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Focus Review

Coupling viruses to dynein and kinesin-1

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It is now clear that transport on microtubules by dynein and kinesin family motors has an important if not critical role in the replication and spread of many different viruses. Understanding how viruses hijack dynein and kinesin motors using a limited repertoire of proteins offers a great opportunity to determine the molecular basis of motor recruitment. In this review, we discuss the interactions of dynein and kinesin-1 with adenovirus, the α herpes viruses: herpes simplex virus (HSV1) and pseudorabies virus (PrV), human immunodeficiency virus type 1 (HIV-1) and vaccinia virus. We highlight where the molecular links to these opposite polarity motors have been defined and discuss the difficulties associated with identifying viral binding partners where the basis of motor recruitment remains to be established. Ultimately, studying microtubule-based motility of viruses promises to answer fundamental questions as to how the activity and recruitment of the dynein and kinesin-1 motors are coordinated and regulated during bi-directional transport.
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Introduction

The transport of intracellular components is of central importance to all forms of eukaryotic life. Proteins, RNA, vesicles and even organelles must be moved from their site of production to locations appropriate for their function. Many of these cargoes are subsequently transported to alternative cellular locations to deliver signals, or undergo recycling and/or degradation. This constant flux of intracellular cargoes over micron distances is principally mediated by dynein and kinesin motors (Hirokawa *et al*, 2009; Kardon and Vale, 2009; Verhey and Hammond, 2009). These molecular motors are powered by the hydrolysis of ATP and transport their associated cargoes along microtubules in a polarized and coordinated manner (Gennerich and Vale, 2009). Phylogenetic analysis of the human and mouse genomes reveals they each encode some 45 kinesin motors that can be grouped into 14 different families (Hirokawa *et al*, 2009; Verhey and Hammond, 2009). With a few exceptions, kinesin motors transport cargoes in an anterograde manner towards the plus end of the microtubules, which are often located in the cell periphery (Hirokawa *et al*, 2009; Verhey and Hammond, 2009). Cytoplasmic dynein motors, on the other hand, transport cargoes in a retrograde manner towards the minus end of microtubules, which are frequently anchored at the microtubule-organizing centre (MTOC; Hook and Vallee, 2006; Kardon and Vale, 2009). There are many different dynein heavy chains, however, only dynein 1 (cytoplasmic dynein) and dynein 1B/dynein 2, which is involved in intraflagellar transport, are capable of transporting cargoes along microtubules (Pfister *et al*, 2005; Hook and Vallee, 2006; Kardon and Vale, 2009).

Unfortunately for the cell, many different viruses are capable of subverting the same efficient microtubule transport system to facilitate their replication and enhance their spread (Dohner *et al*, 2005; Greber and Way, 2006; Radtke *et al*, 2006; Brandenburg and Zhuang, 2007; Ward, 2011). The extent of use of the microtubule cytoskeleton and its associated motors depends upon the replication strategy of the particular virus. Several viruses use the microtubule transport system to move their nucleic acid/protein cores to intracellular replication sites immediately after they have gained entry to the cell. Others take advantage of the microtubule cytoskeleton to move newly assembled viral progeny to the plasma membrane to facilitate their spread into surrounding cells and tissues. Viruses also use the network to transport nucleic acid and protein components involved in virion assembly to specific cellular locations or to move partially assembled progeny at specific stages of their replication cycles.

Research conducted over the past 10 years has largely focused on determining how the microtubule cytoskeleton plays a role at various stages during viral replication and spread. Studies using drugs that disrupt microtubules have highlighted a requirement for the microtubule network during virus replication. A role for microtubules during viral infection is also often inferred from the speed and linear trajectories of fluorescently labelled virions or their constituent parts during live cell imaging (Seisenberger *et al*, 2001; Willard, 2002; Lakadamyali *et al*, 2003; Greber and Way, 2006; Brandenburg and Zhuang, 2007). In a few cases, simultaneous live cell imaging of virions and microtubules has provided direct evidence that viruses can move on microtubules (Suomalainen *et al*, 1999; Rietdorf *et al*, 2001; McDonald *et al*, 2002). Immunofluorescence analysis of infected cells has confirmed that many different viruses associate with microtubules at various stages of their replication cycles (Greber and Way, 2006; Radtke *et al*, 2006). In a

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number of cases, it has also been possible to detect viral-associated motor protein components (Sodeik *et al*, 1997; Rietdorf *et al*, 2001; Greber and Way, 2006; Bremner *et al*, 2009). Inhibition of particular motor complexes using dominant-negative or RNAi approaches has provided important functional data on the role of particular microtubule motors during viral transport processes (Suomalainen *et al*, 1999; Rietdorf *et al*, 2001; Dohner *et al*, 2002; Bremner *et al*, 2009; Salinas *et al*, 2009). The progress in highlighting a role for microtubule transport during viral infection has now opened up a new challenge—to determine how viruses recruit motors and regulate their activity.

Over the years, studies from a large number of groups have revealed that the two most common motor proteins involved in various aspects of viral transport are cytoplasmic dynein and kinesin-1 (Figure 1). Both motors are highly processive and can mediate long distance movement of cargoes towards opposite ends of microtubules. In this review, we focus on recent progress in determining the molecular basis of dynein and kinesin-1 recruitment to virus particles. We discuss viral systems where the molecular links to these two motors have been defined, highlight where important gaps still exist in our knowledge and examine some of the problems associated with identifying the key molecular link between the virus and the motor.

Composition of cytoplasmic dynein and viral transport

The cytoplasmic dynein motor is a large multimeric ~1.5 MDa complex composed of two heavy chains (DHCs), two intermediate chains (ICs), two light intermediate chains (LICs) and several light chains (LCs) (Pfister *et al*, 2005; Kardon and Vale, 2009; Figure 1). The motor activity resides in the heavy chain, which is composed of a cargo binding N-terminus and C-terminal motor domain composed of six AAA ATPase domains arranged in a hexameric ring from which a microtubule binding stalk projects (Kardon and Vale, 2009; Carter *et al*, 2011; Kon *et al*, 2011). The N-terminus, which mediates dimerization of the heavy chain, also contains the LIC and IC interaction sites. The ICs contain binding sites for the LCs as well as for the regulatory, cargo and microtubule binding dynactin complex (Kardon and Vale, 2009). The dynactin complex, which itself is composed of 11 different subunits, has an important accessory role for virtually all the known cellular functions of dynein (Schroer, 2004; Kardon and Vale, 2009). Each dynein motor complex can contain up to three different LC dimers: Tctex/rp3 (DYNLT1/3), Roadblock/LC7 (DYNLRB1/2) and LC8 (DYNLL1/2) (Pfister *et al*, 2005; Kardon and Vale, 2009). Extensive biochemical analysis has revealed that the many different cargo binding and regulatory proteins, including Bicaudal-D, Lis1, NudE, NudC, NudEL and ZW10 are each capable of interacting with a specific set of subunits in the dynein motor complex (Kardon and Vale, 2009). It is thought that the potential combinatorial diversity and numerous interaction surfaces of the many different motor subunits and accessory proteins are central to the ability of dynein to transport such a diverse range of cargoes.

