Virus entry at a glance

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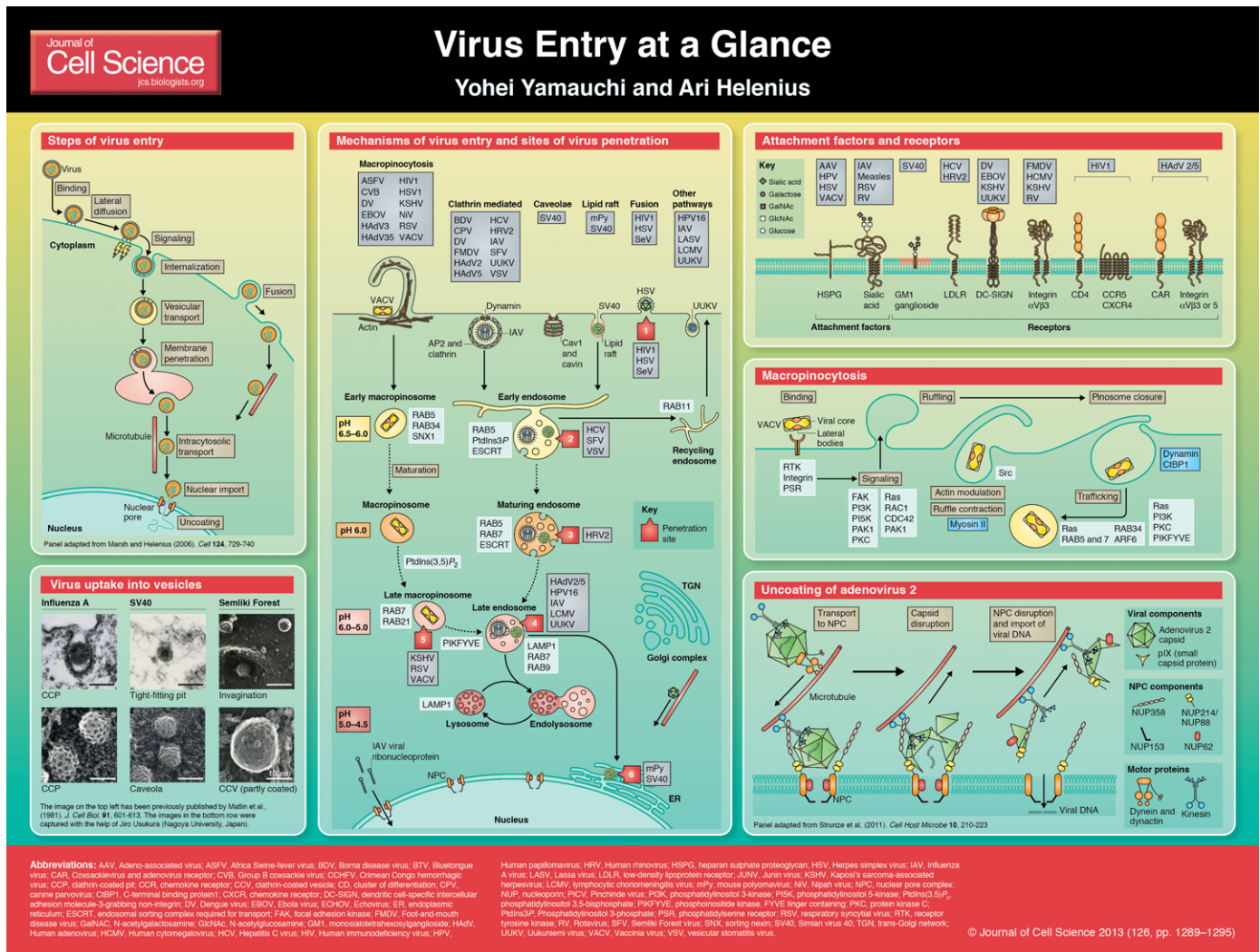*Author for correspondence (ari.helenius@bc.biol.ethz.ch)

The goal of a virus particle is to transport its genome in a replication-competent form from an infected cell to an uninfected cell. To enter a new host cell, the majority of viruses take advantage of the endocytic mechanisms of the cell and wait until reaching endocytic vacuoles or other cytoplasmic compartments before penetrating into the cytosol. After penetration, viruses and viral capsids exploit the cytoplasmic transport systems of the cell, moving to sites of replication within the cytosol (most RNA viruses) or the nucleus (most DNA viruses). The final step in the entry process generally involves uncoating of the viral genome.

After numerous entry studies with a variety of viruses in different cell systems, the overall picture of entry of animal virus into the host cell is becoming increasingly complete. There are essentially six locations for penetration. These are: (1) the plasma membrane, (2) the early endosome, (3) the maturing endosome, (4) the late endosome, (5) the macropinosome and (6) the endoplasmic reticulum (ER). Endolysosomes, amphisomes and lysosomes also remain possible penetration sites, but evidence is lacking. Some viruses can use more than one pathway, for example, by engaging different receptors.

Although the molecular details of virus–cell surface interactions are complex and highly variable, the number of pathways that allow the viruses to reach their sites of penetration seem to be limited to a handful of endocytic mechanisms. The subsequent trafficking steps involve key organelles in the endocytic network that are utilized by endogenous cargo. Only a few viruses seem to be capable of penetrating directly through the cell surface by fusing their envelope with the plasma membrane. Thus, the 'trail map' that is available to incoming viruses is complex, but far from incomprehensible.

In this Cell Science at a Glance article, we describe the stepwise entry program of animal viruses of different families. As illustrated in the poster, the process can be broken down into five discrete steps – attachment, signaling, endocytosis,

(See poster insert)

penetration and uncoating. A more detailed description can be found in previous reviews (Damm and Pelkmans, 2006; Greber, 2002; Grove and Marsh, 2011; Gruenberg, 2009; Marsh and Helenius, 2006; Mercer and Helenius, 2009; Mercer et al., 2010; Schelhaas, 2010; Sieczkarski and Whittaker, 2002).

Attachment

The first step involves attachment of the virus particle to the cell surface. Depending on the virus, the viral proteins responsible for binding form either projections (glycoprotein spikes, fibers) or depressions in the virus surface. The cell surface molecules and groups that serve as binding partners comprise a large spectrum of proteins, lipids and glycans (see poster) (Barth et al., 2003; Bartlett and Park, 2010; Bose and Banerjee, 2002; Byrnes and Griffin, 1998; Chen et al., 1997; Drobni et al., 2003; Kroschewski et al., 2003; Spear et al., 2000; Summerford and Samulski, 1998). The binding specificity of a virus defines in many cases cell and tissue tropism as well as the nature of diseases caused by the virus.

Some of the attachment factors used by viruses might simply help to concentrate the virus particles to the cell surface. Others involve true receptors, which in addition to binding, actively promote virus endocytosis, mediate conformational changes in the virus particle and trigger signaling pathways that promote the infection process. Individual contacts between viral proteins and receptors are often highly specific but of low affinity (reviewed by Skehel and Wiley, 2000). However, being multivalent, viruses usually bind to multiple receptors. This not only enhances avidity, but also allows the formation of receptor-rich membrane microdomains that might induce trans-bilayer signaling, support membrane curvature generation and activate endocytosis. Receptors often follow the virus into the cell during endocytosis (Helenius, 2007).

