

The cell biology of receptor-mediated virus entry

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The cell imposes multiple barriers to virus entry. However, viruses exploit fundamental cellular processes to gain entry to cells and deliver their genetic cargo. Virus entry pathways are largely defined by the interactions between virus particles and their receptors at the cell surface. These interactions determine the mechanisms of virus attachment, uptake, intracellular trafficking, and, ultimately, penetration to the cytosol. Elucidating the complex interplay between viruses and their receptors is necessary for a full understanding of how these remarkable agents invade their cellular hosts.

Introduction

Within an infected cell, viral nucleic acid, be it RNA or DNA, is relatively cosseted by cellular membranes and a protective cytosolic environment, but the cell-free stage that viral genomes must transit to access new host cells is fraught with danger. Viruses mitigate against these risks by packaging their nucleic acid into particles protected by a membrane and/or protein shell. This packaging poses a thermodynamic dilemma for a virus: particles must be resilient enough to protect the genome from environmental and/or immunological insults but also appropriately labile to ensure the contents are released when encountering suitable target cells. Thus, viruses are constructed as metastable molecular assemblages that can be unlocked during entry by specific molecular and/or cellular environmental cues, with minimal energetic input (Marsh and Helenius, 2006). Receptors are key to the unlocking process, either directly triggering the molecular changes that lead to fusion/penetration or by guiding virions to specific cellular sites where environmental cues trigger fusion/penetration and subsequent infection. Thus, the unlocking process is usually directly coupled to the mechanisms through which viral genomes are transferred across a limiting

cellular membrane (usually the plasma membrane or endosome membrane), the principal barrier to infection.

In this review, we discuss how events at the cell surface determine viral entry pathways and, using several different examples, examine some of the strategies viruses use to overcome cellular barriers to infection (Fig. 1). Receptor-mediated signaling will emerge throughout the review as an important component of virus entry that can operate at multiple stages, as will insights into the variations that viruses have developed on the principle themes for entry.

Virus receptors

Initial encounters between a virus and a host cell are mediated through viral surface components, either membrane glycoproteins or sites on a viral capsid (Marsh and Helenius, 2006), binding to glycolipid and/or glycoprotein attachment factors, such as heparan sulfate proteoglycans, on the target cell surface (de Haan et al., 2005; Vlasak et al., 2005). These first interactions, which may lack specificity, are often electrostatic and serve primarily to give a virus an initial catch-hold from which it can then recruit specific receptors that drive the reactions leading to entry. The receptors are cell surface molecules that provide functions essential for productive infection. In simple situations, receptors can efficiently target viruses for endocytosis (Fig. 1 A); alternatively, receptors may be used to activate specific signaling pathways that facilitate entry, or they may directly drive fusion/penetration events at the surface of a target cell or within endocytic compartments by inducing conformational changes in key virus surface structures (Fig. 1). In other cases, the reasons underlying the use of specific receptors are more obscure, and a full appreciation will probably require better understanding of the mode of entry of the virus into the hosts, the architecture of target cells within different tissue environments, and the biology of the virus within its hosts. The use of specific cell surface components with restricted expression patterns is frequently responsible for viral tropism, i.e., the ability of a virus to infect a limited set of target cells.

A number of the cell surface components exploited by viruses have now been identified (Table I). Many viruses use

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Abbreviations used in this paper: CAR, coxsackievirus and adenovirus receptor; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; EGFR, EGF receptor; HCV, hepatitis C virus; LDLR, low-density lipoprotein receptor; L-SIGN, liver-SIGN; PI3K, phosphoinositide 3-kinase.

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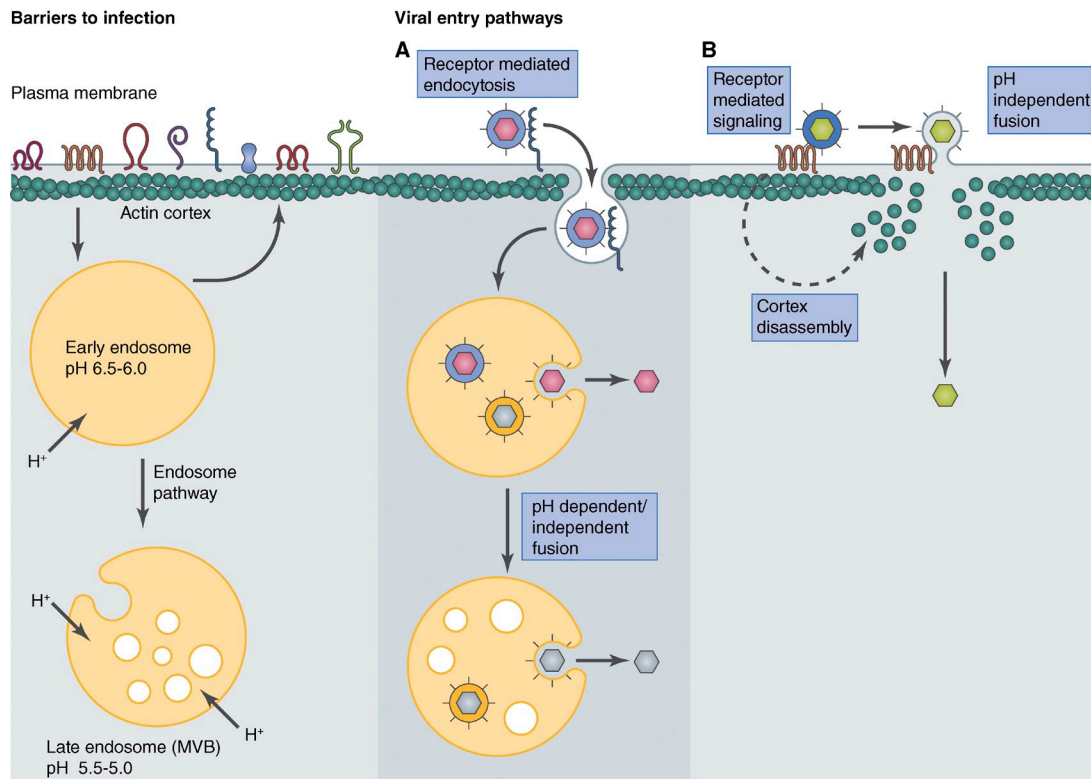