Many different viruses utilize cytoplasmic dynein to facilitate their directed movement towards the MTOC during the initial establishment of infection (Dohner *et al*, 2005; Greber and Way, 2006; Radtke *et al*, 2006; Ward, 2011). These include adenovirus, the α herpes viruses—herpes simplex virus (HSV1) and pseudorabies virus (PrV) and the retrovirus—human immunodeficiency virus type 1 (HIV-1). When examined collectively, these viruses nicely illustrate the variation in our knowledge of the molecular link between the virus and the dynein motor complex. They also highlight some of the issues that have arisen when attempting to determine these interactions. For adenovirus, an authentic link involving a direct interaction between motor subunits and the incoming

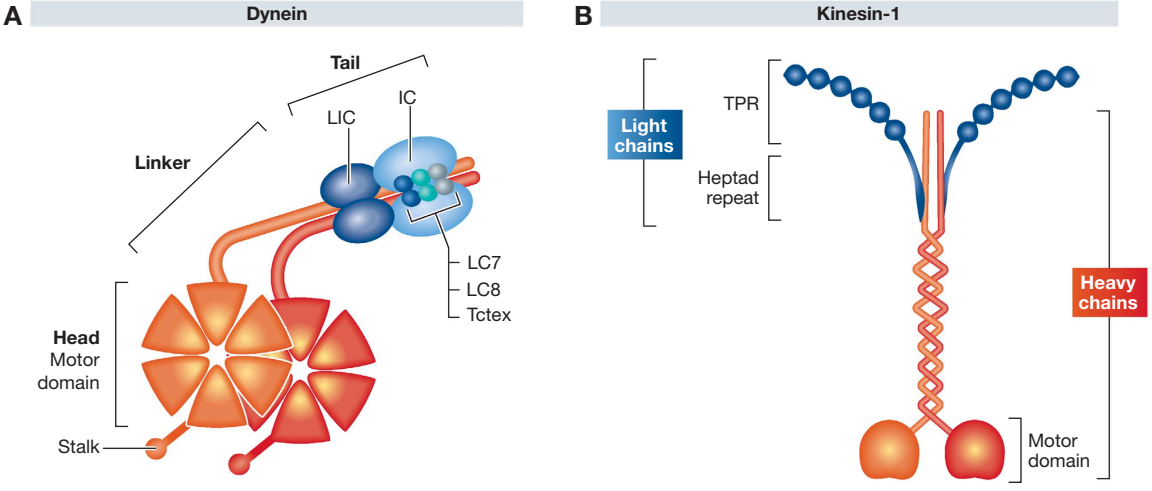


Figure 1 Schematic representation of the subunit composition of dynein and kinesin-1. (**A**) The motor containing cytoplasmic dynein heavy chains are shown in orange and associated intermediate and light chains in shades of blue. The motor domain is composed of six AAA ATPase domains arranged in a hexameric ring from which a microtubule binding stalk projects. The N-terminal tail of the heavy chain mediates its dimerization and contains the binding sites for two intermediate chains (ICs) and two light intermediate chains (LICs). The two intermediate chains (ICs) also interact with three pairs of light chains: Tctex, LC7 and LC8. (**B**) Kinesin-1 is a heterotetramer composed of two motor containing heavy chains (orange) and two light chains (blue). The microtubule binding motor domain is found in the N-terminus of the heavy chain. The light chains associate with the heavy chains via heptad repeat regions in their N-terminus. The C-terminal half of the light chains is composed of six tetratricopeptide repeats (TPR), which represent cargo binding domains.

viral capsid has been defined (Bremner *et al*, 2009). In contrast, for HSV1 exceptional biochemical evidence exists for the direct recruitment of dynein but as yet no specific viral receptor(s) has been identified (Radtke *et al*, 2010). In the case of HIV-1, inhibition of dynein activity abrogates viral transport towards the nucleus during the early stages of infection (McDonald *et al*, 2002). Nevertheless, it remains to be established whether the virus actually recruits dynein during the establishment of infection.

Hexon mediated recruitment of dynein to adenovirus

Currently, the most detailed picture for a dynein-virus link has emerged from studies on the role of microtubule transport during the establishment of adenovirus infection. Fluorescently labelled adenovirus particles undergo rapid microtubule-dependent bidirectional movements after entry into host cells before their replication in the nucleus (Suomalainen *et al*, 1999, 2001; Leopold *et al*, 2000; Salinas *et al*, 2009). The microtubule cytoskeleton is important to establish virus infection as its depolymerization with nocodazole results in a 90% reduction in nuclear targeting of adenovirus (Suomalainen *et al*, 1999; Leopold *et al*, 2000; Mabit *et al*, 2002; Engelke *et al*, 2011). Disruption of dynein activity by overexpression of dynactin subunit p50/dynamitin or the coiled-coil region of p150glued reduces the frequency of virus directed movements towards the MTOC (Suomalainen *et al*, 1999; Leopold *et al*, 2000; Engelke *et al*, 2011). Subsequent work showed that dynein is capable of mediating an interaction between adenovirus and microtubules *in vitro* (Kelkar *et al*, 2004).