Cell surface lectins, such as dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN, also known as CD209), constitute a group of receptors that are subject to current interest. They function as receptors for incoming viruses because they bind to high-mannose N-linked glycans in glycoproteins of viruses such as HIV1, Sindbis, hepatitis C, phlebo-, dengue and Ebola (Geijtenbeek et al., 2000; Klimstra et al., 2003; Lozach et al., 2011b; Lozach et al., 2003; Pöhlmann et al., 2001; Simmons et al., 2003; Tassaneetrithep et al., 2003). While playing an important role in the immunological defense against these and other pathogens, DC-SIGN can thus inadvertently open the door for infection by allowing virus entry and by promoting virus spread in the body (reviewed by Svajger et al., 2010).

After binding to the cell surface, many viruses move laterally along the cell surface before internalization. The movement can either involve random diffusion or it can be directed. The latter is the case for viruses that bind to filopodia and 'surf' towards the cell body through actin retrograde flow (Burckhardt et al., 2011; Coller et al., 2009; Lehmann et al., 2005; Mercer and Helenius, 2008; Schelhaas et al., 2008) (reviewed by Burckhardt and Greber, 2009).

Signaling

Following attachment and receptor clustering, many viruses prime the cell for entry and infection by activating the signaling systems of the cell (see poster) (reviewed by Greber, 2002; Mercer et al., 2010; Nemerow, 2000). The signaling pathways are best characterized for viruses that trigger plasma membrane ruffling and macropinocytosis for endocytic uptake. These include vaccinia virus (VACV), Ebola virus, Kaposi's sarcoma-associated herpesvirus (KSHV), adenovirus and influenza A virus (IAV) (Amstutz et al., 2008; Brindley et al., 2011; Chakraborty et al., 2011; de Vries et al., 2011; Eierhoff et al., 2010; Hunt et al., 2011; Kälin et al., 2010; Meertens et al., 2012; Meier et al., 2002; Mercer and Helenius, 2008; Nanbo et al., 2010; Raghu et al., 2009; Saeed et al., 2010; Schmidt et al., 2011; Shimojima et al., 2006; Valiya Veettil et al., 2010).

Typically, the process involves activation of receptor tyrosine kinases (RTKs), integrins and phosphatidylserine receptors of the TIM (T cell/transmembrane, immunoglobulin and mucin) and TAM (Tyro3, Axl, Mer) families, followed by activation of downstream players, such as Na^+/H^+ exchangers, Rho GTPases (RAC1 and CDC42), p21-activated kinase 1 (PAK1), PI3Ks, Src kinases, protein kinase C (PKC), myosins, and membrane fission and fusion factors. The dynamics of the actin cytoskeleton are transiently modified and the viruses are internalized in large uncoated vacuoles (reviewed by Mercer and Helenius, 2012; Wolfrum and Greber, 2013).

The caveolar and lipid raft-mediated entry of SV40 into HeLa cells is regulated by more than 40 kinases, including focal adhesion kinase (FAK), Src kinase and members of cell adhesion-dependent signaling, such as FYN and AKT1 (Pelkmans et al., 2005). Binding of Group B coxsackievirus (CVB) to its receptor GPI-anchored protein decay-accelerating factor (DAF) on the epithelial surface induces DAF clustering. This triggers activation of Abl kinase to deliver the virus to the tight junctions where it interacts with its receptor CAR, and by activation of FYN to induce endocytosis (Coyne and Bergelson, 2006).

Fusion at the plasma membrane

Only a few viruses can deliver their capsids to the cytosol by fusing their envelope directly with the plasma membrane (see poster). For example, alpha herpesviruses undergo such fusion events following the engagement of the glycoproteins gB and gD with cellular receptors (Arii et al., 2010; Geraghty et al., 1998; Montgomery et al., 1996; Satoh et al., 2008; Shukla et al., 1999; Suenaga et al., 2010) (reviewed by Eisenberg et al., 2012). After binding of gp120 to CD4, further interactions with chemokine receptor CCR5 or CXCR4 trigger gp41-mediated fusion of HIV1 (Alkhatib et al., 1996; Choe et al., 1996; Deng et al., 1996; Dragic et al., 1996; Feng et al., 1996; Klatzmann et al., 1984) (reviewed by Klasse, 2012).

Endocytosis

Endocytosis of viruses can take many forms, including clathrin-mediated endocytosis (CME), caveolar or lipid raft-mediated endocytosis, macropinocytosis and still poorly characterized variations of these themes (see poster) (reviewed by Mercer et al., 2010). Some viruses are able to use more than one pathway, which introduces a further level of ambiguity to the classification of virus entry pathways. For example spherical IAV can activate macropinocytosis (de Vries et al., 2011). However, in most of the cases, the virus recruits clathrin and epsin1, and enters clathrin-coated vesicles (CCVs) through clathrin-coated pits (CCPs) (Chen and Zhuang, 2008; Matlin et al., 1981; Rust et al., 2004).

CME is commonly observed as the uptake mechanism for viruses of small and intermediate size (Helenius et al., 1980). Clathrin-coated vesicles have a diameter of 60–200 nm (Kirchhausen, 2000; Pearse, 1976), but as shown for vesicular stomatitis virus (VSV), the vesicles can be deformed to fit larger particles (Cureton et al., 2009). Some viruses, such as dengue, enter preexisting CCPs (van der Schaar et al., 2008), whereas others, such as reovirus, VSV and IAV, induce formation of CCPs at their site of binding (Ehrlich et al., 2004; Johannsdottir et al., 2009; Rust et al., 2004).

Macropinocytosis is an actin-dependent, transient, endocytic process for the nonspecific uptake of fluid, solutes and sometimes particles in response to the activation of cell surface receptors (Meier et al., 2002; West et al., 1989). It is an important entry pathway for a growing number of predominantly larger viruses, such as poxviruses, filoviruses, IAV, adenovirus and HIV1 (Brindley et al., 2011; Callahan et al., 2003; de Vries et al., 2011; Hunt et al., 2011; Mercer and Helenius, 2008; Nanbo et al., 2010; Saeed et al., 2010; Shimojima et al., 2006). As already mentioned, the process involves the activation of a complex signaling pathway that transiently modifies the dynamics of the actin cytoskeleton. The virus-containing macropinosomes then move deeper into the cytoplasm where they undergo acidification, maturation and fusion with late endosomes or lysosomes.

To elicit macropinocytosis, some viruses have learned to disguise themselves as cell debris or apoptotic bodies. For example, VACV uses phosphatidylserine on its membrane to mimic an apoptotic body that is destined for degradation (Mercer and Helenius, 2008). This mode of entry is also used by lentiviral vectors and dengue virus (Meertens et al., 2012; Morizono et al., 2011).

Viruses in the polyomavirus family bind to gangliosides on the cell surface. They either enter through caveolar indentations in the plasma membrane or generate such indentations by tight binding to receptors. Internalization occurs in small tight-fitting vesicles that are devoid of a clathrin coat (Eash et al., 2006; Ewers et al., 2010; Hummeler et al., 1970; Kartenbeck et al., 1989). Like viruses that are internalized by CME, these viruses are transported to early endosomes and they follow the flow to late endosomes. Eventually, they reach the ER where initial uncoating and penetration into the cytosol occurs (Engel et al., 2011; Geiger et al., 2011; Inoue and Tsai, 2011; Schelhaas et al., 2007).

