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Role of Dynein in Viral Pathogenesis

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22.1 General Tenets of Virus–Host Interactions

A general principal of the interaction between viruses and the host is how viruses facilitate their existence and propagation by co-opting host cell components, membranes, proteins, and machineries to their advantage. This is true for virtually every aspect of the replication cycle of viruses from virus entry to the generation of progeny virus particles following assembly. Thus, this chapter will describe the state of the art machineries that viruses use from viral infection (entry) to the end stage, when new, progeny virus particles disseminate from cells. This may be a harsh process, in that several viruses promote dramatic rearrangement of cellular organelles and eventual catastrophe of the cell leading to cell death via apoptosis and cell lysis. Indeed, there are few instances of a peaceful coexistence between host cell and virus, with dramatic virus-mediated modulations of host cell signaling, morphology, and organellar rearrangements being more common. The grand challenge of this field of research is the identification of suitable targets and the development of novel candidate anti-viral drugs.

22.2 Blocking Dynein Function in Virus-Infected Cells: Potential Drug Development to Poison Viral Replication Steps

Realistically, the development of drugs that target dynein activities during viral replication would rely on the disruption of characterized and specific interactions between viral proteins and dynein. Whether this would be appropriate for all viruses is questionable. For example, viruses that swiftly infect and destroy cells by...
rapidly programming apoptosis might not be good candidates. On the other hand, viruses that are latent in cellular tissue reservoirs, for example retroviruses, might be more suitable since the re-activation of the expression of this type of virus would require viability during the viral expression stage. For example, currently there are no cures for several viral diseases and no effective vaccines despite some promising results [1–3]. The two characterized replication steps of human immunodeficiency virus type 1 (HIV-1) that require and/or utilize dynein function (i.e. viral ingress and egress) may very well both be targeted with future anti-viral compounds [4]. Nevertheless, a plethora of drugs that target processes of the viral replication cycle including virus entry, reverse transcription of the viral RNA genome, viral import into the nucleus, integration into the host genome, and viral maturation [5–10] are mainstays (e.g. Fig. 22.1). These have been instrumental in maintaining the quality of life and life expectancy of infected individuals. However, in addition to unwanted metabolic side effects induced by drugs, HIV-1’s ability to adapt leads to sequence variation in the viral genetic material and the inevitable development of resistance to all current drug therapies [11], leading to treatment failure. Thus, there is an urgent need to identify additional therapeutic targets for drug design to block viral replication that succumbs to adaptation. Recent discoveries demonstrate the potential of stopping HIV-1 by targeting the machineries and host proteins used for viral assembly [12,13] or by blocking host cell protein function [14–18], and indeed these methods can be used for other viruses. These new strategies have provided optimism for the development of a new generation of anti-viral compounds in the fight against HIV-1 infection and progression to acquired immunodeficiency syndrome (AIDS). Likewise, for viruses such as Herpes simplex virus type 1 (HSV-1) and the hepatitis C virus (HCV), both major human pathogens with high medical importance, the use of motor proteins during ingress and egress make these machineries highly suitable for drug targeting. Because viruses are parasitic in nature, an even greater reason exists to fully understand the molecular mechanisms underlying host cell protein function and viruses’ dependence on these for additional rounds of infection. This is the general thrust of all research on the molecular biology of viruses that can potentially have an impact on human health and disease outcomes.

