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CELL SCIENCE AT A GLANCE

Viral escape from endosomes and host detection at a glance

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ABSTRACT

In order to replicate, most pathogens need to enter their target cells. Many viruses enter the host cell through an endocytic pathway and hijack endosomes for their journey towards sites of replication. For delivery of their genome to the host cell cytoplasm and to avoid degradation, viruses have to escape this endosomal compartment without host detection. Viruses have developed complex mechanisms to penetrate the endosomal membrane and have evolved to co-opt several host factors to facilitate endosomal escape. Conversely, there is an extensive variety of cellular mechanisms to counteract or impede viral replication. At the level of cell entry, there are cellular defense mechanisms that recognize endosomal membrane damage caused by virus-induced membrane fusion and pore formation, as well as restriction factors that block these processes. In this Cell Science at a Glance article and accompanying poster, we describe the different mechanisms that viruses have evolved to escape the endosomal compartment, as well as the counteracting cellular protection mechanisms. We provide examples for enveloped and non-enveloped viruses, for which we discuss some unique and unexpected cellular responses to virus-entry-induced membrane damage.

KEY WORDS: Detection, Endosomes, Escape, Virus

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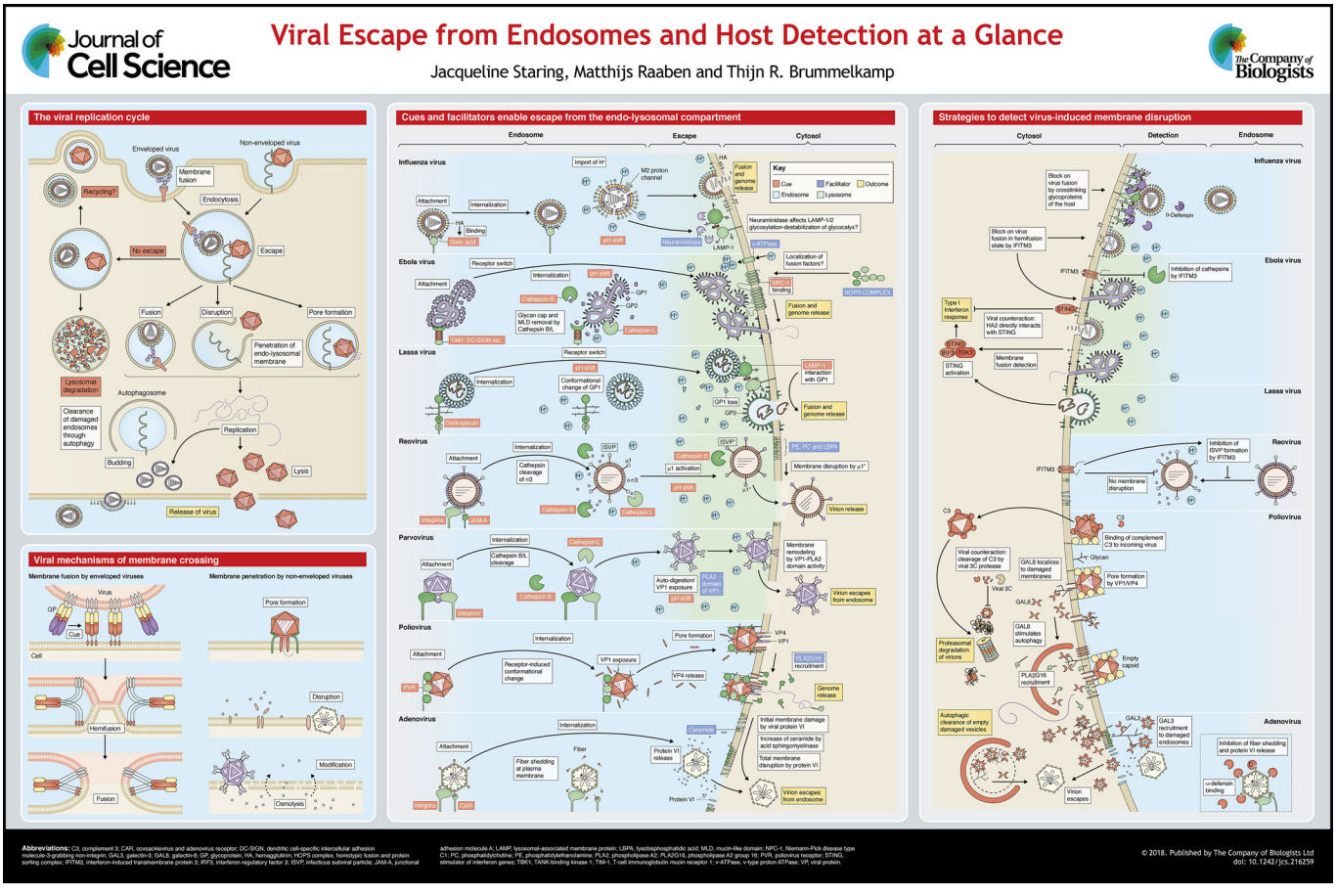
Introduction