Endosomes

The endosomal network that receives the incoming viruses is composed of several different types of organelles. These are dynamic, and are involved in complicated trafficking and sorting processes that include hundreds of cellular factors. The internalized viruses are either directed to early endosomes or they move along as cargo in newly formed macropinosomes. Both endosomes and macropinosomes are mildly acidic and contain cargo that is being targeted to lysosomes for degradation. In both cases, transport involves a maturation process that prepares the vacuoles for fusion with the hydrolase-filled lysosomes. The maturation process of endosomes involves further acidification, followed by the formation of intralumenal vesicles, a switch from RAB5 to RAB7, a switch in phosphatidylinositides and, finally, microtubule-mediated movement towards the perinuclear region (reviewed by Huotari and Helenius, 2011).

Depending on the requirements, which differ between viruses (for example the pH needed to activate membrane fusion), penetration into the cytosol is triggered either in the early or in the late endosomes or macropinosomes. Thus, late penetrating viruses, unlike those that exit from early endosomes, not only depend on a further drop in pH, but also on factors that are required for the maturation process, such as RAB5, RAB7, and ESCRT (endosomal sorting complex required for transport) components (Lozach et al., 2011a). For example, we have found that depletion of histone deacetylase 8 (HDAC8) blocks centrosome cohesion and microtubule organization (Yamauchi et al., 2011), and depletion of Cullin-3 affects endolysosomal trafficking (Huotari et al., 2012). Infection by IAV, which is a late penetrating virus, is blocked in both cases.

Penetration

The penetration event involves the delivery of the genome and accessory proteins to the cytosol. It is one of few events during virus entry that requires an active process initiated by the virus. In the case of enveloped animal viruses, penetration invariably involves membrane fusion, which is mediated by specific viral glycoproteins. As a result of fusion, viral capsids are released into the cytosol. Endosomes and macropinosomes are the most common sites for these fusion events. Here, the viruses fuse their envelope with the limiting membrane of the endocytic vacuoles from the lumenal side (Helenius et al., 1980).

The viral fusion proteins are oligomeric type I integral membrane proteins. After a conformational change, which is induced by cellular cues such as the low pH, they expose hydrophobic peptides in their ectodomains. By inserting these peptides into the target membranes, the viral fusion proteins form a bridge between the virus and the endosomal membrane (reviewed by Harrison, 2005). Fusion occurs when further conformational changes in the fusion proteins bring the two membranes into close contact. Cues other than pH, such as lipid composition, proteolytic cleavage and redox reactions, can also have a role in the reaction (Bertram et al., 2011; Simmons et al., 2011; Simmons et al., 2005; Wahlberg and Garoff, 1992; Zaitseva et al., 2010).

The mechanisms of penetration by non-enveloped viruses are less well characterized. Adenoviruses cause the lysis of endosomes, allowing escape into the cytosol (Meier et al., 2002). Picornaviruses undergo a conformational change that allows the particles to form a pore through which the viral RNA is released into the cytosol (Prchla et al., 1995; Schober et al., 1998). Parvoviruses have acid-activated phospholipase activity, which is thought to help their escape from vacuoles (Farr et al., 2005). Polyomaviruses pass through the ER and take advantage of ER-associated degradation (ERAD) pathways to penetrate into the cytosol (Geiger et al., 2011; Inoue and Tsai, 2011; Schelhaas et al., 2007).

Intracellular transport

After reaching the cytosol, viruses and viral capsids have to find their way to the site of replication in the nucleus or to specific locations in the cytoplasm. Many associate with microtubule-based motors, such as dynein and dynactin, and move along microtubules towards the nucleus (Bremner et al., 2009; Dodding and Way, 2011; Döhner et al., 2002; Engelke et al., 2011; Leopold et al., 2000; Radtke et al., 2010; Sodeik et al., 1997; Suomalainen et al., 1999; Yamauchi et al., 2008). For

transport into the nucleus, they bind nuclear import receptors, such as importins, by using them to target their capsids or genome to nuclear pore complexes (NPCs) (Darshan et al., 2004; Klucevsek et al., 2006; Nakanishi et al., 2002; Schmitz et al., 2010; Wodrich et al., 2006) (reviewed by Puntener and Greber, 2009).

Large virus capsids, such as those of herpes- and adenoviruses, are too large to enter the nucleus through the NPCs. They have evolved mechanisms to release only their DNA genome through NPCs (Greber et al., 1997; Jovasevic et al., 2008; Ojala et al., 2000; Pasdeloup et al., 2009; Preston et al., 2008; Strunze et al., 2011). Viruses with smaller capsids, such as hepatitis B and polyoma viruses, can enter through the pores in either an intact or modified form (Kann et al., 1999; Nakanishi et al., 1996; Qu et al., 2004; Rabe et al., 2009; Rabe et al., 2003). Influenza virus has solved the problem of excessive genome size by dividing its genome into eight separate RNA segments, which are packaged individually into viral ribonucleoproteins (vRNPs) that are small enough to enter through the pores. Each vRNP contains nuclear localization signals necessary for importin α- and β-mediated nuclear import (Boulo et al., 2007; Cros et al., 2005; Kemler et al., 1994; Mayer et al., 2007; Wu et al., 2007).

Uncoating

The final step in the entry program of most viruses is the release of the genome from a protective, confining capsid structure to enable transcription and replication. As a rule, this occurs once the virus capsids have reached the final location. This is because the viral RNA or DNA cannot be easily moved once liberated from the capsid. Actually, uncoating is typically a stepwise process that occurs during different stages of entry. In some cases, such as polyoma and adenoviruses, disassembly of the particle already begins before penetration into the cytosol (reviewed by Cerqueira and Schelhaas, 2012; Suomalainen and Greber, 2013). In the case of picornaviruses, uncoating is an integral part of penetration, as the viral RNA enters into the cytosol leaving the capsid behind in the endosome (reviewed by Fuchs and Blaas, 2010).

The picture emerging from uncoating studies suggests that mechanisms are highly variable. Some viruses rely on host cell factors, such as ribosomes, proteasomes and molecular motors, whereas others employ their own structural components, such as proteolytic enzymes (Helenius, 2007). Adenoviruses exploit dynein, kinesin and nucleoporins to impose physical forces to open up viral capsids that are attached to the NPC (see poster) (Greber et al., 1993; Pérez-Berná et al., 2012; Strunze et al., 2011). Uncoating of HIV1 is determined by host factors, such as cyclophilin A and TRIM5α, by the stability of the capsid, and by reverse transcription of viral RNA into DNA, and is stimulated by TNPO3, a nuclear import receptor (Arhel et al., 2007; Sayah et al., 2004; Shah et al., 2013; Stremlau et al., 2004; Stremlau et al., 2006).

Perspectives

Ongoing studies in the field of endocytic membrane trafficking are providing us with increasingly detailed information about the interactions between host cells and pathogens. Screening efforts using drugs and small interfering RNAs are, at the same time, rapidly expanding our understanding of the cellular factors involved. Whereas viruses themselves owing to their relative simplicity offer few targets for antivirals, the virus–cell interactions provide numerous potential targets. However, in order to be able to develop antiviral strategies aiming at cellular rather than viral targets, more information is required regarding the host cells, especially about the processes by which the cells promote and oppose infection. To fully exploit such information, which is increasingly complex, interdisciplinary approaches will be necessary, combining cell biology, infection biology, systems biology, bioinformatics, medicine and other fields.