22.2.1 Virus Infection and Ingress

The mechanisms by which viruses gain entry into cells rely on two fundamental cellular processes: membrane fusion and endocytosis (Figs. 22.1 and 22.2). Whereas freely diffusing virus can find target cells expressing the appropriate receptors, albeit inefficiently, other phenomena that enable more directed targeting and greater efficiency exist. This includes virus cell surfing, which occurs on thin, actin-rich membrane extensions such as filopodia and nanotubes. For many viruses, this extracellular trafficking is critical to virus transmission from one cell to another (e.g. coronavirus severe acute respiratory syndrome (SARS-CoV), respiratory syncitial virus, HIV-1, murine leukemia virus, and human T-cell leukemia virus type 1 (HTLV-1); see also Section 22.8). Motility of viruses towards the cell...
Figure 22.1 Early replication steps of retroviruses. Viral entry of HIV-1 (shown here) and other retroviruses is characterized by receptor–ligand interactions followed by viral entry. The outer envelope of retroviruses fuses with the plasma membrane to release the viral core that contains the genomic RNA. In retroviruses such as human foamy virus, a specific interaction with dynein is achieved and immunoneutralization experiments show that this translocation toward the nucleus occurs in a dynein-dependent manner. During this translocation step, the viral genomic RNA is reverse-transcribed to complementary DNA to generate the pre-integration complex. At the nuclear pore, the pre-integration complex is transported into the nucleus for eventual integration into the host DNA. Additional details on the specific virus–dynein interactions are discussed in the text.
Figure 22.2 Early replication steps of HSV-1 and adenovirus. Viral entry is characterized by receptor—ligand interaction followed by viral entry. The attachment of adenoviruses to the membrane of the target cell is mediated by the viral fiber protein and cellular Coxsackie/adenovirus receptor. Following this step, a second interaction between viral capsid proteins and integrins on the cell surface occurs that leads to internalisation of the virus through endocytosis. The toxic activity of the viral proteins is later responsible for disruption of the endosomal membrane and delivery of the viral particle into the cytoplasm. In contrast, the entry of HSV-1 into cells requires interaction between virion envelope glycoproteins and cell surface glycosaminoglycans. Following this event is the direct fusion of the virion envelope and cell plasma membrane to allow the entry of the viral capsid into the cytoplasm. Intracellular trafficking is mediated by virus—dynein interactions followed by translocation toward the nucleus on microtubules powered by the minus-end motor, dynein. Both HSV-1 and adenovirus have nuclear intermediates and the viral genetic material is transferred into the nucleus for transcription. Details of the specific virus—dynein interactions are discussed in the text.
body relies principally on the myosin II motor, which propels receptor-tethered virus particles towards the cell body [19–21]. Active actin remodeling at the cell body makes the membrane vulnerable and more penetrable to virus infection and viral entry, by the two mechanisms above. Neurotropic viruses are met with the particular challenge of transporting the virus to the cell body and then onward toward the nucleus, which can be several thousand micrometers away. For other viruses such as HIV-1 and HTLV-1, which infect smaller, monocytic T cells, the distances to travel are seemingly smaller but the viruses encounter identical physical, cytoplasmic impediments to infection [22].

### 22.3 Direct Interactions with Dynein for Viral Entry: Trafficking Towards the Nucleus by Various Viruses

As the virus penetrates into the cytoplasm, viruses initiate their voyage towards the nucleus. One of several possibilities then occurs, depending on whether the virus requires a nuclear intermediate or whether a juxtanuclear domain represents its destination. Nevertheless, viruses are devoid of translocation capability and must now rely on the host to take them where they need to go. For example, upon virus entry the adenovirus capsid hexon subunit interacts with dynein intermediate chain (IC) but not dynactin, a multi-subunit protein complex that is required for cytoplasmic dynein activity and processivity [23,24] (Figs. 22.2 and 22.3; Table 22.1). This event has been shown to be pH dependent and therefore, following the post-entry acidification of the endosomes, efficient transport via this interaction can occur. Adenovirus targeting to the nucleus is also enhanced by direct activation of p38/MAP kinase pathway. The activation of this pathway may represent a countermeasure of sorts to the innate response to infection elicited by the host cell ([25] and see Section 22.4). Adenovirus interactions with dynein TCTEL1 (also known as DYNLT1 or Tctex1) may also influence later steps in the virus’ replication cycle when the decision is made to either induce or repress the signals that lead to apoptosis [26]. Likewise, via an interaction between the later-expressed viral envelope protein p54 and dynein LC-8 [27], the African swine fever virus can be propelled towards the nucleus on microtubules but cannot elicit the activation of caspases and induce apoptosis [27,28]. Ebolavirus’ interaction with DLC-8 has also been mapped to a short, consensus five-amino acid motif (SQTQT) in the viral protein VP-35 [29]. This viral protein has multiple functions during viral replication, but most important is its ability to suppress interferon synthesis following infection and its capacity to bind RNA, both of which are critical for pathogenesis. While research into this virus is impractical because it requires enhanced biosafety conditions, the little that we have learned about ebolavirus molecular biology will have a positive impact on human health in the long-term. Another virus that is studied with difficulty is the hantavirus, which is transmitted from the excrement of small rodents to humans. However, some
progress towards elucidating the role of the hantaviral nucleocapsid protein during virus replication has been made. Nucleocapsid, an RNA-binding protein is found to traffic to the endoplasmic reticulum and Golgi intermediate compartment. This was found to depend on dynein motor activity, since the