Figure 1. **Virus entry strategies.** The cell imposes intrinsic barriers to virus entry including the plasma membrane, actin cortex, and limiting intracellular membranes. (A and B) Viruses have evolved various strategies to overcome these barriers, such as receptor-mediated endocytosis followed by pH-dependent/independent fusion from endocytic compartments (A) or pH-independent fusion at the plasma membrane, coupled with receptor-mediated signaling and coordinated disassembly of the actin cortex (B). Enveloped viruses are shown; nonenveloped viruses use similar strategies, although the mechanisms of action are different. MVB, multivesicular body.

single molecular species as receptors, for example CD155 for poliovirus (Mendelsohn et al., 1989), the low-density lipoprotein receptor (LDLR) for human rhinovirus 2 (Fig. 2 A; Hofer et al., 1994), and dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) for the phleboviruses (a subgroup of bunyaviruses; Lozach et al., 2011b). Alternatively, some viruses can use more than one molecular species as receptors, each with equivalent roles, for example, angiotensin-converting enzyme (ACE) or liver-SIGN (L-SIGN) for SARS coronavirus (Li et al., 2003; Jeffers et al., 2004) and scavenger receptor-B2 (SR-B2) or P-selectin glycoprotein ligand-1 (PSGL-1) for enterovirus 71 (Table I; Nishimura et al., 2009; Yamayoshi et al., 2009). However, other viruses exhibit a more complex receptor dependency that involves engagement with at least two distinct plasma membrane components, each of which is essential (Fig. 2). Human immunodeficiency viruses (HIVs) are the archetype for such a process. After adsorption to cell surface attachment factors, the HIV envelope protein (Env, consisting of trimers of gp120/gp41 heterodimers) binds to the primary receptor CD4 (Dalglish et al., 1984; Klatzmann et al., 1984). By relieving constraints that prevent Env from transitioning to thermodynamically more stable conformations, these interactions initiate conformational changes that facilitate strain-specific interactions of gp120 with the coreceptors CCR5 or CXCR4 and allow initial structural changes in gp41, the Env component that promotes

fusion (Choe et al., 1996; Deng et al., 1996; Dragic et al., 1996; Feng et al., 1996; Haim et al., 2011). Engagement of the coreceptor drives further Env structural rearrangements that culminate in fusion of the viral and host membranes (Fig. 2 B; Dragic et al., 1996).

Another intriguing example of a virus requiring multiple cell surface components for entry is hepatitis C virus (HCV). Aside from attachment factors that include heparan sulfate and L-SIGN (Barth et al., 2003; Gardner et al., 2003; Pöhlmann et al., 2003), the HCV envelope glycoprotein E2 interacts directly with two receptors: the tetraspanin CD81 that is thought to be involved in membrane microdomain architecture (Pileri et al., 1998) and SR-B1 that binds several lipoproteins, including high-density lipoprotein, low-density lipoprotein, and very low-density lipoprotein (Scarselli et al., 2002). In addition to these key components, the minimal HCV entry complex requires the tight junction components claudin-1 and occludin. Thus, co-expression of four proteins—CD81, SR-B1, claudin-1, and occludin—is required to confer permissivity for HCV entry (Fig. 2 C; Evans et al., 2007; Liu et al., 2009; Ploss et al., 2009; Dorner et al., 2011). There is limited evidence for a direct interaction between the HCV glycoproteins and claudin-1 or occludin (Evans et al., 2007; Krieger et al., 2010), indicating that these molecules may act by regulating the activities of CD81 and/or SR-B1 rather than binding viruses directly; indeed, heterodimers of claudin-1 and CD81 may be necessary for

Table I. Virus receptors used in this study

Virus	Family	Receptors	Reference
Old World arenaviruses	Arenaviridae	α -Dystroglycan	Cao et al., 1998
New World arenaviruses	Arenaviridae	Transferrin receptor	Radoshitzky et al., 2007
Norovirus	Caliciviridae	HBGA	Huang et al., 2003; Lindesmith et al., 2003
Japanese encephalitis virus	Flaviviridae	Hsp70	Das et al., 2009
Influenza A	Orthomyxoviridae	Sialic acid	Matlin et al., 1981
Henipavirus	Paramyxoviridae	Nephrin B2	Negrete et al., 2005
Bunyavirus	Phleboviridae	DC-SIGN	Kaplan et al., 1996
Hepatitis A virus	Picornaviridae	TIM-1	Lozach et al., 2011b
Poliovirus	Picornaviridae	CD155	Mendelsohn et al., 1989
Rhinovirus (major group)	Picornaviridae	ICAM-1	Greve et al., 1989; Staunton et al., 1989
Rhinovirus (minor group)	Picornaviridae	LDLR	Hofer et al., 1994
John Cunningham polyomavirus	Polyomaviridae	LSTc	Neu et al., 2010
SV40 polyomavirus	Polyomaviridae	GM1	Tsai et al., 2003
Reovirus	Reoviridae	JAM	Barton et al., 2001
Sindbis virus	Togaviridae	Laminin receptor	Wang et al., 1992
SARS coronavirus	Coronaviridae	ACE 2 or L-SIGN	Li et al., 2003; Jeffers et al., 2004
Herpes simplex virus 1/2	Herpesviridae	Nectin-1/2 or HVEM	Montgomery et al., 1996; Geraghty et al., 1998; Krummenacher et al., 1998
Measles virus	Paramyxoviridae	SLAM or Nectin-4	Tatsuo et al., 2000; Noyce et al., 2011
Enterovirus 71	Picornaviridae	PSGL-1 or SR-B2	Nishimura et al., 2009; Yamayoshi et al., 2009
Human T cell leukemia virus 1	Retroviridae	GLUT-1 or Neuropilin-1	Manel et al., 2003; Ghez et al., 2006
Adenovirus 2	Adenoviridae	CAR and α v integrins	Wickham et al., 1993; Bergelson et al., 1997; Tomko et al., 1997
Ebola virus	Filoviridae	TIM-1 and NPC1	Carette et al., 2011; Côté et al., 2011; Kondratowicz et al., 2011
HCV	Flaviviridae	CD81 and SR-B1 (claudin-1 and occludin)	Pileri et al., 1998; Scarselli et al., 2002; Evans et al., 2007; Ploss et al., 2009
Epstein-Barr virus	Herpesviridae	CD21 and MHC-II	Fingerth et al., 1984; Li et al., 1997
Coxsackievirus B	Picornaviridae	DAF and CAR (occludin)	Bergelson et al., 1997; Martino et al., 1998; Coyne et al., 2007
Rotavirus	Reoviridae	Sialic acid and integrins	Yolken et al., 1987; Coulson et al., 1997; Guerrero et al., 2000
HIV	Retroviridae	CD4 and CCR5 or CXCR4	Dagleish et al., 1984; Klatzman et al., 1984; Choe et al., 1996; Deng et al., 1996; Dragic et al., 1996; Feng et al., 1996