Important questions remain: will it be possible to make use of the information regarding virus entry to develop new drugs? Can processes, such as macropinocytosis and endosome maturation, temporarily be shut off to prevent infection and give the immune system time to set up its defenses? Can one interfere with receptor binding and signaling? Can infection be impeded without major side effects to the host? Some successful examples, such as enfuvirtide (fusion inhibitor) and maraviroc (CCR5 antagonist) used in patients infected with HIV1 (Dorr et al., 2005; Kilby et al., 1998; Matthews et al., 2004), suggest that these approaches are realistic.

A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.org. Individual poster panels are available as JPEG files at http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.119685/-/DC1.

References

Alkhatib, G., Combadiere, C., Broder, C. C., Feng, Y., Kennedy, P. E., Murphy, P. M. and Berger, E. A. (1996). CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* **272**, 1955-1958.

Amstutz, B., Gastaldelli, M., Kälin, S., Imelli, N., Boucke, K., Wandeler, E., Mercer, J., Hemmi, S. and Greber, U. F. (2008). Subversion of CtBP1-controlled macropinocytosis by human adenovirus serotype 3. *EMBO J.* **27**, 956-969.

Arhel, N. J., Souquere-Besse, S., Munier, S., Souque, P., Guadagnini, S., Rutherford, S., Prévost, M. C., Allen, T. D. and Charneau, P. (2007). HIV-1 DNA Flap formation promotes uncoating of the pre-integration complex at the nuclear pore. *EMBO J.* **26**, 3025-3037.

Arii, J., Goto, H., Suenaga, T., Oyama, M., Kozuka-Hata, H., Imai, T., Minowa, A., Akashi, H., Arase, H., Kawaoka, Y. et al. (2010). Non-muscle myosin IIA is a functional entry receptor for herpes simplex virus-1. *Nature* **467**, 859-862.

Barth, H., Schafer, C., Adah, M. I., Zhang, F., Linhardt, R. J., Toyoda, H., Kinoshita-Toyoda, A., Toida, T., Van Kuppevelt, T. H., Depla, E. et al. (2003). Cellular binding of hepatitis C virus envelope glycoprotein E2 requires cell surface heparan sulfate. *J. Biol. Chem.* **278**, 41003-41012.

Bartlett, A. H. and Park, P. W. (2010). Proteoglycans in host-pathogen interactions: molecular mechanisms and therapeutic implications. *Expert Rev. Mol. Med.* **12**, e5.

Bertram, S., Glowacka, I., Müller, M. A., Lavender, H., Gnirss, K., Nehlmeier, I., Niemeyer, D., He, Y., Simmons, G., Drosten, C. et al. (2011). Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. *J. Virol.* **85**, 13363-13372.

Bose, S. and Banerjee, A. K. (2002). Role of heparan sulfate in human parainfluenza virus type 3 infection. *Virology* **298**, 73-83.

Boulo, S., Akarsu, H., Ruigrok, R. W. and Baudin, F. (2007). Nuclear traffic of influenza virus proteins and ribonucleoprotein complexes. *Virus Res.* **124**, 12-21.

Bremner, K. H., Scherer, J., Yi, J., Vershinin, M., Gross, S. P. and Vallee, R. B. (2009). Adenovirus transport via direct interaction of cytoplasmic dynein with the viral capsid hexon subunit. *Cell Host Microbe* **6**, 523-535.

Brindley, M. A., Hunt, C. L., Kondratowicz, A. S., Bowman, J., Sinn, P. L., McCray, P. B., Jr, Quinn, K., Weller, M. L., Chiorini, J. A. and Maury, W. (2011). Tyrosine kinase receptor Axl enhances entry of Zaire ebolavirus without direct interactions with the viral glycoprotein. *Virology* **415**, 83-94.

Burckhardt, C. J. and Greber, U. F. (2009). Virus movements on the plasma membrane support infection and transmission between cells. *PLoS Pathog.* **5**, e1000621.

Burckhardt, C. J., Suomalainen, M., Schoenenberger, P., Boucke, K., Hemmi, S. and Greber, U. F. (2011). Drifting motions of the adenovirus receptor CAR and immobile integrins initiate virus uncoating and membrane lytic protein exposure. *Cell Host Microbe* **10**, 105-117.

Byrnes, A. P. and Griffin, D. E. (1998). Binding of Sindbis virus to cell surface heparan sulfate. *J. Virol.* **72**, 7349-7356.

Callahan, M. K., Popernack, P. M., Tsutsui, S., Truong, L., Schlegel, R. A. and Henderson, A. J. (2003). Phosphatidylserine on HIV envelope is a cofactor for infection of monocytic cells. *J. Immunol.* **170**, 4840-4845.

Cerqueira, C. and Schelhaas, M. (2012). Principles of polyoma- and papillomavirus uncoating. *Med. Microbiol. Immunol. (Berl.)* **201**, 427-436.

Chakraborty, S., ValiyaVeettil, M., Sadagopan, S., Paudel, N. and Chandran, B. (2011). c-Cbl-mediated selective virus-receptor translocations into lipid rafts regulate productive Kaposi's sarcoma-associated herpesvirus infection in endothelial cells. *J. Virol.* **85**, 12410-12430.

Chen, C. and Zhuang, X. (2008). Epsin 1 is a cargo-specific adaptor for the clathrin-mediated endocytosis of the influenza virus. *Proc. Natl. Acad. Sci. USA* **105**, 11790-11795.

Chen, Y., Maguire, T., Hileman, R. E., Fromm, J. R., Esko, J. D., Linhardt, R. J. and Marks, R. M. (1997). Dengue virus infectivity depends on envelope protein binding to target cell heparan sulfate. *Nat. Med.* **3**, 866-871.

Choe, H., Farzan, M., Sun, Y., Sullivan, N., Rollins, B., Ponath, P. D., Wu, L., Mackay, C. R., LaRosa, G., Newman, W. et al. (1996). The beta-chemokine receptors CCR3 and CCR5 facilitate infection by primary HIV-1 isolates. *Cell* **85**, 1135-1148.

Coller, K. E., Berger, K. L., Heaton, N. S., Cooper, J. D., Yoon, R. and Randall, G. (2009). RNA interference and single particle tracking analysis of hepatitis C virus endocytosis. *PLoS Pathog.* **5**, e1000702.

Coyne, C. B. and Bergelson, J. M. (2006). Virus-induced Abl and Fyn kinase signals permit coxsackievirus entry through epithelial tight junctions. *Cell* **124**, 119-131.

Cros, J. F., García-Sastre, A. and Palese, P. (2005). An unconventional NLS is critical for the nuclear import of the influenza A virus nucleoprotein and ribonucleoprotein. *Traffic* **6**, 205-213.

Cureton, D. K., Massol, R. H., Saffarian, S., Kirchhausen, T. L. and Whelan, S. P. (2009). Vesicular stomatitis virus enters cells through vesicles incompletely coated with clathrin that depend upon actin for internalization. *PLoS Pathog.* **5**, e1000394.

Damm, E. M. and Pelkmans, L. (2006). Systems biology of virus entry in mammalian cells. *Cell. Microbiol.* **8**, 1219-1227.

Darshan, M. S., Lucchi, J., Harding, E. and Moroianu, J. (2004). The l2 minor capsid protein of human papillomavirus type 16 interacts with a network of nuclear import receptors. *J. Virol.* **78**, 12179-12188.

de Vries, E., Tscherne, D. M., Wienholts, M. J., Cobos-Jiménez, V., Scholte, F., García-Sastre, A., Rottier, P. J. and de Haan, C. A. (2011). Dissection of the influenza A virus endocytic routes reveals macropinocytosis as an alternative entry pathway. *PLoS Pathog.* **7**, e1001329.