**Figure 22.3 Structure of the dynein/dynactin complex and interacting viruses.** The dynein motor complex is shown bearing cargo (e.g. vesicles, virus, viral capsids) with its major subdomains — dynein light chains (DLCs), dynein intermediate chains (DICs), dynein light-intermediate chains (DLICs), and dynein HCs (DHCs) — described in Chapter 15. Examples of virus interactions with dynein LCs as well as the dynein ICs are indicated on the right. Discussions of specific interactions are found in the text. The dynactin complex consists of 11 different polypeptide subunits. Some of them are present in more than one copy per complex. The octameric polymer of the actin-related protein-1 (Arp1) resembles a short actin filament. As with conventional actin, Arp1 can hydrolyze ATP and form filaments. Arp1 binds directly to spectrin. The dynactin subunit p62 functions in linking dynein and dynactin to the cortical cytoskeleton. Spectrin is an important constituent of the cytoskeletal network, underlies the plasma membrane, and controls the distribution of the integral membrane proteins.
expression of dynamitin/p50 dispersed nucleocapsid within the cytoplasm [30]. Nevertheless, while nucleocapsid can bind microtubules, no direct interaction between the nucleocapsid and dynein has been characterized to date [30].

HSV-1 entry also requires nuclear targeting and HSV-1 is one of the most thoroughly studied viruses in this field. Typically, it infects cells via epithelial

### Table 22.1 Viruses that Interact with Dynein Components During Replication

| Virus1                      | Virus Interaction Domain | Dynein Component2 | References |
|----------------------------|--------------------------|-------------------|------------|
| Adeno-associated virus     | Capsid                   | Dynein            | [24]       |
| Adenovirus                 | Capsid                   | Dynein light and light-intermediate chain; TCTEL1 | [23–26,72,123,124] |
| African swine fever virus  | PS4 (13 amino acid motif) | DLC-8             | [27,28]   |
| Bovine immunodeficiency virus | Capsid                 | DLC-8             | [51]       |
| Ebolavirus                 | VP35                     | DLC-8             | [29]       |
| Hantaan virus              | Unknown                  | Unknown           | [30]       |
| Hepatitis B virus          | Unknown                  | Unknown           | [82]       |
| Hepatitis C virus          | Unknown                  | Unknown           | [83]       |
| Hepatitis E virus          | Vp13                     | Dynein            | [125]      |
| Herpes simplex virus 1     | VP26 capsid              | RP3, Tctex-1      | [31,32,34,126–130] |
| Equine herpesvirus         | Unknown                  | Unknown (acetylated tubulin) | [33] |
| Kaposis’s sarcoma herpesvirus | Unknown               | Unknown (acetylated tubulin) | [48] |
| Mason—Pfizer simian virus  | Matrix                   | DYNLT1 (Tctex-1)  | [102,103] |
| Bovine immunodeficiency virus | Capsid                 | LC8               | [51]       |
| Human foamy virus          | Capsid                   | LC8               | [50]       |
| Human immunodeficiency virus type 1 | Pre-integration complex | Dynein            | [49,92,94] |
| Human papillomavirus       | Minor capsid L2          | DYNLT1 and DYNLT3 | [40,41]    |
| Poliovirus                 | Receptor CD155           | Tctex-1           | [35,36,38,131] |
| Rabies virus               | P phosphoprotein         | DYNLL (LC8)       | [42–47]    |
| Sirevirus                  | Hopie Gag extension      | DLC-8             | [132]      |
| Vaccinia virus             | Unknown                  | Unknown           | [107,117,133] |

1 Alphabetically organized; most viruses are discussed in the text.  
2 The name of the dynein subunit as stated in the cited references is indicated. However, it is important to note that for several components multiple names have been used in the literature to refer to the same protein.
cells on oral mucous membranes and then transmits to sensory neurons to establish a latent infection that can be reactivated. The initial stages of infection following entry rely on an interaction between HSV-1 VP26 capsid protein and a dynein light chain (LC) of the Tctex-1 family, DYNLT1 and DYNLT3, as verified using a variety of in vitro experimental analyses ([31]; Figs. 22.2 and 22.3). The viral capsid protein was also found to be associated with microtubules. However, contrary evidence that did not support a direct role for VP26 has been made available and suggests roles for additional components that recruit the dynein motor to HSV-1 capsids [32]. The role of dynein appears to transcend species since the major horse pathogen, equine herpesvirus type 1 (EHV-1), also utilizes dynein following viral entry to infect cells efficiently [33]. However, in this case the virus causes the acetylation of tubulin, eliciting microtubule stabilization. This appears to be a guarantee to provide a stable trafficking scaffold for EHV-1 to reach the nucleus.