Virus particles engage a variety of cell surface molecules to facilitate entry. Some virus particles use single-receptor species; others use alternative molecules, either of which is sufficient, whereas other viruses require a specific combination of receptors. Factors in parentheses may not directly interact with virus particles; however, they are necessary for virus entry. Examples from each category are given and illustrate the diversity of receptors. The majority of the viruses listed are human pathogens. ACE, angiotensin-converting enzyme; DAF, decay-accelerating factor; HBGA, histoblood group antigen; HVEM, herpesvirus entry mediator; JAM, junctional adhesion molecule; PSGL-1, P-selectin glycoprotein ligand-1; SLAM, signaling lymphocyte-activation molecule.

infection (Harris et al., 2008, 2010). HCV requires clathrin-mediated endocytosis and low endosomal pH for productive infection (Blanchard et al., 2006; Meertens et al., 2006; Tscherne et al., 2006). That HCV uses such a complex array of cell surface components to achieve this goal suggests that receptor engagement plays a more substantial role in virus entry than just guiding virions into clathrin-coated vesicles. Hints that this may be the case include the observation that HCV particles associate with host lipoproteins that bind both SR-B1 and/or the LDLR and that SR-B1 can facilitate the bidirectional transport of cholesterol from lipoproteins, raising the possibility that virion-associated lipoproteins can locally modify the lipid environment of a host cell membrane (Scarselli et al., 2002; Shimizu et al., 2011). In addition, HCV entry can be modulated by receptor tyrosine kinases (EGF receptor [EGFR] and EphA2), possibly through mechanisms that influence CD81 interaction with claudin-1 (Lupberger et al., 2011).

In addition to HIV and HCV, other viruses including adenoviruses, rotaviruses, picornaviruses, and herpesviruses require multiple cell surface components (Table I; López and Arias, 2004; Coyne and Bergelson, 2006; Heldwein and

Krummenacher, 2008; Burckhardt et al., 2011). Simply, the use of multiple receptors will increase binding avidity, but, of more consequence, the sequential engagement of distinct receptor moieties allows the timing of key events in virus fusion/penetration to be tightly coordinated (López and Arias, 2004; Burckhardt et al., 2011). Although viruses have the potential to cluster homogenous or heterogenous receptors, we know relatively little of the stoichiometry of receptor engagement. How viruses assemble multimeric receptor complexes on the surfaces of cells and the impacts that variations in this process have on fusion/penetration dynamics, sites of entry, and subsequent uncoating remain poorly understood. Lateral motion on the cell surface or along filopodia has been observed for several viruses and may help viruses encounter necessary coreceptors in numbers sufficient to generate productive entry events (Lehmann et al., 2005; Burckhardt and Greber, 2009). Alternatively, it may bring viruses to positions of endocytosis or where fusion/penetration is more likely to lead to productive infection. High-resolution mapping of most cell surface receptors by EM, super-resolution light nanoscopy, and live-cell single-molecule tracking remains to be performed. In the case of virus receptors, mapping the