Deng, H., Liu, R., Ellmeier, W., Choe, S., Unutmaz, D., Burkhart, M., Di Marzio, P., Marmon, S., Sutton, R. E., Hill, C. M. et al. (1996). Identification of a major co-receptor for primary isolates of HIV-1. *Nature* **381**, 661-666.

Dodding, M. P. and Way, M. (2011). Coupling viruses to dynein and kinesin-1. *EMBO J.* **30**, 3527-3539.

Döhner, K., Wolfstein, A., Prank, U., Echeverri, C., Dujardin, D., Vallee, R. and Sodeik, B. (2002). Function of dynein and dynactin in herpes simplex virus capsid transport. *Mol. Biol. Cell* **13**, 2795-2809.

Dorr, P., Westby, M., Dobbs, S., Griffin, P., Irvine, B., Macartney, M., Mori, J., Rickett, G., Smith-Burchnell, C., Napier, C. et al. (2005). Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. *Antimicrob. Agents Chemother.* **49**, 4721-4732.

Dragic, T., Litwin, V., Allaway, G. P., Martin, S. R., Huang, Y., Nagashima, K. A., Cayanan, C., Maddon, P. J., Koup, R. A., Moore, J. P. et al. (1996). HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* **381**, 667-673.

Drobni, P., Mistry, N., McMillan, N. and Evander, M. (2003). Carboxy-fluorescein diacetate, succinimidyl ester labeled papillomavirus virus-like particles fluoresce after internalization and interact with heparan sulfate for binding and entry. *Virology* **310**, 163-172.

Eash, S., Manley, K., Gasparovic, M., Querbes, W. and Atwood, W. J. (2006). The human polyomaviruses. *Cell. Mol. Life Sci.* **63**, 865-876.

Ehrlich, M., Boll, W., Van Oijen, A., Hariharan, R., Chandran, K., Nibert, M. L. and Kirchhausen, T. (2004). Endocytosis by random initiation and stabilization of clathrin-coated pits. *Cell* **118**, 591-605.

Eierhoff, T., Hrincius, E. R., Rescher, U., Ludwig, S. and Ehrhardt, C. (2010). The epidermal growth factor receptor (EGFR) promotes uptake of influenza A viruses (IAV) into host cells. *PLoS Pathog.* **6**, e1001099.

Eisenberg, R. J., Atanasiu, D., Cairns, T. M., Gallagher, J. R., Krummenacher, C. and Cohen, G. H. (2012). Herpes virus fusion and entry: a story with many characters. *Viruses* **4**, 800-832.

Engel, S., Heger, T., Mancini, R., Herzog, F., Kartenbeck, J., Hayer, A. and Helenius, A. (2011). Role of endosomes in simian virus 40 entry and infection. *J. Virol.* **85**, 4198-4211.

Engelke, M. F., Burckhardt, C. J., Morf, M. K. and Greber, U. F. (2011). The dynactin complex enhances the speed of microtubule-dependent motions of adenovirus both towards and away from the nucleus. *Viruses* **3**, 233-253.

Ewers, H., Romer, W., Smith, A. E., Bacia, K., Dmitrieff, S., Chai, W., Mancini, R., Kartenbeck, J., Chambon, V., Berland, L. et al. (2010). GM1 structure determines SV40-induced membrane invagination and infection. *Nat. Cell Biol.* **12**, 11-18.

Farr, G. A., Zhang, L. G. and Tattersall, P. (2005). Parvoviral virions deploy a capsid-tethered lipolytic enzyme to breach the endosomal membrane during cell entry. *Proc. Natl. Acad. Sci. USA* **102**, 17148-17153.

Feng, Y., Broder, C. C., Kennedy, P. E. and Berger, E. A. (1996). HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* **272**, 872-877.

Fuchs, R. and Blaas, D. (2010). Uncoating of human rhinoviruses. *Rev. Med. Virol.* **20**, 281-297.

Geiger, R., Andritschke, D., Friebe, S., Herzog, F., Luisoni, S., Heger, T. and Helenius, A. (2011). BAP31 and BiP are essential for dislocation of SV40 from the endoplasmic reticulum to the cytosol. *Nat. Cell Biol.* **13**, 1305-1314.

Geijtenbeek, T. B., Kwon, D. S., Torensma, R., van Vliet, S. J., van Duijnhoven, G. C., Middel, J., Cornelissen, I. L., Nottet, H. S., KewalRamani, V. N., Littman, D. R. et al. (2000). DC-SIGN, a dendritic cell-specific HIV-1-binding protein that enhances trans-infection of T cells. *Cell* **100**, 587-597.

Geraghty, R. J., Krummenacher, C., Cohen, G. H., Eisenberg, R. J. and Spear, P. G. (1998). Entry of alphaherpesviruses mediated by poliovirus receptor-related protein 1 and poliovirus receptor. *Science* **280**, 1618-1620.

Greber, U. F. (2002). Signalling in viral entry. *Cell. Mol. Life Sci.* **59**, 608-626.

Greber, U. F., Willetts, M., Webster, P. and Helenius, A. (1993). Stepwise dismantling of adenovirus 2 during entry into cells. *Cell* **75**, 477-486.

Greber, U. F., Suomalainen, M., Stidwill, R. P., Boucke, K., Ebersold, M. W. and Helenius, A. (1997). The role of the nuclear pore complex in adenovirus DNA entry. *EMBO J.* **16**, 5998-6007.

Grove, J. and Marsh, M. (2011). The cell biology of receptor-mediated virus entry. *J. Cell Biol.* **195**, 1071-1082.

Gruenberg, J. (2009). Viruses and endosome membrane dynamics. *Curr. Opin. Cell Biol.* **21**, 582-588.

Harrison, S. C. (2005). Mechanism of membrane fusion by viral envelope proteins. *Adv. Virus Res.* **64**, 231-261.

Helenius, A. (2007). Virus entry and uncoating. In *Fields Virology*, pp. 99-118. Philadelphia, PA: Wolters Kluwer/ Lippincott Williams & Wilkins.

Helenius, A., Kartenbeck, J., Simons, K. and Fries, E. (1980). On the entry of Semliki forest virus into BHK-21 cells. *J. Cell Biol.* **84**, 404-420.

Hummeler, K., Tomassini, N. and Sokol, F. (1970). Morphological aspects of the uptake of simian virus 40 by permissive cells. *J. Virol.* **6**, 87-93.

Hunt, C. L., Kolokoltsov, A. A., Davey, R. A. and Maury, W. (2011). The Tyro3 receptor kinase Axl enhances macropinocytosis of Zaire ebolavirus. *J. Virol.* **85**, 334-347.

Huotari, J. and Helenius, A. (2011). Endosome maturation. *EMBO J.* **30**, 3481-3500.

Huotari, J., Meyer-Schaller, N., Hubner, M., Stauffer, S., Katheder, N., Horvath, P., Mancini, R., Helenius, A. and Peter, M. (2012). Cullin-3 regulates late endosome maturation. *Proc. Natl. Acad. Sci. USA* **109**, 823-828.

Inoue, T. and Tsai, B. (2011). A large and intact viral particle penetrates the endoplasmic reticulum membrane to reach the cytosol. *PLoS Pathog.* **7**, e1002037.