However, recent evidence regarding HSV-1 indicates that the scenario is not so simple. Beate Sodeik’s group tested the role of 23 viral proteins that are potentially exposed to the cytoplasm during viral ingress and egress of HSV-1. These analyses revealed that multiple inner viral tegument proteins including pUS3, pUL36, pUL37, ICP0, pUL14, pUL16, and pUL21 recruited dynein and dynactin but also were able to recruit the opposing motor proteins, kinesin-1 and kinesin-2, simultaneously [34] (Fig. 22.2). These results explained to a certain extent how HSV-1 capsids exhibited both plus- and minus-end movements, a likely scenario for most viruses that hijack the motor proteins and the microtubule network for intracellular translocation. The involvement of dynein in poliovirus entry and shuttling towards the cell body is also still being worked out. The interaction between the poliovirus single-membrane-spanning receptor CD155 and dynein LC Tctex-1 was believed to be responsible for intracellular trafficking following entry [35], but recent models suggest a slightly more complex scenario. Studies using motor neurons from transgenic mice revealed that retrograde transport of poliovirus was both receptor-dependent and receptor-independent [36]. Importantly, poliovirus protein 3A, a characterized anti-apoptotic protein, was shown to interact with the type 1 lissencephaly protein (LIS-1), a key regulator of cytoplasmic dynein. While the authors promoted the idea that this was relevant for cell viability, the virus–host interaction could represent another regulatory point at which poliovirus controls intracellular trafficking that may also include other motor proteins [37,38]. Moreover, a growing number of studies show that many viruses are able to recruit and interact with both dynein and kinesin motors, a finding that would be consistent with intracellular trafficking of vesicles and endosomal membranes that harbor both motor proteins [39].

Some of the viral factors with characterized interactions with dynein fulfill additional roles during virus replication. Human papillomavirus infection is again characterized by a well-documented interaction between its capsid L2 protein
and the dynein LCs DYNLT1 and DYNLT 3 [40,41]. However, L2 is found to accompany the viral DNA in the nucleus, suggesting that it plays a dual role in the early events of viral replication for this virus. Rabies virus is another case in point, where initial characterization of an interaction between the phosphoprotein P with dynein light chain LC8 (DYNLL) in \textit{in vitro} and \textit{in vivo} studies was shown to be important during viral replication [42–45]. Certainly these data indicate a reliance on the dynein motor and stable microtubules for ingress, but an additional role for the P protein has been uncovered, this time in a much later viral replication step, in transcriptional regulation [46,47]. By mutating the LC8 binding domain of rabies virus P, the authors revealed that this major effect was independent of its role in intracellular (cytoplasmic) trafficking [46,47]. Because mutating the binding sites only attenuated infection, it is likely that this virus guarantees its replication and propagation by multiple means that could include additional interactions with motor proteins mediated by other viral proteins.

Similarly to EHV-1, human herpesvirus 8 (HHV-8), also known as Kaposi’s sarcoma-associated herpesvirus, also induces the stabilization of microtubules by acetylating tubulin as a result of the viral-induced activation of Rho GTPases in primo infection [48]. The HHV-8 herpesvirus contributes to the development of Kaposi’s sarcoma, an otherwise rare form of cancer that is sometimes associated with HIV-1-infected patients who have developed AIDS, and to some B-cell lymphomas. In the virus that causes AIDS, after fusion with the plasma membrane, the core, containing the genomic RNA and the viral and host-cell proteins, is transported along microtubules in a dynein-dependent manner toward the nucleus [49] (Fig. 22.1). The ability of HIV-1 to interact with the dynein motor is shared with many of the viruses above. However, HIV-1 RNA must be reverse-transcribed into double-stranded cDNA and then transported into the nucleus for integration into the host-cell genome. This defines retroviral infection as a genetic disease since the genomic material, in the form of a proviral DNA, can propagate from one cell to another during cell division. Detailed correlative electron and confocal imaging have provided a snapshot of the physical space and revealed apparent tethering of the HIV-1 capsid to what seemed to be a motor (like dynein) protein bound to microtubules. This was supported further by experiments that employed the microtubule-disrupting drug nocodazole and by dynein immuno-neutralization injection experiments. Both of the retroviruses human foamy virus and bovine immunodeficiency virus also utilize this mode of transport during viral entry to traffic toward the nucleus with characterized interactions between retroviral capsid proteins and DLC-1 (aks DYNLL or LC8), in which tethering to microtubules was shown to be the result of DLC-1 binding to microtubules [50,51]. This machinery could be targeted by small peptides, as was done to inhibit productive HIV-1 infection [4]. Section 22.4 contains a discussion of how viruses utilise dynein during egress and assembly.
22.4 Innate Immune Response to Viral Infection