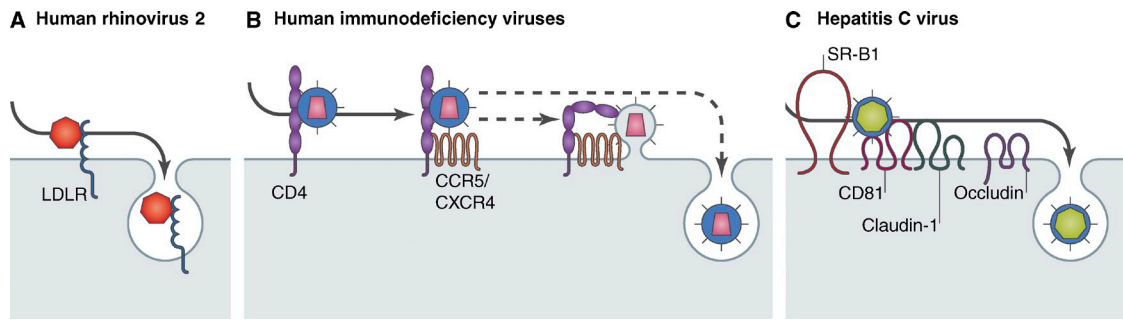


Figure 2. Virus receptors. Virus entry is initiated by specific interactions between virus particles and receptors. (A) Human rhinovirus 2 undergoes receptor-mediated endocytosis after interaction with LDLR. (B) CD4 is the primary receptor for HIVs, but virus penetration requires further interactions with chemokine receptor CCR5 or CXCR4. Initial observations indicated that coreceptor engagement triggered fusion directly at the plasma membrane; however, recent studies suggest that fusion can also occur after endocytosis (Miyachi et al., 2009). Although these mechanisms appear mutually exclusive, it is possible that both may operate, and additional studies are required to establish the relevant pathway for key target cells in vivo. (C) HCV entry requires at least four host factors. The virus particle is thought to directly interact with SR-B1 and CD81, whereas the tight junction components claudin-1 and occludin are indirectly involved. Data suggest that CD81/claudin-1 heteromers are necessary for infection. It is currently unknown how HCV is directed to clathrin-coated vesicles.

normal distributions of receptor components and how these distributions are modulated by physiological or viral ligands is likely to provide key insights to how receptor engagement facilitates virus entry and may suggest novel strategies for abrogating these events.

Exploiting receptors to cross epithelial barriers

Many mammalian viruses initially gain access to their hosts by crossing epithelial barriers in the respiratory, digestive, or reproductive tracts, either with or without infection of the epithelial cells themselves. Although these epithelial tissues act as barriers between body cavities and underlying tissues, viruses have become adept at finding ways across. Some viruses exploit cells of the immune system, such as macrophages and dendritic cells, which have innate capacities to cross or extend processes across epithelia, as “Trojan horses” to penetrate the epithelial barrier (Shannon-Lowe et al., 2006; Stamatakis et al., 2009; Lemon et al., 2011). Others have developed remarkable capacities to exploit epithelial cell surface proteins. The entry of coxsackievirus B provides a striking example. This virus infects its human hosts through the epithelial lining of the gut. For infection of polarized epithelial (Caco-2) cells in culture, coxsackievirus B requires the coxsackievirus and adenovirus receptor (CAR), which is located on the basolateral surface and within tight junctions and is inaccessible to apically delivered viruses (Cohen et al., 2001). The virions initially bind to an apically expressed glycosylphosphatidylinositol-linked protein, CD55/decay-accelerating factor (DAF), the clustering of which activates Abl kinase and drives Rac-dependent actin reorganization that in turn leads to translocation of virus particles to tight junctions where they engage CAR and undergo endocytosis (Coyle and Bergelson, 2006). Binding to CD55 also activates the non-receptor tyrosine kinase Fyn, which phosphorylates caveolin, thus facilitating endocytosis (Coyle and Bergelson, 2006). As CD55 cannot link directly to the actin cytoskeleton, it is unclear how actin-dependent translocation of virus–receptor complexes occurs, nor is it clear how the virus transits tight junctions and undergoes endocytosis. Nevertheless, this system provides an

exquisite example of how sequential receptor engagement and receptor-induced signaling are coupled to facilitate virion translocation and entry. Recent findings indicate that a related picornavirus, echovirus 11, also undergoes DAF-dependent transport to the tight junctions, although a junctional coreceptor has yet to be identified (Sobo et al., 2011).

Like coxsackievirus B, hepatitis A virus is a fecal orally transmitted picornavirus; however, its principal site of replication is the liver, and it must therefore have developed mechanisms to cross the gut epithelium. In vitro studies suggest that hepatitis A virus–specific IgA facilitates transcytosis of virus particles through polarized epithelial cells via the polymeric immunoglobulin receptor (Dotzauer et al., 2005). Critically, complexed IgA can subsequently mediate hepatitis A virus entry to hepatocytes via asialoglycoprotein receptors (Dotzauer et al., 2000). Thus, IgA acts as a bridging component for sequential receptor-mediated hepatitis A virus transit and infection. This process appears to be independent of the standard hepatitis A virus receptor T cell immunoglobulin and mucin domain 1 (TIM-1; Kaplan et al., 1996).

In contrast, adenoviruses exploit both the activities of immune sentinel cells and receptor polarity to penetrate the respiratory epithelium. Adenovirus type 2 uses CAR and $\alpha v\beta 3/\alpha v\beta 5$ integrins for productive entry (Wickham et al., 1993; Bergelson et al., 1997; Tomko et al., 1997). As with CAR, $\alpha v\beta 3$ and $\alpha v\beta 5$ are located on the basolateral membrane of polarized respiratory epithelial cells, and intact epithelial monolayers are resistant to adenovirus type 2 infection from the apical side. Uptake of adenovirus type 2 into macrophages associated with the apical surface of the epithelium induces the secretion of cytokines, in particular, CXCL8 (IL-8). In response to CXCL8, receptors expressed on respiratory epithelial cells (CXCR1/2) induce redistribution of both $\alpha v\beta 3$ and CAR to the apical surface, where they mediate virus entry (Lütschig et al., 2011). Not only do these examples illustrate the sophisticated ways in which some viruses sequentially exploit distinct cell surface moieties and receptor-signaling activities to successfully mediate infection or overcome the barrier function of epithelia, but they also demonstrate how analyzing virus entry in experimental systems that

mimic normal tissues can provide new insights to infection mechanisms. Significantly, both coxsackievirus B and adenovirus type 2 entry require the activation of specific kinases that are potential targets for pharmacological intervention.