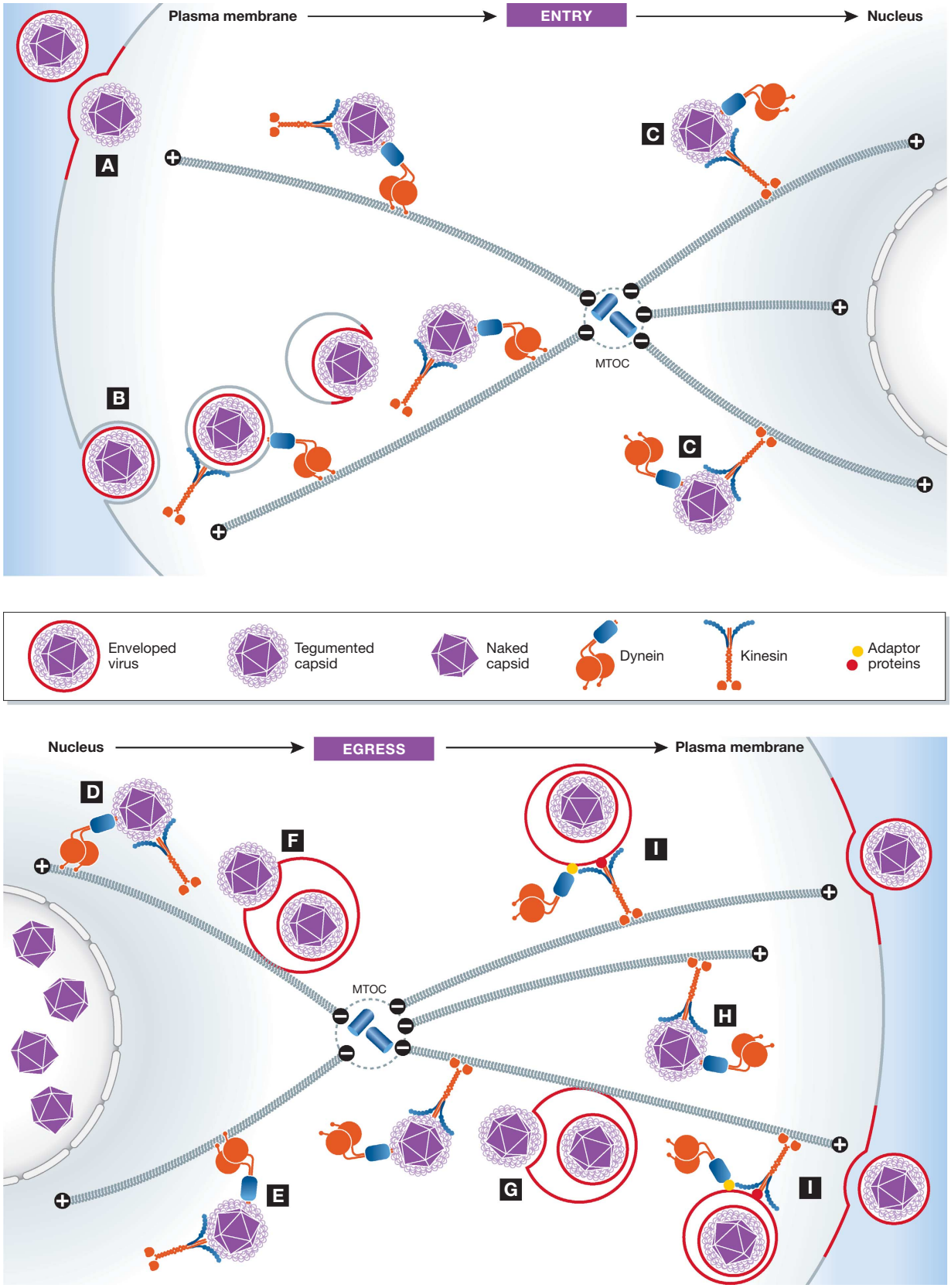
Given the substantial evidence for a role of dynein during the establishment of adenovirus infection, it is surprising that the motor has only recently been detected on incoming virus particles (Bremner *et al*, 2009). The same study also finally provided the identity of the viral and motor components responsible for dynein recruitment. Bremner *et al* found that the hexon capsid subunit of adenovirus interacts directly with both the dynein IC and LIC1 subunits. Interestingly, these interactions are dependent upon hexon being exposed to low pH. This suggests that only viruses that have passed through an endocytic compartment during entry are capable of recruiting dynein (Bremner *et al*, 2009). Various perturbations of the dynein–hexon interaction, including microinjection of dynein IC or hexon antibodies, knockdown of dynein or overexpression of hexon disrupt accumulation of the virus at the centrosome/nucleus (Bremner *et al*, 2009). Live cell imaging demonstrated that this reduced accumulation is due to a decrease in run length rather than the velocity of the virus. Dynactin, which is also recruited to the incoming virus is not required for recruitment of dynein but does have an essential role in promoting nuclear accumulation of the virus. Consistent with this, dynactin was not found in association with dynein IC or LICs in hexon pull-down experiments. The dynein accessory proteins, NudE, NudEL, LIS and ZW10 were found to be associated with incoming virions to varying extents. However, neither dominant-negative inhibition of NudE, NudEL and LIS nor siRNA depletion of ZW10 affected dynein recruitment or virus transport (Bremner *et al*, 2009). Collectively, these data offer a relatively simple model for motor recruitment in which the hexon trimer in the viral capsid couples directly to dynein via its IC and LIC subunits. This suggestion is consistent with a recent computational model of bi-directional transport of adenovirus, which was based on live cell imaging (Gazzola *et al*, 2009). It may be that the region of hexon that binds IC and/or LIC is a structural mimic of a cellular adaptor that normally links cargoes to dynein. Indeed, it has recently been shown that LIC mediate the direct recruitment of the dynein motor to lysosomes and late endosomes (Tan *et al*, 2011).

Herpes virus tegument proteins interact with dynein

During the initial establishment of infection, non-enveloped cytosolic HSV1 and PrV capsids undergo bidirectional microtubule-dependent movements that ultimately result in a net retrograde motility towards the nucleus, where the virus can establish a latent infection (Sodeik *et al*, 1997; Dohner *et al*, 2002; Smith *et al*, 2004; Diefenbach *et al*, 2008; Lyman and Enquist, 2009; Antinone and Smith, 2010; Figure 2). The activity of the dynein–dynactin motor complex, which is recruited by these incoming capsids, is required to establish infection (Sodeik *et al*, 1997; Dohner *et al*, 2002; Mabit *et al*, 2002). HSV1 capsids purified from extracellular virions can also bind and traffic along microtubules in a dynactin-dependent manner *in vitro*, but only in the presence of cytosol and energy (Wolfstein *et al*, 2006). Consistent with this, dynein and dynactin can bind these purified viral capsids but not those derived from the nucleus (Wolfstein *et al*, 2006; Radtke *et al*, 2010).

Identification of the link between dynein and adenovirus was greatly facilitated by the relatively few candidate proteins that remain associated with virions during their transit to the nucleus. This is not the case for α herpes viruses (Diefenbach *et al*, 2008; Radtke *et al*, 2010). For example, HSV1 consists of 8 capsid and 26 potential tegument proteins that are associated with the capsid (Radtke *et al*, 2010). Identification of potential HSV1 and PrV dynein binding proteins has relied on a combination of live imaging of fluorescently labelled viruses as well as biochemical approaches using purified virions. Imaging recombinant viruses encoding various combinations of RFP- and GFP-tagged viral proteins reveals that while VP1/2 (UL36) and UL37 can be detected, the majority of tegument proteins are lost from capsids undergoing retrograde transport to the nucleus (Luxton *et al*, 2005; Antinone and Smith, 2010), consistent with previous extensive ultrastructural studies, for example, see (Granzow *et al*, 2005; Maurer *et al*, 2008). Deletion analysis has confirmed that the majority of tegument proteins are not required for nuclear directed capsid transport (Antinone *et al*, 2006). As observed with adenovirus, recruitment of dynein to purified capsids is not dependent on dynactin (Radtke *et al*, 2010). Interestingly, purified capsids can also bind directly to dynactin, although this interaction does not appear to enhance dynein motor recruitment (Radtke *et al*, 2010). Biochemical analysis, however, reveals that the interaction between viral capsids and dynein is enhanced when they are treated with a high salt buffer, which removes the outer tegument proteins. Based on the differential extraction properties of the tegument proteins, it now appears that an inner tegument component contains the principle receptor(s) for dynein interaction (Wolfstein *et al*, 2006; Radtke *et al*, 2010). This elegant biochemical

analysis, which is consistent with results obtained from live imaging, has considerably narrowed the list of potential dynein interacting proteins (Radtke *et al*, 2010). Based on the available data, VP1/2 (UL36) and UL37 are currently the strongest candidates to recruit dynein, although there is still no evidence that either interacts with any motor subunit



(Radtke *et al*, 2010). Consistent with this suggestion, loss of UL37 significantly delays translocation of PrV to the nucleus (Krautwald *et al*, 2009).