Johannsdottir, H. K., Mancini, R., Kartenbeck, J., Amato, L. and Helenius, A. (2009). Host cell factors and functions involved in vesicular stomatitis virus entry. *J. Virol.* **83**, 440-453.

Jovasevic, V., Liang, L. and Roizman, B. (2008). Proteolytic cleavage of VP1-2 is required for release of herpes simplex virus 1 DNA into the nucleus. *J. Virol.* **82**, 3311-3319.

Kälin, S., Amstutz, B., Gastaldelli, M., Wolfrum, N., Boucke, K., Havenga, M., DiGennaro, F., Liska, N., Hemmi, S. and Greber, U. F. (2010). Macropinocytotic uptake and infection of human epithelial cells with species B2 adenovirus type 35. *J. Virol.* **84**, 5336-5350.

Kann, M., Sodeik, B., Vlachou, A., Gerlich, W. H. and Helenius, A. (1999). Phosphorylation-dependent binding of hepatitis B virus core particles to the nuclear pore complex. *J. Cell Biol.* **145**, 45-55.

Kartenbeck, J., Stukenbrok, H. and Helenius, A. (1989). Endocytosis of simian virus 40 into the endoplasmic reticulum. *J. Cell Biol.* **109**, 2721-2729.

Kemler, I., Whittaker, G. and Helenius, A. (1994). Nuclear import of microinjected influenza virus ribonucleoproteins. *Virology* **202**, 1028-1033.

Kilby, J. M., Hopkins, S., Venetta, T. M., DiMassimo, B., Cloud, G. A., Lee, J. Y., Alldredge, L., Hunter, E., Lambert, D., Bolognesi, D. et al. (1998). Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nat. Med.* **4**, 1302-1307.

Kirchhausen, T. (2000). Clathrin. *Annu. Rev. Biochem.* **69**, 699-727.

Klasse, P. J. (2012). The molecular basis of HIV entry. *Cell. Microbiol.* **14**, 1183-1192.

Klatzmann, D., Champagne, E., Chamaret, S., Gruest, J., Guetard, D., Hercend, T., Gluckman, J. C. and Montagnier, L. (1984). T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature* **312**, 767-768.

Klimstra, W. B., Nangle, E. M., Smith, M. S., Yurochko, A. D. and Ryman, K. D. (2003). DC-SIGN and L-SIGN can act as attachment receptors for alphaviruses and distinguish between mosquito cell- and mammalian cell-derived viruses. *J. Virol.* **77**, 12022-12032.

Klucevsek, K., Daley, J., Darshan, M. S., Bordeaux, J. and Moroianu, J. (2006). Nuclear import strategies of high-risk HPV18 L2 minor capsid protein. *Virology* **352**, 200-208.

Kroschewski, H., Allison, S. L., Heinz, F. X. and Mandl, C. W. (2003). Role of heparan sulfate for attachment and entry of tick-borne encephalitis virus. *Virology* **308**, 92-100.

Lehmann, M. J., Sherer, N. M., Marks, C. B., Pypaert, M. and Mothes, W. (2005). Actin- and myosin-driven movement of viruses along filopodia precedes their entry into cells. *J. Cell Biol.* **170**, 317-325.

Leopold, P. L., Kreitzer, G., Miyazawa, N., Rempel, S., Pfister, K. K., Rodriguez-Boulan, E. and Crystal, R. G.

(2000). Dynein- and microtubule-mediated translocation of adenovirus serotype 5 occurs after endosomal lysis. *Hum. Gene Ther.* **11**, 151-165.

Lozach, P. Y., Lortat-Jacob, H., de Lacroix de Lavalette, A., Staropoli, I., Foung, S., Amara, A., Houles, C., Fieschi, F., Schwartz, O., Virelizier, J. L. et al. (2003). DC-SIGN and L-SIGN are high affinity binding receptors for hepatitis C virus glycoprotein E2. *J. Biol. Chem.* **278**, 20358-20366.

Lozach, P. Y., Huotari, J. and Helenius, A. (2011a). Late-penetrating viruses. *Curr. Opin. Virol.* **1**, 35-43.

Lozach, P. Y., Kühbacher, A., Meier, R., Mancini, R., Bitto, D., Bouloy, M. and Helenius, A. (2011b). DC-SIGN as a receptor for phleboviruses. *Cell Host Microbe* **10**, 75-88.

Marsh, M. and Helenius, A. (2006). Virus entry: open sesame. *Cell* **124**, 729-740.

Matlin, K. S., Reggio, H., Helenius, A. and Simons, K. (1981). Infectious entry pathway of influenza virus in a canine kidney cell line. *J. Cell Biol.* **91**, 601-613.

Matthews, T., Salgo, M., Greenberg, M., Chung, J., DeMasi, R. and Bolognesi, D. (2004). Enfuvirtide: the first therapy to inhibit the entry of HIV-1 into host CD4 lymphocytes. *Nat. Rev. Drug Discov.* **3**, 215-225.

Mayer, D., Molawi, K., Martínez-Sobrido, L., Ghanem, A., Thomas, S., Baginsky, S., Grossmann, J., García-Sastre, A. and Schwemmle, M. (2007). Identification of cellular interaction partners of the influenza virus ribonucleoprotein complex and polymerase complex using proteomic-based approaches. *J. Proteome Res.* **6**, 672-682.

Meertens, L., Carnec, X., Lecoin, M. P., Ramdasi, R., Guivel-Benhassine, F., Lew, E., Lemke, G., Schwartz, O. and Amara, A. (2012). The TIM and TAM families of phosphatidylserine receptors mediate dengue virus entry. *Cell Host Microbe* **12**, 544-557.

Meier, O., Boucke, K., Hammer, S. V., Keller, S., Stidwill, R. P., Hemmi, S. and Greber, U. F. (2002). Adenovirus triggers macropinocytosis and endosomal leakage together with its clathrin-mediated uptake. *J. Cell Biol.* **158**, 1119-1131.

Mercer, J. and Helenius, A. (2008). Vaccinia virus uses macropinocytosis and apoptotic mimicry to enter host cells. *Science* **320**, 531-535.

Mercer, J. and Helenius, A. (2009). Virus entry by macropinocytosis. *Nat. Cell Biol.* **11**, 510-520.

Mercer, J. and Helenius, A. (2012). Gulping rather than sipping: macropinocytosis as a way of virus entry. *Curr. Opin. Microbiol.* **15**, 490-499.

Mercer, J., Schelhaas, M. and Helenius, A. (2010). Virus entry by endocytosis. *Annu. Rev. Biochem.* **79**, 803-833.

Montgomery, R. I., Warner, M. S., Lum, B. J. and Spear, P. G. (1996). Herpes simplex virus-1 entry into cells mediated by a novel member of the TNF/NGF receptor family. *Cell* **87**, 427-436.

Morizono, K., Xie, Y., Olafsen, T., Lee, B., Dasgupta, A., Wu, A. M. and Chen, I. S. (2011). The soluble serum protein Gas6 bridges virion envelope phosphatidylserine to the TAM receptor tyrosine kinase Axl to mediate viral entry. *Cell Host Microbe* **9**, 286-298.

Nakanishi, A., Clever, J., Yamada, M., Li, P. P. and Kasamatsu, H. (1996). Association with capsid proteins promotes nuclear targeting of simian virus 40 DNA. *Proc. Natl. Acad. Sci. USA* **93**, 96-100.

