer. The transmembrane domain is inserted into the membrane bilayer during synthesis on membrane-bound ribosomes and appears not to rearrange during subsequent processing, activation or fusion. Type I and type II fusion proteins possess similar transmembrane domains. Not all transmembrane domains can participate in fusion reactions; a certain amount of conformational flexibility is required.

The transmembrane domain is required to complete the fusion reaction. Constructs in which the external, fusogenic domain of the influenza HA protein was attached only to the outer leaflet of the viral bilayer by a covalent bond with a lipid were capable of inducing hemifusion only, but were unable to complete the reaction.

2. *Fusion peptide.* This is a second relatively hydrophobic sequence that inserts into the cell membrane bilayer, and thus serves to bind the virus and cell membranes together. Exposure of the fusion peptide, enabling it to penetrate the target cell membrane, is an essential aspect of fusion protein activation, and requires a conformational change from a precursor form (**Figure 2(b)**). In type I proteins, this results from proteolytic activation; the influenza fusion peptides, for example, comprise the newly created N termini. Type II fusion peptides are located in a protruding loop of the protein structure, which is exposed by a poorly understood interaction with lipids, notably cholesterol. As with the transmembrane domain, a certain amount of conformational flexibility is required in the fusion peptide.

3. *A rigid, oligomeric rod-like structure connecting the fusion peptide with the transmembrane domain.* This consists of a helical coiled-coil in type I proteins (**Figure 2(b)**), and an arrangement of β-sheet domains in type II proteins. Once the fusion peptide has inserted into the target membrane, fusion is completed by the rearrangement of this metastable structure to its lowest free energy form (**Figures 2(d)–2(e)**). In order to assume this form, the rigid oligomer folds back upon itself, forming a 'hairpin' (**Figures 2(d)–2(e)**), thus dragging the cell membrane, tethered by the fusion peptide, toward the viral membrane, tethered by the transmembrane domain. The free energy released by this rearrangement is transferred to the lipid bilayers, providing the energy necessary to complete the fusion reaction. In the final fused product, the fusion peptide and the transmembrane domain are adjacent to each other in the same membrane, held in proximity by the fully stable, rigid hairpin (**Figure 2(f)**).

Membrane Synthesis and Viral Assembly

Viruses generally use the housekeeping mechanisms already operating in the infected cell in order to make maximal use of their limited genomes. Hence, viral membrane protein synthesis is carried out on host cell membrane-bound ribosomes, which inserts them into the endoplasmic reticulum membrane in the correct orientation (**Figure 3**). There they are glycosylated by the host cell machinery and assembled into appropriate oligomers, as directed by their own primary amino acid sequence. Most viral glycoproteins are then passed on to the Golgi by cellular mechanisms, where they are further glycosylated by host cell enzymes. For this reason, the envelope proteins of vesicular stomatitis virus (VSV), influenza, and a few other enveloped viruses have provided valuable tools to study the glycosylation and transport of membrane proteins through the cellular endoplasmic reticulum–Golgi–plasma membrane system. Because host cell protein synthesis is often inhibited by infection with these viruses (by a variety of cytopathic mechanisms), large amounts of a single viral membrane protein are produced and correctly processed in infected cells, without competition by cellular proteins.

Likewise, viral proteins are targeted to specific cellular locations by cellular processes. The viral proteins display the same amino acid sequence 'addresses' as host cell proteins, which are recognized by the host cell glycosylation and transport machinery. For example, the single VSV glycoprotein, named G, is glycosylated in the endoplasmic