Yeast two hybrid experiments combined with *in vitro* binding assays have revealed that the HSV1 proteins pUL9, pUL34 and VP26 (pUL35) can interact with different subunits of the dynein motor complex (Ye *et al*, 2000; Martinez-Moreno *et al*, 2003; Douglas *et al*, 2004). The viral helicase pUL9 and pUL34 interact with dynein LCs and ICs, respectively (Ye *et al*, 2000; Martinez-Moreno *et al*, 2003). However, the functional significance of these interactions in the retrograde transport of HSV1 is unclear as neither protein is a capsid or tegument component (Diefenbach *et al*, 2008). The small capsid protein VP26 (pUL35) can bind directly to the dynein LCs Tctex (DYNLT1) and RP3 (DYNLT3) (Douglas *et al*, 2004). Microinjected capsids lacking VP26 assembled using a baculovirus expression system do not accumulate at the nuclear envelope (Douglas *et al*, 2004). However, subsequent studies in which cells were infected with a recombinant virus lacking the pUL35 gene revealed that capsids were still capable of undergoing dynein-dependent retrograde transport in the absence of VP26 (Desai *et al*, 1998; Antinone *et al*, 2006; Dohner *et al*, 2006). Viral capsids lacking VP26 were also still capable of binding to dynein (Wolfstein *et al*, 2006; Radtke *et al*, 2010). In addition, HSV1 capsids isolated from the nucleus cannot bind dynein even though they contain VP26 (Wolfstein *et al*, 2006; Radtke *et al*, 2010). Thus, while VP26 may contribute to and/or stabilize dynein recruitment via a LC interaction, the current data all points to the inner tegument components as forming the primary interface (Radtke *et al*, 2010). It may be difficult to pin dynein recruitment down to a single viral protein, as it is likely that inner tegument proteins adopt higher order assemblies that will result in new interaction surfaces. Such assemblies may also lead to cooperativity/avidity effects that promote the recruitment of the dynein–dynactin complex.

Retrograde transport of HIV-1

Higher order protein assemblies or complexes, which can be difficult to recapitulate from purified proteins *in vitro*, may also explain the difficulty experienced in identifying the HIV-1 components mediating dynein recruitment. Incoming HIV-1 cores/reverse transcription complexes associate with the microtubule network after fusion of the viral envelope with the plasma membrane. They then move in a microtubule- and dynein-dependent manner towards the MTOC (McDonald *et al*, 2002). The HIV-1 core is composed of a relatively limited number of components—the viral RNA, nucleocapsid and capsid proteins, as well as the reverse transcriptase and integrase enzymes. Why then should identifying the link to dynein prove so elusive? The difficulty may arise from the metastable nature of the HIV-1 core, which undergoes structural and compositional changes after cell entry including the reverse transcription of viral RNA into DNA. The precise nature of these changes and in particular the timing and scale of loss of the capsid protein from the core remains controversial (Arhel, 2010). The case of HIV-1 highlights how virus transport processes may not be completely independent of capsid maturation processes and those required for nuclear import of the viral genomes.

If HIV-1 recruitment of dynein were to mirror that of adenovirus and HSV1, namely a direct interaction between a viral component and the motor complex, then the p24 capsid protein would be the most likely candidate. The capsid protein assembles into hexameric rings that oligomerize to form the distinctive conical shell, which is delivered into the cytoplasm after membrane fusion. It would appear to be in an ideal position on the surface of the virion to interact with cytoplasmic dynein. Some reports, however, suggest that the core is highly unstable and that the capsid is rapidly disassembled (Fassati and Goff, 2001). Nevertheless, capsid was shown to be associated with microtubule bound cores (McDonald *et al*, 2002). More recently, apparently intact HIV-1 cores were detected close to the nuclear membrane (Arhel *et al*, 2007). Despite capsid protein being a prime candidate, no interaction with any dynein component has been reported. This may be a common theme for capsid interacting proteins, given the observation that a direct interaction between capsid and the restriction factor, Trim5α could only be demonstrated on higher ordered capsid assemblies (Stremlau *et al*, 2006; Ganser-Pornillos *et al*, 2011). It is tempting to speculate that a similar higher order assembly is required to bind dynein or other cellular proteins that subsequently recruit the motor complex. Interestingly, the adenovirus hexon preparations that interact with dynein IC and LICs are also in their native trimeric form (Bremner *et al*, 2009).

An alternative mechanism to the 'direct recruitment' would be that the incoming virion 'piggy backs' on an existing retrograde trafficking pathway involving dynein. One possible cellular trafficking pathway may involve importins, which can bind dynein and target components to the nuclear pore complex to facilitate their nuclear import (Hanz *et al*, 2003; Yudin *et al*, 2008; Wagstaff and Jans, 2009). HIV-1 integrase interacts with the importins 7 and α3 (Fassati *et al*, 2003; Hearps and Jans, 2006; Ao *et al*, 2007, 2010; Zaitseva *et al*, 2009). Intriguingly, when expressed in yeast, HIV-1

Figure 2 Transport of herpes virus during entry and egress. ENTRY: Depending on the cell type, viruses enter by (**A**) directly fusing with the plasma membrane or (**B**) via an endocytic-based mechanism. Regardless of the mode of entry, viruses within endosomes or more usually as non-enveloped capsids probably recruit both kinesin and dynein even though they move in net retrograde (minus end) direction along microtubules towards the nucleus. Depending on the position MTOC and organization of the microtubule cytoskeleton relative to the nucleus, it is also possible that kinesin-1-dependent plus-end directed movement along microtubules (**C**) may be required for the virus to reach the nuclear envelope. EGRESS: Following their exit from the nucleus, the tegument of non-enveloped capsids recruits kinesin-1 and dynein to facilitate their bidirectional transport on microtubules (**D**, **E**). Viruses will move along microtubules until they encounter membrane compartments into which they can bud to form enveloped virions (**F**, **G**). The location of these membrane compartments will vary depending on the position of the MTOC and organization of the microtubule cytoskeleton, which will be cell type dependent. Consequently, viral movements towards these membrane compartment may require a net minus-end (dynein) or plus-end (kinesin-1) driven transport depending on the site of envelopment (**F**, **G**) with respect to the MTOC. Some viruses, however, may never encounter the right membrane compartment and will continue to move as non-enveloped capsids throughout the cell (**E**, **H**). After envelopment, viruses within vesicular compartments (**I**) will be transported in a net anterograde manner, possibly by kinesin-1, towards the plasma membrane, where they fuse and are released.