The first step in the life cycle of any virus is the attachment to host cells; for this reason, viruses have evolved to interact with proteins, lipids and sugar moieties on the cell surface, which generally triggers uptake of the virion through the endosomal system (Yamauchi and Helenius, 2013; Cossart and Helenius, 2014). Using this ‘Trojan-horse-like’ entry pathway, viruses gain access to the interior of the target cell, while their genetic material is still shielded from detection by the immune system. By hijacking the endocytic pathways of the host, viruses are able to evade the barrier imposed by the plasma membrane and its connected underlying



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Box 1. Membrane fusion and membrane penetration

Fusion proteins that are embedded in the membrane of enveloped viruses facilitate fusion with cellular membranes, and whereas they can greatly vary in structure, (class I, class II or class III viral fusion proteins) all have a shared mechanism of action: a ligand-triggered conformational change that results in the apposition and eventual merging of the viral lipid envelope and the host membrane (Harrison, 2015). Whereas fusion of two lipid bilayers is thermodynamically favorable, there is, however, a high kinetic barrier (Chernomordik and Kozlov, 2003; Chernomordik et al., 2006). Viral fusion proteins overcome this barrier by utilizing the liberated free energy during the conformational change to pull the viral and host membranes in close proximity through the insertion of fusion loops or peptides, thereby favoring fusion (Bullough et al., 1994; Chen et al., 1999). The different steps that lead to membrane fusion are quite well understood, mainly owing to the availability of crystal structures of pre- and post-fusion conformations of fusion proteins, the best example of which is the hemagglutinin protein from influenza A virus (Skehel and Wiley, 2000; Wilson et al., 1981; Chen et al., 1998) (see poster). Non-enveloped viruses must disrupt the endosomal membrane to access the cytoplasm. However, the mechanism of penetration is not completely understood. Similarly to enveloped viruses, membrane penetration of non-enveloped viruses is driven by conformational rearrangements of viral structural proteins. Three major structural classes of membranolytic viral factors can be distinguished: amphipathic α-helical domains (e.g. adenovirus protein VI; Wiethoff et al., 2005), myristoylated residues (e.g. N-myristoylated VP4 of poliovirus and rhinoviruses; Panjwani et al., 2014; Danthi et al., 2003; Moscufo et al., 1993) and lipid-remodeling enzymatic domains [e.g. parvovirus VP1, which encodes an N-terminal phospholipase type 2 (PLA2); Farr et al., 2005]. Depending on the viral content that needs to be delivered into the cytoplasm (i.e. naked genome or a nucleocapsid), endosomal disruption can be mechanistically accomplished through transient modification of the limiting membrane, formation of a membrane pore, or complete disruption of the endosomal membrane (see poster).

structures, such as the cortical actin network. Different endocytic cell entry routes for viruses have been described, including clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and clathrin- and caveolae-independent pathways (Boulant et al., 2015; Matlin et al., 1981; Chardonnet and Dales, 1970; Kartenbeck et al., 1989; Rojek et al., 2008; Nanbo et al., 2010).

Endocytosis is highly complex and dynamic, and involves recycling, trafficking, maturation and fusion of endocytic vesicles (Grant and Donaldson, 2009). Viruses that are running the endocytic gauntlet need to make sure they escape the endosomal compartment before being recycled back into the extracellular space (Zila et al., 2014; Mainou and Dermody, 2012; Grove and Marsh, 2011) or subjected to degradation in the harsh environment of the lysosome (see poster). To this end, enveloped viruses (e.g. Filoviridae, Arenaviridae, Orthomyxoviridae) make use of sophisticated molecular machinery that drives fusion of the viral envelope with the membrane of an endosome, thereby releasing their genomic content into the cytoplasm (Box 1). Non-enveloped viruses on the other hand (e.g. Adenoviridae, Parvoviridae, Picornaviridae), have evolved different strategies that involve membrane-modifying proteins which can physically pierce the endosomal membrane to allow release of the genomic content into the cytoplasm (see poster).