Nakanishi, A., Shum, D., Morioka, H., Otsuka, E. and Kasamatsu, H. (2002). Interaction of the Vp3 nuclear localization signal with the importin alpha 2/beta heterodimer directs nuclear entry of infecting simian virus 40. *J. Virol.* **76**, 9368-9377.

Nanbo, A., Imai, M., Watanabe, S., Noda, T., Takahashi, K., Neumann, G., Halfmann, P. and Kawaoka, Y. (2010). Ebolavirus is internalized into host cells via macropinocytosis in a viral glycoprotein-dependent manner. *PLoS Pathog.* **6**, e1001121.

Nemerow, G. R. (2000). Cell receptors involved in adenovirus entry. *Virology* **274**, 1-4.

Ojala, P. M., Sodeik, B., Ebersold, M. W., Kutay, U. and Helenius, A. (2000). Herpes simplex virus type 1 entry into host cells: reconstitution of capsid binding and uncoating at the nuclear pore complex in vitro. *Mol. Cell. Biol.* **20**, 4922-4931.

Pasdeloup, D., Blondel, D., Isidro, A. L. and Rixon, F. J. (2009). Herpesvirus capsid association with the nuclear pore complex and viral DNA release involve the nucleoporin CAN/Nup214 and the capsid protein pUL25. *J. Virol.* **83**, 6610-6623.

Pearse, B. M. (1976). Clathrin: a unique protein associated with intracellular transfer of membrane by coated vesicles. *Proc. Natl. Acad. Sci. USA* **73**, 1255-1259.

Pelkmans, L., Fava, E., Grabner, H., Hannus, M., Habermann, B., Krausz, E. and Zerial, M. (2005). Genome-wide analysis of human kinases in clathrin- and caveolae/raft-mediated endocytosis. *Nature* **436**, 78-86.

Pérez-Berná, A. J., Ortega-Esteban, A., Menéndez-Conejero, R., Winkler, D. C., Menéndez, M., Steven, A. C., Flint, S. J., de Pablo, P. J. and San Martín, C. (2012). The role of capsid maturation on adenovirus priming for sequential uncoating. *J. Biol. Chem.* **287**, 31582-31595.

Pöhlmann, S., Baribaud, F. and Doms, R. W. (2001). DC-SIGN and DC-SIGNR: helping hands for HIV. *Trends Immunol.* **22**, 643-646.

Prchla, E., Plank, C., Wagner, E., Blaas, D. and Fuchs, R. (1995). Virus-mediated release of endosomal content in vitro: different behavior of adenovirus and rhinovirus serotype 2. *J. Cell Biol.* **131**, 111-123.

Preston, V. G., Murray, J., Preston, C. M., McDougall, I. M. and Stow, N. D. (2008). The UL25 gene product of herpes simplex virus type 1 is involved in uncoating of the viral genome. *J. Virol.* **82**, 6654-6666.

Puntener, D. and Greber, U. F. (2009). DNA-tumor virus entry–from plasma membrane to the nucleus. *Semin. Cell Dev. Biol.* **20**, 631-642.

Qu, Q., Sawa, H., Suzuki, T., Semba, S., Henmi, C., Okada, Y., Tsuda, M., Tanaka, S., Atwood, W. J. and Nagashima, K. (2004). Nuclear entry mechanism of the human polyomavirus JC virus-like particle: role of importins and the nuclear pore complex. *J. Biol. Chem.* **279**, 27735-27742.

Rabe, B., Vlachou, A., Panté, N., Helenius, A. and Kann, M. (2003). Nuclear import of hepatitis B virus capsids and release of the viral genome. *Proc. Natl. Acad. Sci. USA* **100**, 9849-9854.

Rabe, B., Delaleau, M., Bischof, A., Foss, M., Sominskaya, I., Pumpens, P., Cazenave, C., Castroviejo, M. and Kann, M. (2009). Nuclear entry of hepatitis B virus capsids involves disintegration to protein dimers followed by nuclear reassociation to capsids. *PLoS Pathog.* **5**, e1000563.

Radtke, K., Kieneke, D., Wolfstein, A., Michael, K., Steffen, W., Scholz, T., Karger, A. and Sodeik, B. (2010). Plus- and minus-end directed microtubule motors bind simultaneously to herpes simplex virus capsids using different inner tegument structures. *PLoS Pathog.* **6**, e1000991.

Raghu, H., Sharma-Walia, N., Veettil, M. V., Sadagopan, S. and Chandran, B. (2009). Kaposi's sarcoma-associated herpesvirus utilizes an actin polymerization-dependent macropinocytic pathway to enter human dermal microvascular endothelial and human umbilical vein endothelial cells. *J. Virol.* **83**, 4895-4911.

Rust, M. J., Lakadamyali, M., Zhang, F. and Zhuang, X. (2004). Assembly of endocytic machinery around individual influenza viruses during viral entry. *Nat. Struct. Mol. Biol.* **11**, 567-573.

Saeed, M. F., Kolokoltsov, A. A., Albrecht, T. and Davey, R. A. (2010). Cellular entry of ebola virus involves uptake by a macropinocytosis-like mechanism and subsequent trafficking through early and late endosomes. *PLoS Pathog.* **6**, e1001110.

Satoh, T., Arii, J., Suenaga, T., Wang, J., Kogure, A., Uehori, J., Arase, N., Shiratori, I., Tanaka, S., Kawaguchi, Y. et al. (2008). PILRalpha is a herpes simplex virus-1 entry coreceptor that associates with glycoprotein B. *Cell* **132**, 935-944.

Sayah, D. M., Sokolskaja, E., Berthoux, L. and Luban, J. (2004). Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV-1. *Nature* **430**, 569-573.

Schelhaas, M. (2010). Come in and take your coat off - how host cells provide endocytosis for virus entry. *Cell. Microbiol.* **12**, 1378-1388.

Schelhaas, M., Malmström, J., Pelkmans, L., Haugstetter, J., Ellgaard, L., Grünewald, K. and Helenius, A. (2007). Simian Virus 40 depends on ER protein folding and quality control factors for entry into host cells. *Cell* **131**, 516-529.

Schelhaas, M., Ewers, H., Rajamäki, M. L., Day, P. M., Schiller, J. T. and Helenius, A. (2008). Human papillomavirus type 16 entry: retrograde cell surface transport along actin-rich protrusions. *PLoS Pathog.* **4**, e1000148.

Schmidt, F. I., Bleck, C. K., Helenius, A. and Mercer, J. (2011). Vaccinia extracellular virions enter cells by macropinocytosis and acid-activated membrane rupture. *EMBO J.* **30**, 3647-3661.

Schmitz, A., Schwarz, A., Foss, M., Zhou, L., Rabe, B., Hoellenriegel, J., Stoeber, M., Panté, N. and Kann, M. (2010). Nucleoporin 153 arrests the nuclear import of hepatitis B virus capsids in the nuclear basket. *PLoS Pathog.* **6**, e1000741.

Schober, D., Kronenberger, P., Prchla, E., Blaas, D. and Fuchs, R. (1998). Major and minor receptor group human rhinoviruses penetrate from endosomes by different mechanisms. *J. Virol.* **72**, 1354-1364.

Shah, V. B., Shi, J., Hout, D. R., Oztop, I., Krishnan, L., Ahn, J., Shotwell, M. S., Engelman, A. and Aiken, C. (2013). The host proteins transportin SR2/TNPO3 and cyclophilin A exert opposing effects on HIV-1 uncoating. *J. Virol.* **87**, 422-432.