integrase traffics to the MTOC in a microtubule- and dynein-dependent manner before nuclear import (Desfarges *et al*, 2009). An alternative 'piggy back' mechanism may be provided by the pathway used by the cell for dealing with aggregated proteins (Dohner *et al*, 2005; Wileman, 2007). In this pathway, aggregates are transported in a dynein-dependent manner towards the MTOC where they undergo proteosomal or autophagosomal degradation (Garcia-Mata *et al*, 2002; Johnston *et al*, 2002; Wileman, 2007). It is conceivable that incoming virus particles could be transported via such a mechanism. This, however, would necessitate two important additional steps. The first would be the identification and marking of the virus for transport and degradation either by post-translational modifications such as ubiquitination or by association of additional proteins that are already destined for degradation. There is no evidence that incoming HIV-1 components are themselves highly ubiquitinated. Curiously, the best candidates to mediate an aggresome-like transport mechanism for HIV-1 may be the very factors that target incoming virions for degradation. Trim5α, which associates with incoming virions, like other family members, is an E3 ubiquitin ligase that can undergo autoubiquitination (Meroni and Diez-Roux, 2005; Campbell *et al*, 2008; Langelier *et al*, 2008; Pertel *et al*, 2011). In addition, Trim5α is transported on microtubules and, when overexpressed, forms aggregates that are degraded by autophagy (Diaz-Griffero *et al*, 2006; Campbell *et al*, 2007). However, it seems unlikely that Trim5α is responsible for mediating retrograde transport of HIV, given that its ability to bind to capsid correlates with its antiviral activity (Sebastian and Luban, 2005; Stremlau *et al*, 2006). Nonetheless, the Trim protein family is very large and the function of most members remains unknown. It is also intriguing that several family members appear to promote or enhance retroviral replication (Uchil *et al*, 2008). If such a mechanism exists, then the second essential step after transport to the MTOC would be a Houdini-like escape of the viral nucleic acid from the cellular degradation machinery before the viral genome is destroyed. It is conceivable that viral uncoating would also remove any degradative complex to allow nuclear import of the genome and associated proteins. Such a mechanism would mean there will be a fine balance between degradation and progression of virus replication. Interestingly, inhibition of the proteosome enhances retroviral replication in permissive and can rescue reverse transcription in restrictive cells (Wei *et al*, 2005; Wu *et al*, 2006).

Viral coupling to dynein LCs and transport

The example of HSV and HIV-1 underlines the difficulties in establishing which viral protein(s) bind which dynein subunits to recruit the motor for the purposes of transport. Of all the dynein motor subunits, the LC8 family members DYNLL1/2 stand out above all others in binding viral proteins from a number of different viruses including African swine fever, rabies, ebola, human foamy viruses (Jacob *et al*, 2000; Raux *et al*, 2000; Alonso *et al*, 2001; Poisson *et al*, 2001; Rodriguez-Crespo *et al*, 2001; Petit *et al*, 2003; Kubota *et al*, 2009). Despite evidence for dynein-mediated retrograde transport for several of these viruses, in no case has biochemical evidence of a virus-LC8 link to the motor itself been demonstrated. LC8 also independently associates with Myosin V, the transcription factor Trps1, as well as the yeast nucleoporin Nup159 where five LC8 molecules cooperate to promote dimerization of the protein (Espindola *et al*, 2000; Kaiser *et al*, 2003; Stelter *et al*, 2007). It has been proposed that LC8 primarily acts as a hub to promote dimerization of its interacting partners, and that its role as a dynein cargo adaptor is perhaps secondary (Barbar, 2008). Dimerization of LC8 generates two interfaces that bind two TKQTQTT motifs in the dimeric dynein ICs (Benison *et al*, 2006, 2007). To act as a cargo adaptor, one of these LC8 interfaces would have to interact with the IC and the other with a viral cargo. The stability of the LC8 dimer and nature of its interactions with DIC would make such a scenario very unlikely (Barbar, 2008; Radnai *et al*, 2010). Therefore, to demonstrate it forms a functional dynein-virus link, it is imperative to show that LC8 associated with viruses can also interact with other dynein subunits. Indeed, studies with rabies suggest that the LC8 interaction is probably not involved in viral transport. A virus lacking its LC8 binding motif was still capable of transport from the peripheral to the central nervous system but did have a significant reduction in the transcriptional activity of its viral polymerase (Tan *et al*, 2007). The LC8 binding sequences in the rabies phosphoprotein P also have a role in its nuclear import (Moseley *et al*, 2007). Thus, while LC8 appears to participate in the rabies replication cycle it seems unlikely that it is functionally connected to dynein-mediated viral transport.

As with LC8, there is again controversy over the potential cargo binding function of the Tctex family LCs. Structural studies have suggested that Tctex is unlikely to interact simultaneously with both IC and cargo proteins (Williams *et al*, 2007). Another study has, however, suggested that cargo and IC binding sites on Tctex might be independent (Wu *et al*, 2005). Data from Human Papilloma Virus would support the latter of these two hypotheses (Florin *et al*, 2006; Schneider *et al*, 2011). Association of the virus with microtubules requires the C-terminal 40 amino acids of L2, a minor capsid protein (Florin *et al*, 2006). The same sequences were also required to associate with the dynein IC (Florin *et al*, 2006). More recent studies demonstrate that L2 interacts directly with the Tctex LCs (DYNLT1/3), which both associate with virions (Schneider *et al*, 2011). This implies that Tctex might bridge IC and L2. RNAi-mediated depletion of either LC results in a loss in infectivity and an accumulation of L2 in the cytoplasm. A structural understanding of the L2–Tctex interaction should help resolve the outstanding issues over the cargo binding function of Tctex.