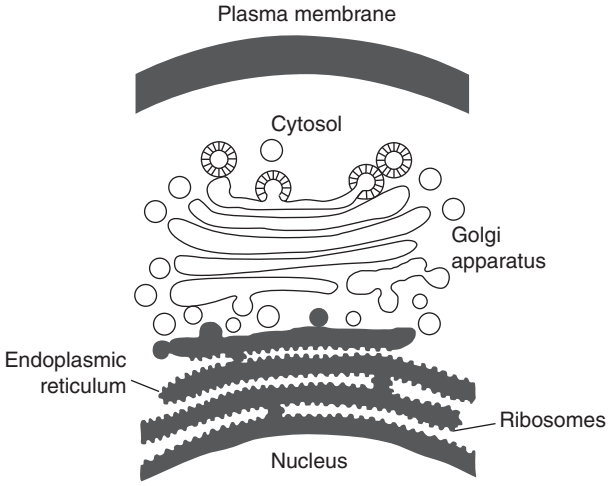

Figure 3 The endoplasmic reticulum–Golgi–plasma membrane system of a cell. All viral and cellular integral membrane proteins are synthesized by ribosomes bound to the endoplasmic reticulum membrane. Proteins destined for the plasma membrane are transported first to the proximal region of the Golgi (the *cis* face), then sequentially through the Golgi cisternae, to the *trans* face and out to the plasma membrane. In polarized cells, targeting to the apical or basolateral surface of the cell occurs from the *trans* face of the Golgi. Assembly and budding of different enveloped viruses occurs at characteristic points within this membrane system.

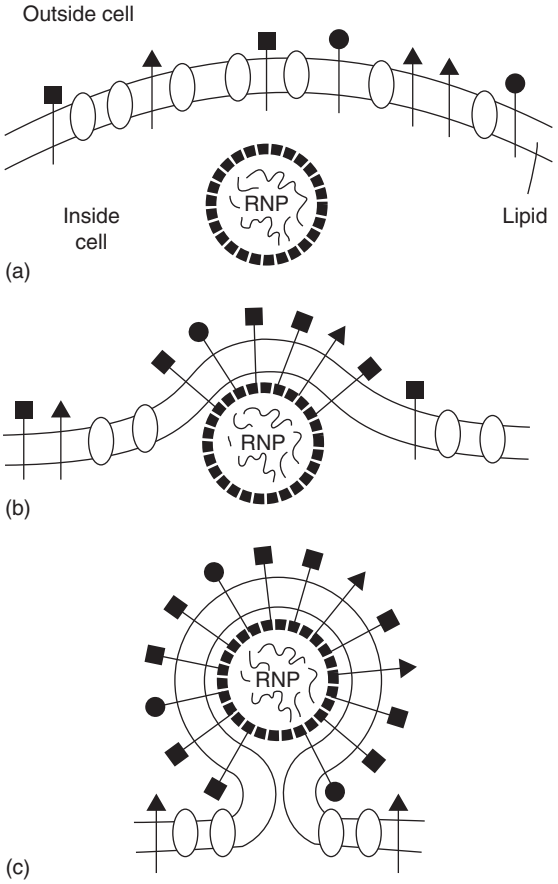

Figure 4 One kind of virus budding. Viral glycoproteins, inserted into the cellular membrane at the endoplasmic reticulum and processed through the Golgi to the plasma membrane (see Figure 3), associate with the assembled viral nucleocapsid. The direct association pictured here is characteristic of togaviruses. For other viruses, possessing helical nucleocapsids, the association is mediated by a peripheral membrane protein. Cellular membrane proteins are excluded from the envelope of the mature virion. This may occur during assembly, as pictures, or by prior formation of a viral membrane patch (or raft), before the nucleocapsid arrives at the membrane.

reticulum, the oligosaccharide is modified in the Golgi, and the mature protein is targeted to the basolateral plasma membrane of polarized cells after entry into the late Golgi. The influenza HA protein, on the other hand, is glycosylated and delivered to the apical plasma membrane of the same polarized cells after passage through the intracellular membrane system. The retention of coronavirus glycoproteins by the endoplasmic reticulum, and of bunyavirus glycoproteins by the Golgi, reflects the operation of the same cellular mechanisms that retain resident cellular proteins in these organelles. The localization of viral membrane proteins in turn, determines the location of viral assembly and budding.

