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# Virus entry at a glance

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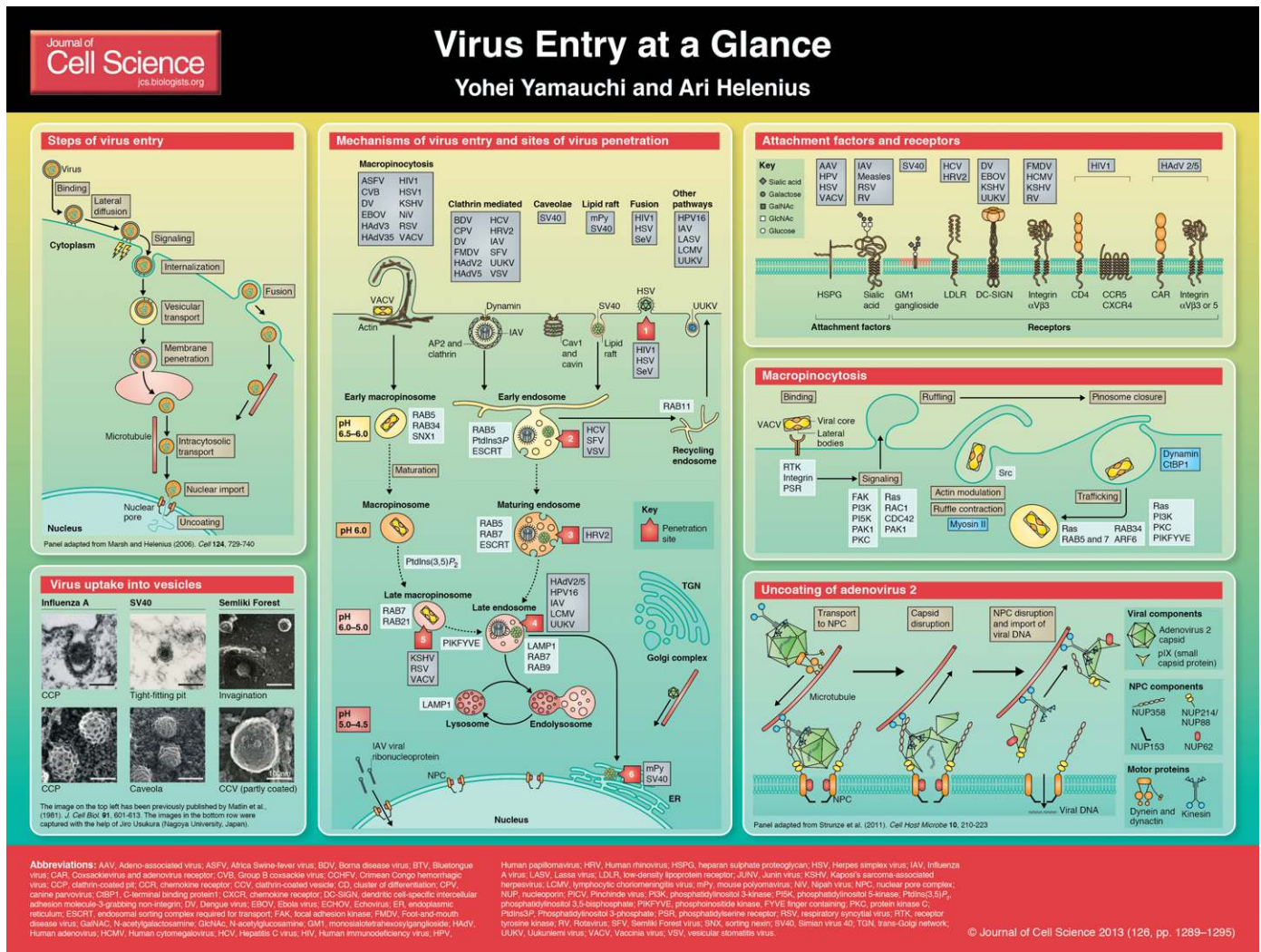
The goal of a virus particle is to transport its genome in a replication-competent form from an infected cell to an uninfected cell. To enter a new host cell, the majority of viruses take advantage of the endocytic mechanisms of the cell and wait until reaching endocytic vacuoles or other cytoplasmic 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,



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; Tassaneitrihet 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; Collier 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; Kälén 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 Veetil 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<sup>+</sup>/H<sup>+</sup> 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 (Curetton 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 intraluminal 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 luminal 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; Klucsevsek 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  $\alpha$ - and  $\beta$ -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 TRIM5 $\alpha$ , 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.

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

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