Viral infection exposes cells to viral RNA and DNA, inevitably leading to innate anti-viral host responses. Generally, these innate anti-viral responses represent fundamental defense mechanisms of the cell to incoming pathogens and are initiated through the recognition of viral products, such as the viral dsRNA and DNA by the pathogen-recognition toll-like receptors [52,53]. The Toll-like receptor family consists of more than 10 members that are expressed on the cell surface membrane or endosomes. Interferon is generally synthesized following the initial recognition events and has a number of effects on cell function including the induction of interferon-stimulated genes (ISG). These ISG’s include those encoding cytokines and the double-stranded RNA-activated protein kinase (PKR) and their expression creates a highly inhospitable environment for viruses [54,55]. Other interferon-stimulated genes encode HIV-1 restriction factors such as tetherin [56] and TRIM5α [57], which can severely limit HIV-1 replication [58].

However, viruses are notoriously efficient at counteracting these innate anti-viral responses following virus infection by creating a host cell environment that is more favourable to viral replication [59,60]. Viruses can block interferon synthesis, intracellular trafficking, and release of anti-viral cytokines from cells, thereby promoting viral replication [61,62]. Furthermore, complex retroviruses, such as HIV-1, encode auxiliary factors that counteract interferon-induced virus restriction factors such as tetherin [63,64] and viruses such as reovirus, the vaccinia virus [65,66]. Others express genes that can have a severe impact on PKR function. Other viruses such as HCV elicit parallel pathways to downregulate the synthesis of ISG mRNAs. This is achieved by the super-induction of PKR and eIF2α phosphorylation, processes known to severely limit both cellular and viral mRNA translation. The result of this virus-induced situation is the suppression of cap-dependent mRNA translation and the preferential synthesis of HCV proteins via the canonical cap-independent translation using an internal ribosome entry site [55,67,68]. Of note are reovirus mRNAs, which are translated over cellular mRNAs, even in the presence of a phosphorylated eIF2α and the assembly of translationally silent stress granules [69]. These aspects of virus–host biology are currently the focus of intense research: if we can block the viruses’ ability to commandeer innate responses, the natural course of events against infection and viral disease will prevail, thereby limiting the toll on human lives.

The transit of viral capsids towards the nucleus may in fact be considered to be an early step of the cell’s innate immune response to infection. Cellular surveillance machineries may consider incoming virus particles as “foreign” or aggregates of proteins and thus traffic them to the microtubule-organizing center (MTOC) for aggresome formation. Aggresomes are proteinaceous bodies in which accumulate proteins destined for degradation; they usually assemble at juxtanuclear...
domains situated around the MTOC. Thus, dynein motors are largely responsible for the transport of cargo to this site [70]. However, a strong link between virus replication and aggresome formation exists, supporting the view that viruses capitalize on the cell’s response to traffic material to these sites of aggregation [70,71]. Hantavirus has also been shown to accumulate in vimentin cage-like structures that are characteristic of aggresomes at the MTOC [30]. The association of virus assembly sites with aggresomes may also allow viruses to immobilize and inactivate proteins that would otherwise inhibit infection, such as the demonstrated degradation of the MRE11–RAD50–NBS1 complex, which, if active, may damage viral DNA during adenovirus infection [72].

22.5 Dyneins and Stress Granule Assembly: A Novel Concept in Innate Responses to Viral Infection

Stress granules have been the focus of numerous recent investigations. They are aggregations of translationally silent ribonucleoproteins forming discrete yet prominent cytoplasmic foci 1–5 μm in diameter. Stress granules assemble as a result of various cellular stresses mediated by both eIF2α-dependent and -independent mechanisms [73,74]. Stress granule assembly is induced via a stress-induced phosphorylation of eIF2α (by PKR, for instance) that reduces the availability of the eIF2α/tRNAi Met/GTP ternary complex responsible for translation initiation codon recognition of an mRNA. Under these conditions, the assembly of the translation initiation complex disassembles and promotes the formation of stress granules that harbor translationally silent mRNAs.