Composition of kinesin-1, the first plus-end motor

Multiple members of the kinesin superfamily will undoubtedly contribute to various transport steps during viral infection but here we will only focus on kinesin-1, which is also known as conventional kinesin or Kif5 (Figure 1). Kinesin-1, which was the first plus-end directed microtubule motor to be identified, is involved in a wide range of cellular processes by virtue of its ability to interact with many different types of cargo (Hirokawa *et al*, 2009; Verhey and Hammond, 2009). Kinesin-1 is a heterotetramer composed of two heavy and two light chains (Figure 1). The microtubule binding motor domain is found in the N-terminus of the heavy chain, which can be encoded by three different genes (Kif5A,

Kif5B and Kif5C). Kif5A and Kif5C are only expressed in neuronal cells, whereas Kif5B is ubiquitous (Hirokawa *et al*, 2009; Verhey and Hammond, 2009). Each heavy chain dimer associates with two copies of KLC1 or KLC2, which are expressed in most cell types. A single kinesin-1 tetramer always contains two identical heavy and light chains (Gyoeva *et al*, 2004). The LCs associate with the heavy chains via heptad repeat regions near their N-terminus. Cargoes can bind directly to specific sites on the kinesin-1 heavy chain. However, they are also capable of interacting with the motor via the tetratricopeptide repeats (TPRs) in the C-terminal half of the kinesin LC (Gindhart, 2006; Hammond *et al*, 2008). The expression of multiple KLC1 splice variants, each with a different C-terminus is also thought to contribute to cargo binding specificity (Gyoeva *et al*, 2000; McCart *et al*, 2003; Wozniak and Allan, 2006). Like dynein, our understanding of kinesin-1 recruitment to viral cargoes varies significantly depending upon the virus studied (Dohner *et al*, 2005; Greber and Way, 2006; Radtke *et al*, 2006; Ward, 2011). Here, we will only discuss the interaction of kinesin-1 with vaccinia and herpes viruses, which currently represent the most extensively studied systems.

Recruitment of kinesin-1 to vaccinia virus

Kinesin-1 appears to have several important roles during the replication cycle of vaccinia virus (Schepis *et al*, 2007). Nevertheless, so far the only stage where progress has been made in identifying a viral kinesin-1 binding partner is in the egress of the intracellular enveloped virus (IEV) from their perinuclear site of formation to the plasma membrane (Roberts and Smith, 2008; Ward, 2011). IEV are formed when infectious intracellular mature virions become 'wrapped' by a double membrane cisternae derived from trans-Golgi or endosomal membranes (Smith *et al*, 2002; Roberts and Smith, 2008). The mechanistic basis for this wrapping step is poorly understood but involves several integral viral membrane proteins as well as the viral proteins, E2 and F12 (Smith *et al*, 2002; Domi *et al*, 2008; Dodding *et al*, 2009). The resulting 'wrapped' IEV is able to recruit kinesin-1 and undergo anterograde microtubule-dependent transport to the cell periphery, where its outer membrane fuses with the plasma membrane to release an infectious virion into the extracellular environment (Geada *et al*, 2001; Hollinshead *et al*, 2001; Rietdorf *et al*, 2001; Ward and Moss, 2001a, b; Dodding *et al*, 2009; Morgan *et al*, 2010; Figure 3). The recruitment of kinesin-1 to IEV is dependent on A36, an integral viral membrane protein (Rietdorf *et al*, 2001; Ward and Moss, 2004). In the absence of A36, IEV remains largely restricted to their perinuclear site of assembly, as they are unable to spread to the cell periphery (Rietdorf *et al*, 2001; Ward and Moss, 2001a; Ward *et al*, 2003; Dodding and Way, 2009). Loss of A36 consequently results in a small plaque phenotype, due to the dramatic impact on the cell-to-cell spread of the virus (Ward and Moss, 2001a; Smith *et al*, 2002; Doceul *et al*, 2010). Residues 81–111 of A36 are actually capable of interacting directly with the cargo binding TPRs of KLC (Ward and Moss, 2004). The interaction between A36 and KLC has recently been confirmed in infected cells using fluorescence resonance energy transfer approaches (Jeshtadi *et al*, 2010). Curiously, residues 81–111 of A36 contain a short WD motif that is similar to the KLC binding site in

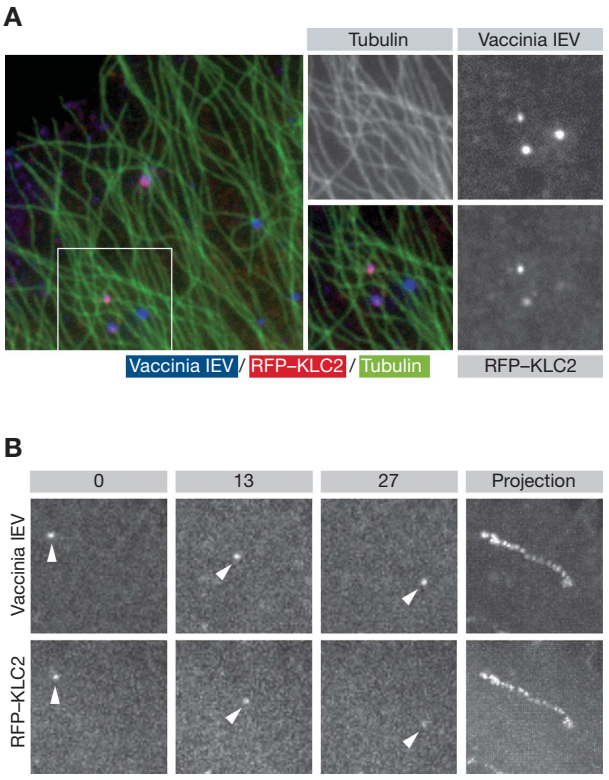


Figure 3 Vaccinia IEV recruit kinesin-1 and move on microtubules. (**A**) Immunofluorescence images showing recruitment of kinesin-1 (RFP–KLC, red) to vaccinia IEV (blue) associated with microtubules (green). (**B**) Stills taken from live cell imaging of the movement of YFP-tagged vaccinia IEV in cells expressing RFP-tagged kinesin light chain 2. The time in seconds is indicated and the right panel shows a maximum intensity projection to highlight the path taken by the virus.

Calsyntenin-1 (Konecna *et al*, 2006; Araki *et al*, 2007; Dodding and Way, 2009; Morgan *et al*, 2010). A related WE sequence that is similar to the functional KLC binding motif in Caytaxin and γ-BAR (also known as Gadkin) (Aoyama *et al*, 2009; Schmidt *et al*, 2009) is also present at residues 64–65 of A36 (Morgan *et al*, 2010; Dodding *et al*, in preparation). Recent data using overexpression approaches, however, suggest that the WD and WE motifs in A36 are not required for vaccinia to reach the plasma membrane and induce actin tails (Morgan *et al*, 2010). In contrast, we have found using recombinant viruses that these two motifs are required for kinesin-1 recruitment and viral transport to the plasma membrane (Dodding *et al*, in preparation).