Receptor-mediated endocytosis

Receptor engagement initiates events that enable viruses to transit the barrier imposed by the plasma membrane and associated structures. In most cells, the cortex (an elaborate network of actin fibers, actin-binding proteins, membrane-linker proteins [e.g., ERM proteins], motor proteins, and other components tens of nanometers thick) supports and modulates the physical and dynamic properties of the plasma membrane (Taylor et al., 2011). From the virus perspective, little attention has been paid to the actin cortex, in part because of the paucity of tools to study the structure but also because of the extent to which the cortex varies in different cell types, particularly in tissue culture lines. The cortex has the potential to prevent or delay the transit of large molecular assemblies from the cytoplasm toward the plasma membrane—for example, it excludes ribosomes from regions adjacent to the plasma membrane—and presumably similarly restricts incoming virus particles (Marsh and Bron, 1997). In the few examples in which it has been studied, virus-induced receptor-mediated signaling can cause local actin perturbation to allow viruses that undergo penetration at the cell surface to transit the cortex (Fig. 1 B; Wang et al., 2005; Yoder et al., 2008; Taylor et al., 2011). For HIV, Env engagement with the coreceptor CXCR4 on resting CD4⁺ T cells leads to G α _i signaling and subsequent activation of the actin-depolymerizing protein cofilin to induce local cortex reorganization that facilitates infection (Yoder et al., 2008). Cross-linking EGFR and α v β 3 integrin by human cytomegalovirus at the cell surface results in the cooperative activation of phosphoinositide 3-kinase (PI3K) and Src, culminating in actin reorganization through RhoA and cofilin, events that correlate with translocation of human cytomegalovirus capsids to the nucleus and infection (Wang et al., 2005).

Endocytosis provides a mechanism through which viruses can pass through the cortex by exploiting intrinsic properties of endocytic vesicles to migrate (Fig. 1 A). The requirement for exposure to low pH, lysosomal enzymes, or even the reducing environment of the ER (see below) by many viruses ensures that they are captured by endocytic vesicles before undergoing the fusion/penetration reactions that allow them to transit the membrane barrier (Fig. 3). Recent system-based approaches have identified several endocytic mechanisms, either constitutively active or induced, that viruses can exploit (Mercer et al., 2010b). One obvious feature of this endocytic involvement is that virus size tends to influence the mechanism of uptake. Thus, small viruses (approximately <140 nm in diameter) tend to use small endocytic vesicles. The best characterized of these is the clathrin-mediated pathway that is essential for productive infection by many viruses. Initially demonstrated for the alphavirus Semliki Forest virus (Helenius et al., 1980; Marsh and Helenius, 1980), a more recent study shows, for example, that human rhinovirus 2 is internalized via the constitutive clathrin-mediated endocytosis of its receptor LDLR (Snyers

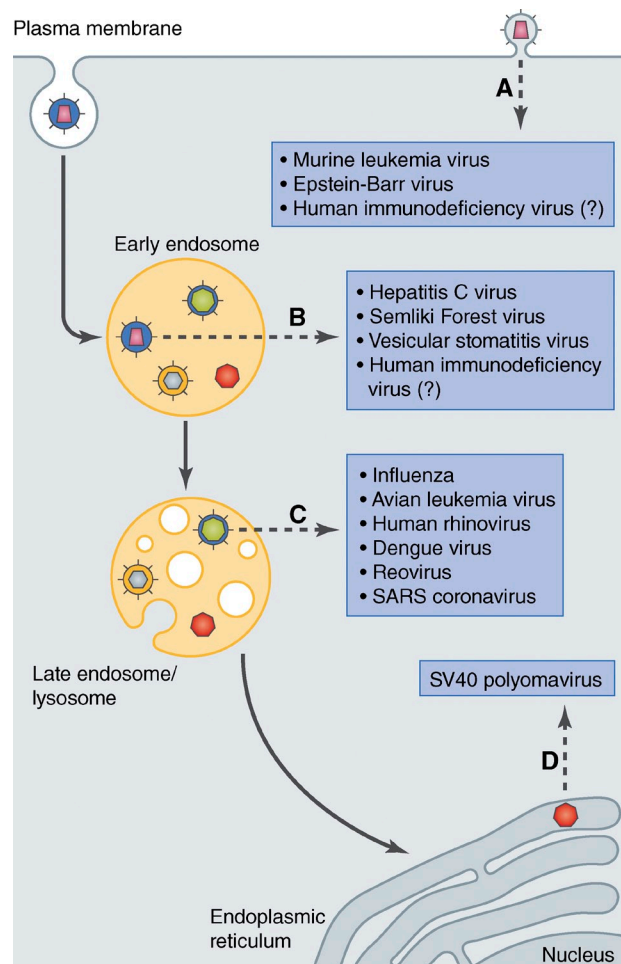


Figure 3. Sites of virus particle fusion/penetration. Virus particles must transport genetic material across limiting membranes; this can be achieved at various locations within the cell. (A) Enveloped virus particles can fuse directly at the plasma membrane at neutral pH after interaction with cell surface receptors. (B and C) Alternatively, internalized virus particles can escape from the endosomal network. This is often dependent on endosome acidification and occurs at either mild pH (6.5–6) from the early endosome (B) or low pH (5.5–4) from late endosome and/or lysosome (C). In addition to the acidic environment, other molecular cues may be required to trigger fusion/penetration, for example, membrane lipid content (Semliki Forest virus and Dengue virus) or proteolytic cleavage (reovirus and SARS coronavirus; Skehel et al., 1982; Schlegel and Wade, 1984; Mothes et al., 2000; Brabec et al., 2003). (D) Polyomaviruses such as SV40 undergo atypical transport through the endosomal pathway to the ER, where partially disassembled virus particles are shuttled to the cytosol by the retrotranslocation machinery.

et al., 2003). Clathrin-mediated endocytosis is also required for DC-SIGN-mediated uptake of phleboviruses, with endocytic sorting signals in the N-terminal cytoplasmic domain of DC-SIGN being essential for endocytosis and infection (Lozach et al., 2011b).