Some viral infections induce the assembly of stress granules, including reovirus and respiratory syncitial virus [69,75], but others block their assembly during infection; for example, HIV-1, West Nile virus, rotavirus, and poliovirus [76–78]. Interestingly, the assembly of stress granules depends on dynein and microtubules [79,80]. Considering this dependence on dynein activity for assembly, it is possible that viruses co-opt factors of the dynein motor complex during infection, but as a consequence either induce or silence stress granule assembly. This is an emerging field of endeavor [81] but, all told, stress granules and other silencing ribonucleoprotein bodies may represent “dangerous” areas and structures of the cell that viral replication complexes, proteins, and RNAs/DNAs would need to avoid to guarantee expression and survival.

22.6 Dynein Involvement in Viral Egress and Assembly

While the use of minus-end-directed dynein motor activity to direct viral capsids towards the nucleus is common to many diverse viruses (Table 22.1), the
implication of dynein during viral egress, during the transit of viral components towards the cell periphery and the assembly of most viruses, is not immediately apparent. Indeed, studies on hantavirus and the hepatitis viruses reveal that dynein motors contribute to localization and perhaps juxtapositioning of the viral components required for assembly at virus factories [30,82,83]. Specific proteins from the hepatitis B virus (HBV) and HCV, for example, elicit changes in the localization of viral and cellular components and appear to be dependent on dynein activity. Disrupting dynein function via dynamitin/p50 overexpression, for instance, disrupts both nuclear targeting as well as lipid droplet organization around the MTOC; both are critical to viral assembly [82,83]. The trafficking of HSV-1 to the Golgi complex may depend on dynein activities during the acquisition of membrane immediately prior to cell exit. Recent investigations have revealed that dynein exhibits plus-end movement that is controlled by LIS-1 and tubulins and the tethering of mammalian NUDC to kinesin-1 (a plus-end-directed motor) [84,85]. There is clearly support for the presence of both dynein and kinesin motors driving viral components toward assembly sites [86]. Paradoxically, regulatory genes of HTLV-1 and HIV-1 both enhance and disrupt microtubule integrity and polarization [87–89], but this may directly relate to the timing of the replication cycle.

### 22.7 Using Dynein To Traffic to Virus Assembly Domains

Integrated targeting of viral components must be coordinated by retroviruses to complete assembly at the plasma membrane. Concerted aggregation of viral proteins and the genomic material, a large 9–12 kb RNA, should be achieved in a small space at the plasma membrane. Retroviruses such as HIV-1 engineer additional targeting strategies that have been worked out by extensive analyses. For instance, membrane targeting domains called lipid rafts and tetraspanin-rich domains serve as scaffolds for viral assembly [90,91]. These exist at internal limiting membranes and at the plasma membrane. Dynein’s implication in viral RNA targeting was first revealed by the observation of an aggregation of HIV-1 genomic RNA at the MTOC when heterogeneous nuclear ribonucleoprotein RNA binding proteins were depleted in HIV-1-expressing cells [92]. While this suggested that minus-end transport was not disrupted (since the RNA could readily traffic to the MTOC following export from the nucleus), a blockade to outbound RNA traffic from the MTOC was observed. A critical event in the replication of this virus includes the selection of viral RNA for encapsidation into progeny viruses. This must be done in a regulated manner since only two copies of the viral RNA genome are selected for encapsidation into each virus. The MTOC region has been identified as the site of genomic RNA selection using both biophysical fluorescence resonance energy transfer experiments [93] and by indirect measurements by microscopy and virological assays [92]. The genomic RNA was
then shown to assemble into ribonucleoproteins for trafficking on endosomal membranes. The localization of these endosomal membrane-associated ribonucleoproteins, which harbor viral structural and host proteins along with the viral genomic RNA, was tightly controlled by dynein activity [92,94] (Fig. 22.4). Using siRNA against the dynein heavy chain (HC) or by overexpressing dynamitin/p50, the viral ribonucleoproteins were released along with late endosomal membranes to the cell periphery [94], indicating that there was an active positioning in the