Here, we depict the arms race between viruses and host cells at the level of the endo-lysosome. We highlight the endosomal escape strategies of different viruses and describe the cellular cues that are involved. In addition, we discuss host detection mechanisms at the endo-lysosomal level.

Box 2. Endovesicular acidity

Acidification has been described as a membrane fusion trigger for orthomyxoviruses, rhabdoviruses, α-viruses, flaviviruses, bunyaviruses and arenaviruses (Ochiai et al., 1995; Roberts et al., 1999; Sourisseau et al., 2007; Mosso et al., 2008; Lozach et al., 2010; Cosset et al., 2009), but it is also a well-known trigger for non-enveloped viruses (Bayer et al., 1998; Chung et al., 2005). The vacuolar ATPase (v-ATPase) is a multi-subunit complex and proton pump that functions to acidify intracellular compartments (Nelson and Taiz, 1989) (see poster). Its role in virus entry has been well established, and v-ATPase inhibitors such as bafilomycin A_1 (Yoshimori et al., 1991) are frequently used as a method of inhibition of cell entry by enveloped viruses that depend on a low pH for membrane fusion. For enveloped viruses, activation of many class I fusion proteins by low pH involves the removal or refolding of globular head domains, which keep the fusion subunit in its pre-fusion state (Godley et al., 1992; Kemble et al., 1992; Rachakonda et al., 2007). Several protonation events are thought to drive this separation; histidine residues of viral capsid proteins, which can function as pH sensors, have especially been implicated here (Kampmann et al., 2006). In addition to membrane fusion proteins, other structural viral proteins facilitate infection of enveloped viruses in a low pH environment. For example, endosomal acidification is not only important for inducing conformational changes in the hemagglutinin fusion protein of influenza A virus, but it also opens up its M2 proton channel, which acidifies the interior of the viral particle (Schnell and Chou, 2008; Stouffer et al., 2008; Cady et al., 2009) (see poster). Subsequently, this dissociates the viral genome (i.e. existing as ribonucleoprotein complexes) from the viral M1 protein, thereby facilitating release from the virion into the host cell cytoplasm (Helenius, 1992).

Cues and facilitating factors for endosomal escape

A variety of cellular factors trigger the conformational rearrangements in viral capsid proteins that drive membrane fusion and pore formation (see poster). Well-known cues that induce these structural changes include receptor binding, low pH (Box 2), proteolytic processing by endosomal proteases or a combination of these triggers (White and Whittaker, 2016). Moreover, factors also exist to facilitate the entry process. For instance, a switch from cell membrane attachment receptor to intracellular receptor has been described as a process for endosomal escape used by some hemorraghic fever viruses (Jae et al., 2013; Carette et al., 2011). In addition, a specific lipid and/or sugar composition of the endovesicular compartment can be a requirement for viruses to initiate their entry process. However, viruses can often use alternative receptors or entry routes and may respond to multiple proteolytic triggers and entry cues. Key examples for some prototype viruses are described in more detail below.

Receptor binding

Conformational changes induced by receptor binding have a big impact on the uncoating and endovesicular escape of several non-enveloped viruses. For example, poliovirus initiates infection by binding to target cells via an interaction with its cellular receptor, the poliovirus receptor (PVR, also known as CD155) (Racaniello, 1996; Mendelsohn et al., 1989). Very early after endocytosis, conformational changes in the poliovirus capsid are promoted by PVR binding (Tsang et al., 2001) and result in exposure of the hydrophobic domains of the capsid protein VP1 (Fricks and Hogle, 1990) and the release of the myristoylated VP4 peptide (Chow et al., 1987; Danthi et al., 2003). These conformational changes result in a more hydrophobic capsid, known as the 135S-particle or A-particle (Fenwick and Cooper, 1962; de Sena and Mandel, 1977). This facilitates interaction with the membrane and induces the formation of protein-based transmembrane pores, through which the genomic