Although highly effective in many cases, the strategy of passive receptor-mediated uptake may limit the rate of entry, leaving a virus particle exposed on the cell surface. Thus, some viruses have developed the means to trigger their uptake into endocytic vesicles. Influenza A virus, for example, is internalized by both clathrin-mediated endocytosis and clathrin/caveolin-independent mechanisms (Rust et al., 2004).

For clathrin-mediated endocytosis, at least, influenza A virus attachment to sialic acid moieties on membrane glycoproteins and ganglioside initiates de novo clathrin-coated pit formation under surface-bound virions in a process that appears to involve ubiquitin-dependent recruitment of the clathrin adaptor protein Epsin-1 (Rust et al., 2004; Chen and Zhuang, 2008). An independent study has demonstrated that activation of PI3K, but not Akt, is required for influenza A virus entry, and inhibition of PI3K prevents virus uptake into endosomes (Ehrhardt et al., 2006). It is proposed that influenza A virus-mediated clustering of sialylated receptor tyrosine kinases, such as EGFR or c-Met, activates tyrosine kinase and PI3K signaling (Eierhoff et al., 2010). However, it remains unclear whether this signal propagation is linked to virus internalization by a clathrin-dependent or -independent route. Virus-induced receptor clustering also seems to be important for signaling-dependent DC-SIGN-mediated infection of phleboviruses (Lozach et al., 2011b).

Other endocytic mechanisms used by viruses have been identified (Mercer et al., 2010b). Less is known about the molecular mechanisms and receptors involved or whether these pathways are constitutively active or driven by receptor engagement. One such example is the pathway used by the polyomavirus SV40. This nonenveloped virus measures only 40 nm in diameter and exhibits a penetration mechanism that is currently unique to some polyomaviruses. SV40 particles bind directly to the cell surface via the sialic acid moieties of GM1 gangliosides, for which there are 360 binding sites on the virion surface (Stehle et al., 1994). Aggregation of GM1 by multivalent particles results in lipid phase separation and the induction of membrane deformation (Ewers et al., 2010). These two properties drive SV40 particles into tightly fitting membrane tubules that extend into the cell interior. Membrane tubulation is dependent on the long acyl chains of GM1 but is independent of cellular energy (Ewers et al., 2010). Subsequent scission of these invaginations requires tyrosine kinase activity and actin rearrangements (Pelkmans et al., 2002; Ewers et al., 2010; Römer et al., 2010). It has been suggested that caveolae coat proteins and dynamin are also recruited (Pelkmans et al., 2001, 2002); however, other studies indicate that Cav-1 is not essential for SV40 infection (Damm et al., 2005; Ewers et al., 2010). Interestingly, membrane deformation by SV40 has parallels with the endocytosis of shiga and cholera toxins (Römer et al., 2007, 2010). Although there is no sequence homology, similar pentameric ganglioside binding sites on SV40 and the two toxins, in conjunction with the rigid structure of the long-chained glycosphingolipids, appear to induce asymmetric compressive stress that promotes local membrane tubulation (Neu et al., 2010). Some related polyomaviruses also induce tubulation and may share a common route of internalization (Ewers et al., 2010).

Physically larger virus particles, including poxviruses, filoviruses, herpesviruses, and the recently described mimiviruses (La Scola et al., 2003), cannot be accommodated by small endocytic vesicles and instead induce the formation of larger structures such as phagosomes or macropinosomes. Phagocytosis is receptor driven and involves the actin-dependent formation of vesicles, the membrane of which is closely apposed to the surface of the internalized particle (Mercer et al., 2010b).

Mimiviruses are the largest known viruses. With fibrils extending out to a diameter of 750 nm from an icosahedral capsid, these viruses are similar in size to small bacteria. Although typically found in amoebal hosts, in vitro mimivirus can infect professional phagocytes, such as macrophages, via PI3K and dynamin-II-dependent phagocytosis (Ghigo et al., 2008).

In contrast, macropinocytosis, which usually mediates the uptake of large volumes of extracellular fluid and bulky cargo such as apoptotic bodies (Mercer and Helenius, 2008; Mercer et al., 2010b), involves actin remodeling mediated by Rac-1 GTPase and its effector p21-activated kinase 1 (Pak-1), leading to the extension of membrane ruffles and blebs from the cell surface. These large membrane protrusions can fold/drop back on themselves, enclosing extracellular material (Swanson, 2008). Macropinocytosis can occur constitutively in professional phagocytes such as dendritic cells but can be induced in other cell types by activation of tyrosine kinases such as EGFR (Swanson, 2008). Kaposi's sarcoma-associated herpesvirus, adenovirus (2 and 3), echovirus 1, Ebola virus, and Vaccinia, the prototype poxvirus, are internalized via macropinocytosis (Amstutz et al., 2008; Liberali et al., 2008; Mercer and Helenius, 2008; Raghu et al., 2009; Mercer et al., 2010a; Nanbo et al., 2010; Saeed et al., 2010; Valiya Veetil et al., 2010; Schmidt et al., 2011). Poxviruses have the unusual characteristic of producing two forms of infectious particle. Mature virions are brick-shaped particles that form in the cytoplasm of infected cells and possess a single-bilayer membrane. These particles are released when infected cells lyse. A second form, the so-called extracellular virus, is a mature virion that undergoes further envelopment by wrapping in membrane cisternae derived from the TGN or endosomes. These particles are secreted before cell lysis and have two membranes (Roberts and Smith, 2008). During entry, mature virus particles attach to preexisting filopodia and migrate toward the cell body, where they induce strain-specific atypical macropinocytosis via membrane blebbing or filopodial extension (Mercer et al., 2010a). The cellular receptors for Vaccinia virus are unknown, and it remains unclear how these processes are initiated. However, attachment of mature virions activates EGFR, Rho-GTPases, and actin remodeling (Mercer and Helenius, 2008; Mercer et al., 2010a). Phosphatidylserine associated with the mature virion membrane has been proposed to contribute to Vaccinia virus-induced macropinocytosis in a process mimicking the uptake of apoptotic cells (Mercer and Helenius, 2008), though another study disputes this (Laliberte and Moss, 2009). Recent work suggests that entry of the extracellular virion also involves macropinocytosis, though phosphatidylserine is not involved, and entry is not affected by exogenous addition of the phosphatidylserine-binding protein annexin 5 (Schmidt et al., 2011).