**Figure 22.4** Late replication steps of the retroviruses HIV-1 and M-PSV, which require dynein activity. The late stages of retroviral replication are characterized by transcription of the proviral DNA and the generation of a genomic RNA (blue squiggle) in the nucleus. Upon nuclear export, the RNA must be translated to make the major structural protein Gag (as well Gag/Pol, which encodes viral enzymes) in a juxtanuclear domain. The genomic RNA of M-PSV follows the same fate to the cytoplasm but the synthesis of M-PSV Gag is followed by Gag trafficking to the MTOC that is mediated by a specific interaction with dynein, as described in Section 22.7, with the cognate genomic RNA where this virus assembles. The genomic RNA and Gag of HIV-1 have potentially two fates: the genomic RNA is used for translation of Gag polyprotein and, also, the RNA must be selected for and encapsidated into new virus particles. Gag binds and selects for the genomic RNA at the MTOC region, and these viral components must be trafficked to the plasma membrane (PM) for virus assembly. This can be achieved by the association of Gag with intracellular endosomal membranes via a myristoylation domain of matrix (A) or the assembly of a ribonucleoprotein complex containing Gag and the RNA (B). Both complexes contain multiple host factors (not shown). The trafficking toward the plasma membrane is achieved in a multi-subunit complex that likely contains both minus- and plus-end motor proteins, dynein and kinesin. Other components of these retroviruses (e.g. envelope (Env) protein) take the secretory pathway via the endoplasmic reticulum (ER) and Golgi (on left), leading the assembly and budding of new viruses.
cytoplasm by the minus-end activity of dynein. Because virtually all models for RNA trafficking propose a coordinated tug of war between the activities of opposing motor forces (e.g. the motor proteins dynein and kinesin are in the same complex but one beats out the other to dictate the direction in which a complex, viral capsid, vesicle, or ribonucleoprotein moves on microtubules [86,95—97], both motor activities should be present on the retroviral ribonucleoproteins during viral egress.

The expression of Rab7-interacting lysosomal protein (RILP) has a dramatic effect on HIV-1 genomic RNA localization in HIV-1-expressing cells by rerouting the RNA to the MTOC. This effect, in fact, could be due to RILP’s ability to directly interact with the subunits of endosomal sorting complex required for transport (ESCRT)-II (EAP20 and EAP36) [98,99], or to small Rab GTPases to which RILP binds on endosomal membranes. Alternatively, this localization phenotype could be the result of RILP’s ability to recruit components of the dynein/dynactin complex (p150glued) or the dynein motor itself [100,101].

The Mason-Pfizer simian virus (M-PSV) utilizes dynein LC (DYNLT1) Tctex-1 to target intracellular viral assembly sites adjacent to the nucleus, at the MTOC [102,103] (Fig. 22.4). Thus, in contrast to the assembly pathway taken by HIV-1, for M-PSV, a D-type retrovirus, assembly occurs at the MTOC. A morphogenetic switch mediated by a hydrophobic pocket in the amino-terminal matrix domain of Gag directs an interaction with the dynein LC DYNLT1 and is responsible for targeting to this unique assembly domain, at least when compared to the assembly pathway taken by HIV-1 and other retroviruses [103]. Interestingly, a single point mutation in the dynein-binding domain not only prevents DYNLT1 binding but changes the site of assembly to that exhibited by HIV-1: the plasma membrane (Fig. 22.4). Thus, although the assembly sites may be different for HIV-1 and M-PSV, for example, this type of switch might not be at play for genomic RNA trafficking of these retroviruses since, by inference, the M-PSV genomic RNA might also be packaged at the MTOC like that of HIV-1 [93]. Nevertheless, retroviral genomic RNA localization might also be dictated by nuclear trafficking events, perhaps associated with the viral regulatory protein Rev or chromosome region maintenance 1 (CRM1) nuclear export factors that have been localized to the MTOC region [104]. Morphological switches mediated by specific interactions with organelles and motor proteins will likely determine trafficking polarity in cells and the winner in the dynein—kinesin tug of war. Gag, host proteins, and the viral RNA, present on endosomal membranes, may be cargo that is available for directed transport on microtubules toward plasma membrane assembly sites (Fig. 22.4). Interactions of viral proteins with dynein mediators such as LIS-1 and other host proteins [37,84,85] could very well provide the switch from minus-end to plus-end motor-directed traffic. Curiously, the HIV-1 regulatory protein, Tat, enhances microtubule polymerization [87] and interacts with LIS-1 protein [105], whereas HIV-1 Rev, vaccinia virus, and African swine fever virus break down microtubules [88,106,107].
22.8 Cell-to-Cell Transmission