Shimojima, M., Takada, A., Ebihara, H., Neumann, G., Fujioka, K., Irimura, T., Jones, S., Feldmann, H. and Kawaoka, Y. (2006). Tyro3 family-mediated cell entry of Ebola and Marburg viruses. *J. Virol.* **80**, 10109-10116.

Shukla, D., Rowe, C. L., Dong, Y., Racaniello, V. R. and Spear, P. G. (1999). The murine homolog (Mph) of human herpesvirus entry protein B (HveB) mediates entry of pseudorabies virus but not herpes simplex virus types 1 and 2. *J. Virol.* **73**, 4493-4497.

Sieczkarski, S. B. and Whittaker, G. R. (2002). Dissecting virus entry via endocytosis. *J. Gen. Virol.* **83**, 1535-1545.

Simmons, G., Reeves, J. D., Grogan, C. C., Vandenberghe, L. H., Baribaud, F., Whitbeck, J. C., Burke, E., Buchmeier, M. J., Soilleux, E. J., Riley, J. L. et al. (2003). DC-SIGN and DC-SIGNR bind ebola glycoproteins and enhance infection of macrophages and endothelial cells. *Virology* **305**, 115-123.

Simmons, G., Gosalia, D. N., Rennekamp, A. J., Reeves, J. D., Diamond, S. L. and Bates, P. (2005). Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. *Proc. Natl. Acad. Sci. USA* **102**, 11876-11881.

Simmons, G., Bertram, S., Glowacka, I., Steffen, I., Chaipan, C., Agudelo, J., Lu, K., Rennekamp, A. J., Hofmann, H., Bates, P. et al. (2011). Different host cell proteases activate the SARS-coronavirus spike-protein for cell-cell and virus-cell fusion. *Virology* **413**, 265-274.

Skehel, J. J. and Wiley, D. C. (2000). Receptor binding and membrane fusion in virus entry: the influenza hemagglutinin. *Annu. Rev. Biochem.* **69**, 531-569.

Sodeik, B., Ebersold, M. W. and Helenius, A. (1997). Microtubule-mediated transport of incoming herpes simplex virus 1 capsids to the nucleus. *J. Cell Biol.* **136**, 1007-1021.

Spear, P. G., Eisenberg, R. J. and Cohen, G. H. (2000). Three classes of cell surface receptors for alphaherpesvirus entry. *Virology* **275**, 1-8.

Stremlau, M., Owens, C. M., Perron, M. J., Kiessling, M., Autissier, P. and Sodroski, J. (2004). The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. *Nature* **427**, 848-853.

Stremlau, M., Perron, M., Lee, M., Li, Y., Song, B., Javanbakht, H., Diaz-Griffero, F., Anderson, D. J., Sundquist, W. I. and Sodroski, J. (2006). Specific recognition and accelerated uncoating of retroviral capsids by the TRIM5alpha restriction factor. *Proc. Natl. Acad. Sci. USA* **103**, 5514-5519.

Strunze, S., Engelke, M. F., Wang, I. H., Puntener, D., Boucke, K., Schleich, S., Way, M., Schoenenberger, P., Burckhardt, C. J. and Greber, U. F. (2011). Kinesin-1-mediated capsid disassembly and disruption of the nuclear pore complex promote virus infection. *Cell Host Microbe* **10**, 210-223.

Suenaga, T., Satoh, T., Somboonthum, P., Kawaguchi, Y., Mori, Y. and Arase, H. (2010). Myelin-associated glycoprotein mediates membrane fusion and entry of neurotropic herpesviruses. *Proc. Natl. Acad. Sci. USA* **107**, 866-871.

Summerford, C. and Samulski, R. J. (1998). Membrane-associated heparan sulfate proteoglycan is a receptor for adeno-associated virus type 2 virions. *J. Virol.* **72**, 1438-1445.

Suomalainen, M. and Greber, U. F. (2013). Uncoating of non-enveloped viruses. *Curr. Opin. Virol*. **3**, 27-33.

Suomalainen, M., Nakano, M. Y., Keller, S., Boucke, K., Stidwill, R. P. and Greber, U. F. (1999). Microtubule-dependent plus- and minus end-directed motilities are competing processes for nuclear targeting of adenovirus. *J. Cell Biol.* **144**, 657-672.

Svajger, U., Anderluh, M., Jeras, M. and Obermajer, N. (2010). C-type lectin DC-SIGN: an adhesion, signalling and antigen-uptake molecule that guides dendritic cells in immunity. *Cell. Signal.* **22**, 1397-1405.

Tassaneetrithep, B., Burgess, T. H., Granelli-Piperno, A., Trumpfheller, C., Finke, J., Sun, W., Eller, M. A., Pattanapanyasat, K., Sarasombath, S., Birx, D. L. et al. (2003). DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. *J. Exp. Med.* **197**, 823-829.

Valiya Veettil, M., Sadagopan, S., Kerur, N., Chakraborty, S. and Chandran, B. (2010). Interaction of c-Cbl with myosin IIA regulates Bleb associated macropinocytosis of Kaposi's sarcoma-associated herpesvirus. *PLoS Pathog.* **6**, e1001238.

van der Schaar, H. M., Rust, M. J., Chen, C., van der Ende-Metselaar, H., Wilschut, J., Zhuang, X. and Smit, J. M. (2008). Dissecting the cell entry pathway of dengue virus by single-particle tracking in living cells. *PLoS Pathog.* **4**, e1000244.

Wahlberg, J. M. and Garoff, H. (1992). Membrane fusion process of Semliki Forest virus. I: Low pH-induced rearrangement in spike protein quaternary structure precedes virus penetration into cells. *J. Cell Biol.* **116**, 339-348.

West, M. A., Bretscher, M. S. and Watts, C. (1989). Distinct endocytotic pathways in epidermal growth factor-stimulated human carcinoma A431 cells. *J. Cell Biol.* **109**, 2731-2739.

Wodrich, H., Cassany, A., D'Angelo, M. A., Guan, T., Nemerow, G. and Gerace, L. (2006). Adenovirus core protein pVII is translocated into the nucleus by multiple import receptor pathways. *J. Virol.* **80**, 9608-9618.

Wolfrum, N. and Greber, U. F. (2013). Adenovirus signalling in entry. *Cell. Microbiol.* **15**, 53-62.

Wu, W. W., Sun, Y. H. and Panté, N. (2007). Nuclear import of influenza A viral ribonucleoprotein complexes is mediated by two nuclear localization sequences on viral nucleoprotein. *Virol. J.* **4**, 49.

Yamauchi, Y., Kiriyama, K., Kubota, N., Kimura, H., Usukura, J. and Nishiyama, Y. (2008). The UL14 tegument protein of herpes simplex virus type 1 is required for efficient nuclear transport of the alpha transinducing factor VP16 and viral capsids. *J. Virol.* **82**, 1094-1106.

Yamauchi, Y., Boukari, H., Banerjee, I., Sbalzarini, I. F., Horvath, P. and Helenius, A. (2011). Histone deacetylase 8 is required for centrosome cohesion and influenza A virus entry. *PLoS Pathog.* **7**, e1002316.

Zaitseva, E., Yang, S. T., Melikov, K., Pourmal, S. and Chernomordik, L. V. (2010). Dengue virus ensures its fusion in late endosomes using compartment-specific lipids. *PLoS Pathog.* **6**, e1001131.