The filamentous particles of Ebola virus have a diameter of only 80–100 nm but range from 1–2 μ m in length. It is not surprising that these viruses also induce macropinocytosis through Rac-1/Pak-1-dependent membrane ruffling. Although the role of the putative Ebola virus receptor TIM-1 in macropinocytosis is unclear, Ebola virus uptake is promoted by the receptor tyrosine kinase Axl. The virus particle is not thought to directly engage Axl; however, Gas-6, an Axl ligand, has been

shown to play a role in the entry of other viruses and may associate with Ebola virus particles to act as a bridge for indirect interaction with Axl (Shimajima et al., 2006; Nanbo et al., 2010; Saeed et al., 2010; Brindley et al., 2011; Hunt et al., 2011; Kondratowicz et al., 2011; Morizono et al., 2011).

Although it is clear that many viruses—in particular, pH-dependent viruses—have an absolute dependence on endocytosis for productive infection, some viruses may exhibit plasticity in their mechanism of entry. For example, a study has demonstrated entry by direct fusion at the cell surface as well as by fusion after endocytosis for herpesviruses (Heldwein and Krummenacher, 2008). For HIV, pH-independent fusion, the ability of infected cells to form syncytia, and images of putative fusion events at the cell surface have led to the idea that entry occurs by direct fusion at the plasma membrane (Stein et al., 1987). However, work with inhibitors of endocytosis and direct single-particle tracking have recently provided evidence that fusion and infection occur after endocytic uptake (Daecke et al., 2005; Miyauchi et al., 2009; von Kleist et al., 2011). Moreover, HIV infection of macrophages has been suggested to require an atypical form of macropinocytosis (Maréchal et al., 2001; Carter et al., 2011). Thus, factors that influence the kinetics of fusion and internalization, such as receptor density and mobility, may determine whether pH-independent viruses penetrate directly at the cell surface or after endocytosis. The ability to use different mechanisms may have distinct advantages for viruses, providing access to a broader range of cell types or rendering them less susceptible to situations in which a specific pathway is absent or blocked.

The great escape

As with virtually all endocytic cargoes, regardless of the mechanism of uptake, most viruses internalized by endocytosis are delivered to endosomes. Many of these will use endosomal environmental cues, usually low pH, to trigger the membrane fusion/penetration reactions that deliver the viral genetic material to the cytoplasm (Fig. 3; details of the fusion and penetration mechanisms used by different viruses will not be considered here; Kielian and Rey, 2006; Moyer and Nemerow, 2011). Fusion or penetration from endosomes offers several potential advantages to a virus: it ensures that there is no cortical actin barrier to contend with, limits the display of viral components on the surface of the cell where they may be targets for the immune system, and, in the case of viruses that cause membrane lysis, such as adenoviruses, limits membrane damage to a single endosome.

For an invading virus, the endosomal lumen is a dynamic labyrinth of vesicles and tubules. The sorting function of the early and recycling endosomes can potentially return virus-receptor complexes to the cell surface. Alternatively, maturation to late endosomes and lysosomes renders the endosomal lumen a potentially hazardous environment (Dikic, 2006). Thus, many viruses fuse/penetrate at mildly acid pH (approximately pH 6.0) in early endosomes to avoid these fates (Fig. 3 B), whereas others exploit the changing environment within endosomes to precisely regulate the timing or cellular location of fusion/penetration. Endosomal maturation to late endosomes

and lysosomes (involving decreasing luminal pH, increasing levels of active hydrolytic enzymes, and alteration in lipid composition) correlates with movement of endocytic organelles toward the nucleus by microtubule-mediated retrograde translocation. The need for some viruses to be delivered to more perinuclear environments may be particularly important in some cell targets *in vivo* where cell organization is more elaborate and key for cell function. Neurons are an extreme example in which viruses may be taken into the cell by endocytosis at a peripheral synapse such as a neuromuscular junction but require transport, in some cases many tens of centimeters to the cell body and nucleus. In such cases, viruses can exploit endosomal transport along axons and use the lower pH of late endosomes (approximately pH 5.0) or exposure to acid hydrolases to delay penetration until endosomal or lysosomal delivery to a perinuclear location (Fig. 3 C; Lozach et al., 2011a).

Additional molecular cues for fusion/penetration may be provided by the lipid composition of endosomal membranes. The fusion of tick-borne encephalitis virus requires cholesterol in the target membrane (Stiasny et al., 2003), and fusion of Semliki Forest virus is dependent on both cholesterol and sphingolipids (Kielian and Helenius, 1984; Nieva et al., 1994), both of which are available in the plasma membrane as well as endosomal membranes. Dengue virus transits through the early endosomes to fuse with late endocytic organelles (van der Schaar et al., 2008). In addition to low pH, Dengue virus fusion requires the target membrane to contain anionic lipids such as lysobisphosphatidic acid, which is predominantly found within the lysosome (Brotherus and Renkonen, 1977; Zaitseva et al., 2010). Other viruses, including SARS coronavirus and orthoreoviruses, also exhibit atypical pH-dependent entry; in these cases, proteolytic cleavage of the viral envelope or surface proteins by acid-dependent cellular proteases (cathepsins L and B) triggers the structural changes required for fusion (Figs. 3 C and 4; Ebert et al., 2002; Chandran et al., 2005; Simmons et al., 2005). Ebola virus GP1 glycoprotein also undergoes cleavage by cathepsins to reveal a putative binding domain for the late endosomal/lysosomal cholesterol transporter Niemann–Pick C1 (NPC1; Chandran et al., 2005; Schornberg et al., 2006; Côté et al., 2011). Depletion of NPC1 from target cells prevents Ebola virus glycoprotein-dependent fusion, suggesting that NPC1 acts as a postendocytic intracellular receptor necessary for virus penetration (Carette et al., 2011). These and other recent findings have provided increasing clarity on Ebola virus infection, suggesting a putative entry pathway for this infamous virus (Fig. 4).