The budding process consists of the wrapping of a viral glycoprotein-enriched piece of membrane around the previously assembled nucleocapsid, which contains the viral genome (Figure 4). Remarkably, the completed viral envelope contains viral proteins and host cell lipids, with host cell membrane proteins being almost completely excluded. There is much less discrimination, however, between different viral proteins than between viral and cellular proteins, since viral envelope proteins of one kind can assemble with nucleocapsids of another, resulting in the formation of pseudotype virions. Pseudotypes have proven useful in redirecting specific viral genomes to alternate host cells since membrane attachment proteins are major determinants of host cell specificity (see above). It has been suggested that the discrimination between viral and cellular membrane proteins may arise from the exclusion of cellular proteins from virus-associated raft-like lipid phases.

Different viruses have been described, that bud at every stage in the endoplasmic reticulum–Golgi–plasma membrane pathway (Figure 3). While paramyxo-, orthomyxo-, rhabdo-, and togaviruses (and many others) generally bud from the plasma membrane, they have also been shown to bud intracellularly under certain conditions. Some retroviruses assemble at the plasma membrane, while others do not; this has provided a classical basis for distinguishing between different types of retroviruses. Other viruses normally bud intracellularly, from the endoplasmic reticulum or Golgi apparatus, for example, coronaviruses and bunyaviruses respectively, but these have also

been observed to bud further down the pathway. In these cases, the nucleocapsid assembles on the cytoplasmic face of the membrane, and then buds into the intracellular organelle. The newly formed virion may then be secreted out of the cell through the normal secretory pathway, although this does not always occur efficiently.

In all enveloped viruses except togaviruses, budding is mediated by a peripheral membrane protein, usually called M or MA, which links the glycoprotein-containing patch of lipids with the viral nucleocapsid, containing the viral genome. The M proteins interact specifically with nucleocapsids of their own viral species, but they do not always interact specifically with the corresponding viral glycoproteins. Instead, they may concentrate on the cytoplasmic side of the raft-like lipid phases that accumulate various viral glycoproteins. This could provide the structural basis for the formation of pseudotype virions, and might explain why many viruses contain widely varying ratios of glycoproteins to M or nucleocapsid proteins.

In contrast, togaviruses, which lack any M protein, possess an icosahedral nucleocapsid, which interacts directly with the cytoplasmic domain of the viral membrane protein. Completed virions contain an equal number of nucleocapsid and membrane protein molecules. Both are in a similar geometric arrangement, mediated by specific protein–protein interactions between them.

As described above, the lipids of the viral membrane are taken from the host cell membrane during budding. No new lipids are specifically synthesized in response to viral infection. Alterations in cellular lipid metabolism have been reported to result from some viral infections in cultured cells, but these are probably secondary to other cytopathic effects; there is no indication that they play an important role in the progress of infection.

See also: Baculoviruses: Molecular Biology of Nucleopolyhedroviruses; Bunyaviruses: General Features; Coronaviruses: General Features; Filoviruses; Herpesviruses: General Features; Orthomyxoviruses: Molecular Biology; Reticuloendotheliosis Viruses; Togaviruses: General Features.

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Viral Pathogenesis

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Introduction

Viral pathogenesis deals with the interaction between a virus and its host. Included within the scope of pathogenesis are the stepwise progression of infection from virus entry through dissemination to shedding, the defensive responses of the host, and the mechanisms of virus clearance or persistence. Pathogenesis also encompasses the disease processes that result from infection, variations in viral pathogenicity, and the genetic basis of host resistance to infection or disease. A subject this broad cannot be treated in a single entry, and this article focuses on the dissemination of viruses and their pathogenicity.

Sequential Steps in Viral Infection

One of the cardinal differences between viral infection of a simple cell culture and infection of an animal host is the structural complexity of the multicellular organism. The virus must overcome a number of barriers to accomplish the stepwise infection of the host, beginning with entry,