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RNA is believed to be extruded from the early endosome into the cytoplasm (Bostina et al., 2011; Brandenburg et al., 2007; Strauss et al., 2013; Tosteson et al., 2004; Butan et al., 2014). Likewise, adenovirus virions undergo structural rearrangements after binding their receptors [the Coxsackie and adenovirus receptor, CAR (Bergelson et al., 1997) and integrins (Wickham et al., 1993)] and the subsequent endocytosis is thought to mediate complete endosome rupture through the liberation and membrane insertion of viral protein VI in early endosomes (Leopold et al., 1998; Prchla et al., 1995; Martinez et al., 2013; Maier et al., 2012; Meier et al., 2002; Luisoni et al., 2015). For some enveloped viruses (e.g. most Retroviridae, Paramyxoviridae and Herpesviridae), interaction with their cell surface receptor is sufficient to trigger membrane fusion. This reflects their capacity to establish fusion at the plasma membrane at neutral pH, giving them the ability to form enlarged, multi-nucleated cells (syncytia) (Stein et al., 1987; Horvath et al., 1992; Paterson et al., 1985; Morgan et al., 1968). Most enveloped viruses, however, undergo receptor-mediated endocytosis and require a low pH for membrane fusion (see poster).

Proteolytic processing by endosomal proteases

A low endosomal pH is also required for Ebola virus cell entry. However, it is not sufficient to trigger membrane fusion (Bale et al., 2011; Brecher et al., 2012); instead, membrane fusion mediated by the Ebola virus glycoprotein involves the digestion by endosomal proteases cathepsin L and cathepsin B (Brecher et al., 2012; Hood et al., 2010; Martinez et al., 2010; Kaletsky et al., 2007; Chandran et al., 2005). There are also non-enveloped viruses that require endosomal proteolysis for cell entry. For example, during reovirus cell entry, after binding of integrin (Maginnis et al., 2006) and JAM-A (Barton et al., 2001) at the cell surface, the capsid protein σ3 is processed and removed by endosomal cathepsins (Baer et al., 1999; Ebert et al., 2002; Doyle et al., 2012), resulting in full exposure of the myristoylated capsid protein μ1, which harbors the membrane penetration activity (Chandran et al., 2002, 2003; Odegard et al., 2004; Nibert et al., 2005). This leads to eventual viral escape from late endosomes (Mainou and Dermody, 2012).

Intracellular receptor switching

Some hemorrhagic fever viruses require additional interactions with endosomal protein receptors in order to escape the vesicular compartment. In the case of Ebola virus, it has been demonstrated that the proteolytic cleavage by endosomal cathepsins, which remove the mucin-like domain and glycan cap of glycoprotein subunit 1, do not fully activate the fusion subunit of the glycoprotein (Bale et al., 2011; Chandran et al., 2005). In addition, after endosomal proteolytic processing, full membrane fusion by Ebola virus glycoprotein occurs in the lysosome and requires a switch from receptors encountered at the cell surface [e.g. DC-SIGN (Alvarez et al., 2002), TIM1 (Kondratowicz et al., 2011)] to an interaction with the intracellular lysosomal membrane receptor Niemann-Pick C1 (NPC1) (Carette et al., 2011; Cote et al., 2011; Wang et al., 2016). Ebola virus membrane fusion also depends on the activity of the homotypic fusion and protein sorting (HOPS) tethering complex, which may orchestrate the correct localization of one or more viral and/or host fusion factors (Jae and Brummelkamp, 2015; Carette et al., 2011). Similarly to Ebola virus, Lassa virus glycoprotein undergoes a conformational change that is induced by low pH, resulting in a receptor switch from α-dystroglycan to lysosome-associated membrane protein 1 (LAMP1) (Jae et al., 2013, 2014; Li et al., 2016). More specifically, this interaction involves the glycoprotein-1 subunit of Lassa virus glycoprotein and an N-glycosylated residue in the distal luminal domain of LAMP1 (Cohen-Dvashi et al., 2015, 2016; Jae et al., 2014). It has recently been suggested that the interaction between the Lassa virus glycoprotein and LAMP1 is specifically responsible for elevating the pH threshold for membrane fusion (Hulseberg et al., 2018). However, for both Lassa and Ebola virus glycoprotein, it remains to be determined whether the interaction with an intracellular receptor is the sole trigger of membrane fusion under physiological conditions, and whether other viruses employ a similar mechanism. Another arenavirus, Lujo virus, has recently been shown to depend on the endosomal tetraspanin CD63 for membrane fusion (Raaben et al., 2017). Although an interaction with Lujo virus glycoprotein was not reported, it suggests that receptor switching could be a more widespread mechanism for enveloped viruses, and perhaps non-enveloped viruses, to escape the vesicular compartment.