In addition to A36, it has also been proposed that F12 has a direct role in the microtubule-dependent transport of IEV to the plasma membrane (van Eijl *et al*, 2002; Morgan *et al*, 2010). Consistent with this, F12 is associated with IEV moving on microtubules (van Eijl *et al*, 2002; Dodding *et al*, 2009). Moreover, loss of F12 leads to a perinuclear accumulation of IEV and a dramatic reduction in actin tail formation (Zhang *et al*, 2000; van Eijl *et al*, 2002; Dodding *et al*, 2009; Morgan *et al*, 2010). Live cell imaging, however, shows that some IEV are still capable of moving in a linear manner, presumably along microtubules, at ~1 μm/s even in the absence of F12 (Dodding *et al*, 2009). This would suggest that while F12 may be involved in IEV transport, it is not essential. Based on its primary sequence and structural

predictions, which suggest the protein contains 14 TPR-like motifs, it has been suggested that F12 may represent a viral KLC-like mimic to recruit kinesin-1 to IEV (Morgan *et al*, 2010). TPRs, which form protein interaction surfaces in a wide range of proteins, are composed of two small antiparallel α helices joined by a short linker (D'Andrea and Regan, 2003). If F12 is a viral KLC mimic, then it must bind the kinesin-1 heavy chain in a manner that is fundamentally different to KLC as it lacks heptad repeats (Figure 1). Moreover, there is still no published data indicating that F12 can bind directly to the kinesin-1 heavy chain. However, F12 can interact directly with A36 and E2, the latter of which is also predicted to contain 15 TPR-like repeats (Johnston and Ward, 2008; Dodding *et al*, 2009; Morgan *et al*, 2010). The binding site of F12 on A36 overlaps with that of KLC, raising the intriguing possibility that F12, together with E2, functions to inhibit kinesin-1 recruitment until IEV formation is complete (Ward and Moss, 2004; Johnston and Ward, 2008). Such a mechanism would prevent premature transport of incompletely wrapped IEV. However, this does not explain why F12 and E2 remain associated with IEV moving on microtubules, if their primary function is to inhibit A36-mediated KLC recruitment. While the role of F12–E2 complex during IEV formation and transport remains to be determined, current data clearly demonstrate that A36 provides a direct link between the vaccinia and kinesin-1.

Herpes virus tegument also interacts with kinesin-1

HSV1 and PrV undergo anterograde transport during bidirectional movements towards the nucleus as well as later during infection when new viral progeny egress along the axon towards the plasma membrane (Smith *et al*, 2001, 2004; Diefenbach *et al*, 2008; Lyman and Enquist, 2009; Antinone and Smith, 2010; Antinone *et al*, 2010; Ward, 2011; Figure 2). It is likely that one or more kinesin family members drive these plus-end directed motilities. Understanding the mechanism of kinesin recruitment during egress, however, is complicated by the fact that both enveloped and non-enveloped forms of the virus are transported on microtubules (Antinone and Smith, 2006; Antinone *et al*, 2010; Wisner *et al*, 2011). Currently, as for dynein, most progress has been made in understanding kinesin recruitment for the non-enveloped cytoplasmic form of the virus. Kinesin-1 and kinesin-2 can bind directly to purified HSV1 capsids (Radtke *et al*, 2010). Whether their recruitment is mediated by the motor heavy chains, KLC or KAP in the case of kinesin-2 remains to be established. It also remains to be established whether these two motors are actually recruited to viral capsids moving in infected cells. Once again, the inner tegument proteins are implicated in motor binding, as capsids purified from the nucleus, which lack tegument proteins cannot bind either kinesin. As observed for dynein, treatment of purified capsids with 0.5 M salt enhanced kinesin-1 or 2 binding. In contrast to dynein, however, kinesin-1 binding was lost in very high salt conditions (1 M), suggesting that the motors bind distinct features on the HSV1 virion. The only HSV1 tegument protein so far implicated in interaction with kinesin-1 is US11, which interacts with the heptad repeat binding region of the motor heavy chain (Diefenbach *et al*, 2002). HSV1 virions that lack US11 were, however, still capable of binding kinesin-1 (Radtke *et al*, 2010). It is possible that even if US11, which also associates with the KLC-related protein PAT1 (Benboudjema *et al*, 2003) does not directly couple the virus and motor, it may still have a role in virus transport by regulating motor activity. More recently, live cell imaging has suggested that the inner tegument protein VP1/2 (pUL36) may be a good candidate to bind kinesin-1, as new viral progeny lacking the UL36 gene were unable to undergo microtubule directed transport during their egress from the nucleus to the plasma membrane (Luxton *et al*, 2006). Curiously, HSV1 UL36 contains a number of WD/E motifs similar to those found in A36 of vaccinia and other cellular KLC binding proteins (Dodding and Way, 2009; Morgan *et al*, 2010; Dodding *et al*, in preparation). A number of these are also conserved in UL36 from PrV. Interestingly, UL37 from PrV but not HSV1 also contains several WD/E motifs that may represent potential kinesin-1 recruitment sites (M Schären and H Favoreel, personal communication). If these WD/E motifs are involved in kinesin-1 recruitment then their selective disruption would provide important insights into the precise role of kinesin-1 in both entry and egress of HSV1 and PrV.

HSV1 capsids purified from extracellular virions can clearly bind kinesin-1 (Radtke *et al*, 2010). Nevertheless, it has long been a matter of controversy whether it is these non-enveloped particles or the enveloped form of the virus that undergoes axonal transport (Diefenbach *et al*, 2008; Curanovic and Enquist, 2009; Miranda-Saksena *et al*, 2009; Wisner *et al*, 2011). Until recently, all studies addressing this important question were based on fixed images of HSV1-infected cells, for example, see Saksena *et al* (2006) and Snyder *et al* (2006). However, live cell imaging has now revealed that the majority (~70%) of HSV1 undergoing anterograde axonal transport in rat or chicken dorsal root ganglia sensory neurons are enveloped (Antinone *et al*, 2010). These findings are consistent with previous observations using PrV (Antinone and Smith, 2006; Feierbach *et al*, 2007). Moreover, the enveloped HSV1 virions were found to be in close association with markers of the neuronal secretory pathway and to traffic with APP-positive vesicles during egress (Antinone *et al*, 2010; Cheng *et al*, 2011). Detailed ultrastructural analysis of HSV1- and PrV-infected primary rat neurons also came to a similar conclusion, finding that the majority of virions were enveloped and found within vesicles (Maresch *et al*, 2010; Negatsch *et al*, 2010; Huang *et al*, 2011). *In vitro* motility assays have also established that HSV within TGN46-positive organelles are capable of undergoing energy-dependent kinesin-based transport along microtubules (Lee *et al*, 2006).

After years of debate, it now appears a clearer picture of α herpes virus egress is emerging (Figure 2). Following their exit from the nucleus, non-enveloped capsids recruit kinesin-1 and dynein to undergo transport to their site of envelopment, which may vary depending on the cell type. The ability to recruit both motors and move bidirectionally will help ensure that non-enveloped capsids can reach this site, regardless of its location with respect to the MTOC or microtubule polarity (Figure 2). It seems likely that the non-enveloped capsids engaging in anterograde axonal transport represent virions that are yet to come into contact with the right membrane compartment to undergo envelopment. Ultrastructural analysis suggests that envelopment involves

budding into the lumen of a vesicular compartment, which is then transported to the plasma membrane. This immediately raises the question, whether it is a viral or cellular protein that is responsible for recruiting dynein and kinesin-1 to these enveloped capsids. Finally, studies using dominant-negative approaches also point to a role for Myosin Va in promoting release of enveloped virions at the plasma membrane (Roberts and Baines, 2010).