Recent investigations into virus cell-to-cell transmission have revealed that several viruses from different classes are capable of being transmitted directly from one cell to another. These include the Rous sarcoma virus, murine leukemia virus, HIV-1, HTLV-1, and the coronavirus SARS-CoV, amongst others. Cell-to-cell transmission of viruses requires the intimate association of infected and non-infected target cells. This type of transmission is also more likely to occur in densely populated tissues, in which viruses can propagate efficiently.

The most details are known for retroviruses and onco-retroviruses, which bud from the cell surface and transmit via a “virological synapse.” This synapse is formed by receptor–ligand interactions between cell adhesion molecules and is similar to the immunological cytotoxic T-cell synapse during an immune response [108,109]. The intercellular space is referred to as the virological synapse into which virus particles bud. Viruses are then able to efficiently infect the immediately juxtaposed cell, and this can enhance the infectious potential over 100-fold and may provide for a privileged site where viruses will not be recognized by immune surveillance machinery [110]. Targeting to this domain is aided by the reorganization of the microtubule network, including the dramatic repositioning of the MTOC towards the cell-to-cell junction, which is dependent on the viral regulatory protein Tax in HTLV-1 and the Ras-MEK-ERK signaling pathway [111]. The repositioning of the MTOC was found to be dependent both on diacylglycerol concentrations and on dynein activity [112]. Reversed polarity of microtubules is induced by the close juxtapositioning of the MTOC at the plasma membrane, resulting in the possibility that the minus-end motor dynein may traffic viral components towards the microtubule minus ends at the cell-to-cell junction. This could represent and consolidate some of the observations for dynein’s involvement in intracellular trafficking events of structural proteins and viral genomic RNA during egress before virus budding [92]. Nevertheless, multiple cell-to-cell contact sites (polysynapses) were identified for HIV-1 in T-cells [113]. While this does not reconcile the polarization of a single MTOC during cell-to-cell transmission, in the oncoretrovirus HTLV-1, the viral protein Tax yields cells with multiple centrosomes in infected cells [114] that could contribute to virus propagation.

Viral cell-to-cell transmission also occurs on cell membrane extensions termed filopodia or cytonemes and nanotubes, but transmission does not necessarily require direct cell-to-cell juxtapositioning [19–21]. Propulsion of viruses from an infected cell to another is achieved via myosin II–actin retrograde movement, resulting in shuttling of virus-coupled cell surface receptors on membrane extensions towards the cell body. The transmission of several viruses is enhanced by these processes but nevertheless does not appear to depend on dynein activity before the viral capsid penetrates into the cell at the cell body.
22.9 Virus Export from Virus Factories

Several viruses, including poxviruses and the vaccinia virus, replicate in cytoplasmic virus factories. The recruitment of transcription and translation factors and the engineering of virus-specific membranes and smaller “organelles” all contribute to the biogenesis of these virus factories \([83,115,116]\). Both the vaccinia virus and HSV-1 must acquire membrane at the Golgi complex or at juxtanuclear sites, according to current concepts, before exiting the cell \([117,118]\), and this may require active transport that could include the activity of the dynein motor and an intact microtubule cytoskeleton for this directed targeting during viral egress.

22.10 Concluding Remarks

The intracellular translocation of viral components continues to be an extremely enriching area of study (see also \([119–121]\) and for other pathogens \([122]\)). Viruses are inherently immotile and studies on how they are able to commandeer, recruit, and utilise the host cell translocation machinery are continually shedding light on the workings of the cell’s major trafficking machineries. Viruses must also mount countermeasures against anti-viral innate responses while making their way through the host’s cytoplasm. This is usually achieved by utilizing constitutive cellular processes and by directly interacting with host motor proteins and other factors.

Viruses likely harbor and make use of both plus- and minus-end-directed microtubule motor activities during their replication cycles. On this subject, the following are some of the major questions for the future to answer:

- What are the primary mechanisms for the recruitment of molecular motor proteins?
- What determines directionality?
- What viral and host factors are involved?
- Are there molecular switches that occur to dictate the directionality of motor-protein-containing capsids?
- Are these dictated by viral gene products that are expressed in a time-dependent manner?

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