Composition of the endosomal membrane

In addition to the cues described above, some viruses have specific lipid or ionic requirements that can influence the efficiency of endosomal escape (Zaitseva et al., 2010). In the case of enveloped viruses, these requirements generally work directly at the level of membrane fusion. For example, infection with Semliki Forest virus (SFV) demands an optimal amount of cholesterol and sphingomyelin in the endosomal membrane for fusion (Phalen and Kielian, 1991; White and Helenius, 1980; Nieva et al., 1994). Without these factors, the stable insertion of the fusion loop (which resides within the SFV E1 class II fusion protein) into the target cell membrane is not efficiently established (Ahn et al., 2002). Similarly, as well as a low pH, hantaviruses require high cholesterol levels in the endosomal target membrane for membrane fusion (Kleinfelter et al., 2015). This is probably due to a requirement for the change in fluidity or curvature of the endosomal membrane (Needham and Nunn, 1990; Papanikolaou et al., 2005). Lysobisphosphatidic acid (LBPA), a lipid species which is mostly found in late endosomes and multivesicular bodies (Piper and Katzmann, 2007), is required by several viruses to enter the cytosol. As with cholesterol, the anionic charge and membrane fluidic properties of LBPA appear to be important to facilitate membrane modifications by both enveloped and non-enveloped viruses. For example, the pore-forming activity of the bluetongue virus (Reoviridae) Vp5 capsid protein depends on endosomal LBPA levels (Patel et al., 2016) (see poster). Furthermore, zwitterionic phospholipids such as phosphatidylethanolamine and phosphatidylcholine facilitate the structural transition of intermediate subviral particles (from ISVP to ISVP*) of reoviruses (Snyder and Danthi, 2016).

Adenovirus has been shown to use a multistep process involving ceramide lipids for robust endosomal membrane penetration (Burckhardt et al., 2011; Meier et al., 2002; Greber et al., 1993, 1996; Wiethoff et al., 2005; Wodrich et al., 2010). After receptor binding, the adenovirus initiates endocytic uptake by generating small lesions in the plasma membrane through release of the viral membranolytic protein VI. These lesions induce a local influx of Ca^{2+} ions, initiating the membrane-damage repair response. This response entails lysosomal exocytosis and release of acid sphingomyelinase, which degrades sphingomyelin to ceramide lipids in the plasma membrane and stimulates rapid endocytosis of adenovirus particles. Moreover, the ceramide-rich endosomes display enhanced binding of protein VI to the limiting membrane, inducing massive endosomal membrane rupture and subsequent release of the virions (Luisoni et al., 2015) (see poster).

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Enzymatic modifications of the endosomal membrane

Viruses have also evolved strategies to modify the endosomal membrane through either virus- or host-encoded enzymatic activities to facilitate efficient escape. For example, members of the non-enveloped parvovirus family encode a capsid-tethered lipid-modifying enzyme to alter the endosomal membrane after internalization. After receptor binding (e.g. integrins; Weigel-Kelley et al., 2003) and proteolytic processing (via an autolytic process and/or by endosomal cathepsins; Salganik et al., 2012; Akache et al., 2007), parvovirus virions undergo a conformational shift in late endosomes that leads to the exposure of a phospholipase A_2-like domain (PLA2) in their VP1 protein (Suikkanen et al., 2003; Zádori et al., 2001; Farr et al., 2005). This PLA2 domain is capable of damaging liposomes *in vitro* (Canaan et al., 2004). Furthermore, parvovirus mutants that lack this phospholipase activity have reduced infectivity, but regain their infectivity after incubation with the membrane-permeabilizing agent polyethyleneimine (PEI), or co-incubation with adenovirus virions (Farr et al., 2005). Additional studies report that phospholipase inhibitors prevent parvovirus infection (Dorsch et al., 2002), supporting the current model in which the phospholipase activity in VP1 is indeed required for modification of endosomes and subsequent viral entry into the cytoplasm. In a related fashion, members of the picornavirus family were recently shown to depend on a host-encoded lipid-modifying enzyme for endosomal escape. Picornaviruses, like their prototype poliovirus, recruit cellular phospholipase A_2 group XVI (PLA2G16) to virus-induced pores in the endosomal membrane (Staring et al., 2017) (see poster). The catalytic activity of PLA2G16 facilitates the quick release of the viral genome into the cytoplasm, but the exact mechanism by which this is accomplished remains to be determined. Remarkably, the few picornaviruses that are not dependent on PLA2G16 seem to use alternative strategies for membrane penetration, somewhat resembling adenovirus-mediated endosome lysis (i.e. rhinovirus 14; Schober et al., 1998) or encoding a PLA2-like gene (viral 2A protein) in their genome (i.e. parechovirus, avian encephalitis virus and aichivirus; Hughes and Stanway, 2000). Whether these 2A proteins share a similar function as the PLA2 domain of VP1 of parvoviruses remains to be determined. In addition to lipids, it has been suggested that the large carbohydrate network within the endolysosomal lumen, the glycocalyx, also plays a role in viral escape from the vesicular compartment. The neuraminidase protein of influenza A virus strain H5N1 was shown to affect the glycosylation of and LAMP2 at low pH, thereby potentially destabilizing the glycocalyx of the lysosome (Ju et al., 2015).