Regulation of kinesin-1 activity and bidirectional transport

During the establishment of their infectious cycles, adenovirus, HSV1 and PrV undergo both retrograde and anterograde directed transport with frequent changes in direction (Suomalainen *et al*, 1999; Leopold *et al*, 2000; Smith *et al*, 2004; Salinas *et al*, 2009; Antinone and Smith, 2010; Engelke *et al*, 2011). Similar bidirectional transport is also observed for HSV1 and PrV during their egress (Smith *et al*, 2001, 2004). This bidirectional transport may help viruses to avoid obstacles on microtubules such as other cargoes and/or ensure they end up at the right cellular location, as suggested for cellular cargoes (Welte, 2004). The existence of bidirectional transport, however, immediately raises the question as to how the net direction of viral transport towards the MTOC or the cell periphery is controlled during entry and egress? Three possible scenarios have been put forward to explain how changes in directionality of cellular cargoes might arise (Welte, 2004; Akhmanova and Hammer, 2010; Verhey *et al*, 2011). In the first, the cargo would selectively and sequentially bind and/or release either retrograde or anterograde motors. In the second, the cargo simultaneously engages retrograde and anterograde motors that compete in a tug-of-war, with the net direction of travel being defined by the winner. In the third scenario, both motors would be engaged simultaneously but their activity would be coordinated such that competition does not occur.

Several studies have provided evidence that the motility of vesicles both *in vitro* and *in vivo* is consistent with a tug-of-war between dynein and kinesin motors, where the competing activities and number of motors define the direction of travel (Muller *et al*, 2008; Shubeita *et al*, 2008; Soppina *et al*, 2009; Akhmanova and Hammer, 2010; Hendricks *et al*, 2010; Verhey *et al*, 2011). Other observations have demonstrated that motors of opposite polarity regulate the activity of each other as they are mechanically and/or biochemically coupled (Ally *et al*, 2009; Gennerich and Vale, 2009; Akhmanova and Hammer, 2010; Encalada *et al*, 2011). Understanding the nature of this coupling and how the communication between the different motors is regulated is not an easy task. This is in part because most cellular cargoes are relatively heterogeneous and ill defined with respect to their composition as well as the number and activity of their associated motors. Working with viruses may help to overcome some of these difficulties. Viruses have relatively well-defined compositions, many can be genetically manipulated to remove potential motor binding sites and/or introduce fluorescent tags. Virus transport is amenable to quantitative live cell imaging (see references cited throughout review). Viruses can also often be purified to homogeneity to use in motor binding studies and *in vitro* motility assays (Wolfstein *et al*, 2006; Bremner *et al*, 2009; Radtke *et al*, 2010). As discussed for HSV and PrV, it is, however, essential that the right viral components and cellular markers be used to ensure the unambiguous identification of the viral entity being imaged or purified. In contrast to the majority of cellular cargoes, it has also been possible to detect motors associated with viruses and in the case of vaccinia, to even detect kinesin-1 on moving virus in live cells (Greber and Way, 2006; Figure 3). The ability to image motors associated with viruses raises the possibility to use quantitative imaging approaches to correlate the number of motors with speed and direction of viral transport as well as their rate of exchange with the cytoplasmic pool, as has recently been done for the vaccinia actin tail nucleating complex (Weisswange *et al*, 2009).

Another important issue that needs to be resolved if we are to understand motor coordination during bidirectional transport is not only the number but also their activity status and arrangement on the cargo during anterograde and retrograde transport (Erickson *et al*, 2011). The highly localized viral recruitment of motors provides an ideal model system to both develop and employ biosensors that report the activity status of motors to address this fundamental transport question (Figure 3). It also remains to be established whether viruses recruit motors in an inactive or activated state. This issue is important as motors such as kinesin-1 are thought to exist in an inactive closed conformation when they are not associated with cargo (Verhey and Hammond, 2009; Akhmanova and Hammer, 2010; Verhey *et al*, 2011). Binding of cargo is thought to overcome this autoinhibition, although there is some evidence to suggest that the ability to recruit and activate kinesin-1 may not always reside in a single protein (Blasius *et al*, 2007; Verhey and Hammond, 2009; Akhmanova and Hammer, 2010). It is possible that some viruses are capable of recruiting inactive motors, which are then activated by virally encoded regulatory proteins that are not directly involved in coupling the virus to the motor. Possible viral activators of kinesin-1 might include US11 and F12 from HSV1 and vaccinia, respectively (Diefenbach *et al*, 2002; Morgan *et al*, 2010).

Viral infection frequently results in the dramatic modulation of signalling networks from the moment the virus touches the cell, until new progeny leave. It is highly likely that changes in the activity of signalling networks will impact on virus transport as phosphorylation of kinesin-1 light chain negatively regulates association of the motor with cellular cargoes (Morfini *et al*, 2002; Du *et al*, 2010; Amato *et al*, 2011; Vagnoni *et al*, 2011). Activation of JNK signalling pathways also promotes the dissociation of kinesin-1 from the light chain binding protein JIP1 (Horiuchi *et al*, 2007; Verhey and Hammond, 2009; Akhmanova and Hammer, 2010). Phosphorylation of the kinesin-1 heavy chain is also known to inhibit its association with microtubules (Morfini *et al*, 2009). Phosphorylation of the motor at particular stages during viral replication may represent an efficient way to inhibit kinesin-1 recruitment, modulate its activity and/or promote its release. Consistent with this, adenovirus-mediated activation of c-AMP-dependent protein kinase A and p38/MAPK stimulates nuclear targeting of the virus by enhancing the frequency of retrograde transport possibly by reducing the activity of a plus-end directed motor such as kinesin-1 (Suomalainen *et al*, 2001). In addition, Src-mediated phosphorylation of A36 has been shown to promote release of kinesin-1 from vaccinia at the plasma membrane (Newsome *et al*, 2004).

Concluding remarks

The examples we have discussed illustrate the progress in our understanding of how viruses recruit dynein and kinesin-1. They also highlight where our knowledge of motor recruitment is at best patchy, and thus where important future insights are likely to be made. This will include how viral modulation of signalling pathways and accessory proteins regulates both motor recruitment and activity. Live cell imaging of viruses and their associated motors will continue to provide important quantitative information. However, a full molecular understanding will require the development of *in vitro* motility assays together with detailed biochemical, biophysical and structural analyses of viral proteins/complexes bound to their respective motors. Studying the virus–motor interface promises to provide important insights into the general mechanisms of motor recruitment and regulation by cellular cargoes. Ultimately, it may also help facilitate the development of therapeutic tools that specifically inhibit viral transport rather than those occurring between cellular cargoes and their motors.

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Conflict of interest

The authors declare that they have no conflict of interest.

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