However, fusion/penetration is not restricted to endocytic organelles. After their internalization, several polyomaviruses take an intracellular retrograde vesicular pathway to the ER via endosomes before penetration (Kartenbeck et al., 1989). In the ER, these particles undergo partial uncoating mediated by protein-folding factors, including ERp57 and protein disulfide isomerase, and retrotranslocation to the cytosol by the machinery that normally mediates retrograde transport of misfolded ER proteins for cytosolic degradation (Fig. 3 D; Lilley et al., 2006; Schelhaas et al., 2007; Jiang et al., 2009).

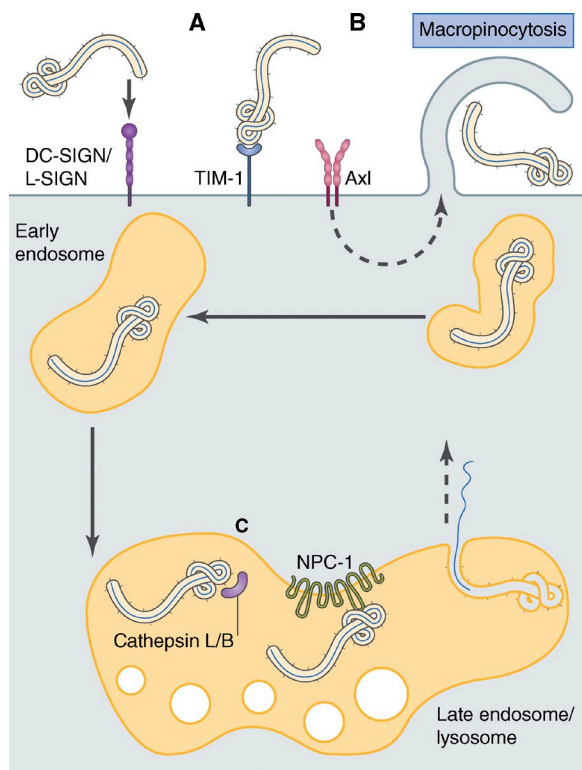


Figure 4. Ebola virus entry. (A) Lectins DC-SIGN and L-SIGN act as attachment factors to concentrate Ebola virus particles at the cell surface (Alvarez et al., 2002; Simmons et al., 2003), facilitating interaction with the receptor TIM-1. (B) Axl receptor tyrosine kinase is thought to promote virus particle uptake via macropinocytosis. Critically, Ebola virus does not directly engage Axl; the Axl ligand Gas-6 may associate with virus particles and facilitate indirect interaction between Ebola virus and Axl, as demonstrated for other viruses (Morizono et al., 2011). (C) Within the late endosome/lysosome, viral glycoprotein GP1 undergoes sequential proteolytic cleavage by cathepsins L and B, allowing interaction with NPC1, a putative endosomal receptor. Ebola virus membrane fusion is dependent on the viral glycoprotein GP2 and occurs from the late endosome/lysosome, although the exact molecular triggers remain unclear.

Navigating the cell interior

For many viruses, the journey into the cell is complete after fusion/penetration from endosomes, and the final steps in uncoating and subsequent replication occur in the cytoplasm, often in association with specific membrane domains. But some DNA (e.g., adenoviruses and herpesviruses) and RNA (e.g., influenza viruses) viruses have to journey through the cytosol to replicate in the nucleus. The cell interior is very crowded. It consists of membrane-bound organelles, meshworks of cytoskeletal fibers, and the viscous cytosol. For large macromolecular complexes, unaided movement is slow. As discussed in the previous section, some viruses use the inherent capacity of endosomes to move along microtubules before fusion/penetration. Others can also exploit the cytoskeleton after fusion/penetration (Greber and Way, 2006).

Several viruses exploit motor proteins to travel along the cytoskeleton within the cell body (Greber and Way, 2006). HIV, Herpes simplex virus, and adenovirus all appear to exploit dynein-mediated retrograde microtubule translocation to facilitate transport to the nucleus and infection (Sodeik et al., 1997; Suomalainen et al., 1999; McDonald et al., 2002). The use of

so-called actin comets to propel virus particles during viral egress is well documented for Vaccinia virus (Taylor et al., 2011). However, the intracellular transport strategy of insect baculoviruses is unique in their capacity to induce comet formation during entry. Upon reaching the cytoplasm, the baculovirus *Autographa californica* P78/83 capsid protein acts as a nucleation site for Arp2/3-dependent actin polymerization that drives the virion through the cell interior. As capsids reach the nucleus, they are held against the nuclear membrane by continuing actin polymerization, promoting their ultimate invasion through nuclear pores (Ohkawa et al., 2010).

Conclusions

Cells raise multiple barriers to prevent virus infection. These are either general physical barriers, such as the plasma membrane or actin cortex, that define the cell or other restriction factors, often induced by interferons, that can be mobilized to limit viral replication. Although most viruses use broadly similar tactics to breach these barriers, many have developed unique approaches that ensure their delivery to optimal cellular sites for replication. The details of these specific mechanisms are starting to emerge. New technologies—in particular, in imaging—will provide key mechanistic insights into how virus receptors are organized, how they are commandeered by viruses to form functional entry complexes, and how they engage the machinery of the cell to mediate infection. Such information will be essential in the development of targeted and specific inhibitors of virus entry and infection.

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