Cellular antiviral defenses at the level of the endolysomal compartment

Viruses are intracellular parasites that depend on their host for multiplication. Whereas the cellular processes described above all favor virus entry and endosomal release of the viral genomic material, there are several systems in play to prevent pathogens from gaining access to the cell interior.

Protection against incoming virions

Antibodies and antiviral peptides, such as defensins, form a first line of defense against incoming virus particles. They can directly interfere with virion binding to receptors and thereby block proper uptake into cells, but also prevent membrane fusion (Leikina et al., 2005) and interfere with capsid destabilization once inside the endosomal compartment (Smith and Nemerow, 2008). For example, α-defensins were shown to bind and stabilize adenovirus particles, subsequently preventing release of protein VI from the capsid and membrane penetration (Smith and Nemerow, 2008). Likewise, θ-defensins inhibit influenza A virus infection by blocking a late step of membrane fusion that is mediated by the viral hemagglutinin protein (Leikina et al., 2005) (see poster). Interestingly, complement component C3 deposited on incoming pathogens co-migrates into endocytic vesicles and can also activate an innate immune signaling cascade (Tam et al., 2014). However, as shown for adenovirus infection, this requires translocation of the capsid–C3 complex into the cytosol. Highlighting the strength of this system, rhinovirus and poliovirus have evolved a mechanism that antagonizes C3 detection by means of proteolytic cleavage of C3 by the virus-encoded 3C protease (Tam et al., 2014). In addition, pattern-recognition receptors can recognize pathogenic factors and form another important line of defense in the endosomal compartment, which is described in more detail elsewhere (Kawai and Akira, 2010; Akira and Takeda, 2004; Lester and Li, 2014).

Detection and inhibition of virus-induced membrane disruption

Endosomal membrane modifications that are caused by viral membrane fusion could also directly serve as a danger signal upon which cells respond. Membrane fusion is a process that frequently occurs in cells as part of several physiological processes (e.g. vesicular trafficking). However, virus-induced membrane fusion can be sensed by cells, and this is dependent on the protein stimulator of interferon genes (STING), together with TANK binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3) (Holm et al., 2012). Furthermore, influenza A virus has evolved to counteract STING activation through a direct interaction between the fusion peptide of hemagglutinin-2 and STING, highlighting this type of restriction as an important antiviral mechanism (Holm et al., 2016). This implies that cells are able to differentiate virus-induced fusion events from cellular events, or sterile membrane damage. The mechanism(s) by which cells spot viral fusion events as danger signals remains to be established, but this is an intriguing area of innate immune sensing that requires further research. Similarly, members of the interferon-induced transmembrane family (IFITM) have been shown to prevent infection of several enveloped viruses at the level of membrane fusion (Desai et al., 2014; Feeley et al., 2011; Li et al., 2013). Three human IFITM proteins (IFITM1-IFITM3) are known to have antiviral activities against several viruses, including dengue virus, Ebola virus, influenza A virus, reovirus, severe acute respiratory syndrome coronavirus (SARS) coronavirus and West Nile virus (Huang et al., 2011; Brass et al., 2009). Mechanistically, there are several lines of evidence indicating that IFITM proteins modify the physical properties of endosomal membranes, thereby inhibiting the formation and/or expansion of fusion pores (Desai et al., 2014; Feeley et al., 2011; Li et al., 2013). Furthermore, overexpression of IFITM3 has been shown to prevent the digestion of reovirus capsid protein μ1, which suggests that IFITM3 can modulate the function of late endosomes, and/or directly interferes with the proteolytic activity that is required for the formation of ISVP* particles (Anafu et al., 2013) (see poster).

Detection and clearance of damaged endosomal membranes

Whereas enveloped viruses fuse with endosomal membranes without affecting cell integrity, non-enveloped viruses can cause significant damage to endosomal membranes. This results in exposure of content in the endosomal lumen to cytosolic proteins, thereby presenting a cellular danger signal. For example, endosomal rupture induced by

adenovirus protein VI triggers innate pro-inflammatory responses, including activation of the inflammasome (Barlan et al., 2011a,b). In addition, as observed for bacterial infections, the exposure of extracellular carbohydrates such as β-galactoside within the endosomal lumen upon membrane damage can recruit cytosolic galectins. These galectin-positive membranes can be subjected to autophagy for further degradation (Thurston et al., 2012). In the case of adenovirus, galectin-3 and galectin-8 are recruited to sites of protein VI-induced membrane damage, but most adenovirus particles are able to escape the endosomal compartment before being targeted for autophagic degradation (Montespan et al., 2017; Maier et al., 2012) (see poster). Moreover, the removal of damaged membranes in the context of infection could even be beneficial for the virus, because the clearance of the damaged membranes dampens the innate immune response of the infected cell (Zeng and Carlin, 2013). For picornaviruses, it has recently been described that galectin-8 can be recruited to sites of virus-induced membrane damage, which targets these membranes for degradation through the autophagic pathway (Staring et al., 2017). It is currently unclear if the sugar moieties that are recognized by galectin-8 become exposed at the cytoplasmic side, or are detected by galectin-8 at the luminal side of the endosome. In order to avoid degradation of their genome, picornaviruses require the activity of the previously mentioned host enzyme PLA2G16. In the absence of this factor, galectin recruitment and subsequent autophagy are sufficient to block infection, through the degradation of the entire virion (including the genome). This additional hurdle in virus entry may very well explain, at least in part, the high particle-to-infectivity ratio of these viruses, where very few viral genomes make it to their expected destination of replication (Bergelson, 2008).

Perspectives

Entering the target cell and breaching the host limiting membrane are the first and arguably the most challenging steps for a virus to accomplish. For many viruses, this barrier is represented by the endosomal membrane. An increasing number of host factors that facilitate viral endosomal escape are being identified, and by doing so, mechanistic commonalities get uncovered. For example, the concept of receptor switching seems to be shared by several enveloped viruses (Jae and Brummelkamp, 2015). Future research will determine if intracellular receptor engagement is a common entry strategy for enveloped, and perhaps also non-enveloped, viruses. Another seemingly collective feature of viral endosomal penetration is the ability to co-opt membrane damage responses of the target cell. Whether they involve recruitment of host phospholipases (entry of the picornavirus) or lysosomal exocytosis (entry of the adenovirus), all play a significant role during viral escape from the endosome. Time will tell whether these escape mechanisms are isolated examples, or whether they are widespread and shared by different virus families.

Surprisingly little is known about the cellular antiviral response at the level of endosomal membrane penetration, particularly for enveloped viruses. It is well established that cells can sense the viral genomic content once it is released into the cytoplasm through the action of several pattern recognition receptors (Thompson et al., 2011; Jensen and Thomsen, 2012), but are cells able to distinguish between physiological membrane fusion events and virus glycoprotein-triggered membrane fusion? Fundamental questions like these remain to be investigated and it will be interesting to see how our mechanistic knowledge of viral escape and detection pathways continues to expand and provide potential new targets for antiviral strategies.

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Competing interests

T.R.B. is co-founder and shareholder of Haplogen GmbH and Scenic Biotech BV.

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Cell science at a glance

A high-resolution version of the poster and individual poster panels are available for downloading at http://jcs.biologists.org/lookup/doi/10.1242/jcs.216259.Supplemental

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