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Emerging roles of cytoskeletal transport and scaffold systems in human viral propagation

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ABSTRACT

Viruses have long been recognized as significant pathogens, contributing to multiple global pandemics throughout human history. Recent examples include the 2009 influenza pandemic and the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019. Despite ongoing experimental and clinical efforts, the development of effective antiviral treatments and vaccines remains challenging due to the high mutation rates of many human pathogenic viruses including influenza virus and SARS-CoV-2. As an alternative approach, antiviral strategies targeting host factors shared by multiple viruses could provide a more universally applicable solution. Emerging evidence suggests that viruses exploit the host cytoskeletal network to facilitate efficient viral replication and propagation. Therefore, a comprehensive understanding of the interactions between viral components and the cytoskeletal machinery may offer valuable insights for the development of broad-spectrum antiviral therapeutics. This review compiles and discusses current knowledge on the interactions between viruses and cytoskeletal elements, including kinesin, dynein, myosin, and vimentin, and explores their potential as therapeutic targets. The potential for these cytoskeletal components to serve as targets for new antiviral interventions is discussed in the context of diverse human viruses, including influenza virus, SARS-CoV-2, herpes simplex virus, human papillomavirus, and human immunodeficiency virus.

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Introduction

To prevent and treat viral diseases, vaccines and direct-acting antivirals (DAAs) are widely employed. Vaccines are administered to induce acquired immunity, offering protection against viral infections, and have been demonstrated to be safe and effective over time. However, many viruses, including influenza viruses, exhibit high susceptibility to genetic mutations (Visher et al. 2016; Peck and Lauring 2018). These mutations lead to frequent antigenic shifts and drifts, allowing viruses to evade immune responses generated by vaccination. In response, DAAs have been developed and are extensively used for patient treatment. Despite this, DAAs face similar challenges due to viral mutations, which contribute to the development of drug resistance (Smyk et al. 2022). In contrast, host factor-targeting therapies may offer a more robust defense against viral mutations, as both progenitor and mutated viruses depend on the same or comparable host mechanisms (Kuk et al. 2022).

Intracellular trafficking plays a fundamental role in the transport of proteins, lipid vesicles, and organelles to specific cellular destinations. The cytoskeleton, composed of microtubules, actin filaments, and intermediate filaments, is integral to intracellular trafficking, as it provides tracks for motor proteins, supports endo/exocytosis, and maintains cellular morphology (Fletcher and Mullins 2010). Microtubule-based motor proteins, kinesins and dyneins, and actin-based myosins, hydrolyze ATP to generate mechanical forces that transport membrane-bound vesicles and molecular components by 'walking' along cytoskeletal tracks (Gennerich and Vale 2009). Myosin, in particular, plays a key role in the trafficking of molecular components within the cell. Numerous pathogenic viruses exploit host intracellular trafficking machinery to enhance their survival and replication (Lukic et al. 2014; Jeon et al. 2022). For instance, intracellular trafficking is critical for the spread of influenza viruses and other pathogens, such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Dohner and Sodeik 2005; Ward 2011; Avilov et al. 2012; Walsh and Naghavi 2019; Kloc et al. 2022). Following influenza virus infection, the expression levels of several motor proteins increase, facilitating the transport of viral components to

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appropriate intracellular sites, thereby promoting efficient viral replication (Amorim et al. 2011; Edinger et al. 2014; Mindaye et al. 2017; Cho et al. 2020; Jeon et al. 2022). Similarly, motor proteins support the replication of HSV, SARS-CoV-2, and HIV by enabling the efficient intracellular transport of viral components (DuRaine et al. 2018; Chen et al. 2021; Naghavi 2021; Pegg et al. 2021). Furthermore, motor proteins are involved in regulating viral assembly and genome replication processes (Kubota et al. 2009; Sankovski et al. 2018). Although intermediate filaments do not directly interact with motor proteins, intermediate filament proteins, such as vimentin, have a significant impact on the viral life cycle (Wu and Pante 2016; Huang et al. 2019). For example, vimentin has been shown to enhance influenza virus replication (Huang et al. 2019) and acts as a co-receptor for SARS-CoV-1 (Yu et al. 2016). As a result, targeting intracellular trafficking components represents a promising therapeutic strategy for combating infections caused by a range of viruses.

This review provides an overview of emerging roles of intracellular trafficking components, particularly motor proteins and intermediate filaments, in the propagation of various human viruses, with a primary focus on influenza viruses, and explores the potential for antiviral strategies that target these components.

Kinesin and viruses

The kinesin superfamily consists of ATP-driven motor proteins critical for microtubule-dependent intracellular transport. Kinesins are composed of both heavy and light chains. The heavy chain features a catalytic motor domain at the N-terminus, a dimerization stalk, and a cargo-binding domain at the C-terminus, which also provides structural support. The light chains aid in cargo binding at the C-terminal of the heavy chain. The human kinesin superfamily is divided into 14 distinct families, from kinesin-1 to kinesin-14 (Lawrence et al. 2004). To date, 44 kinesin heavy chains have been identified in humans (Figure 1). Kinesins play a pivotal role in various stages of viral replication due to their influence on intracellular dynamics. First, viruses may exploit kinesins to facilitate their transport toward the nucleus following viral entry into the host cell. While kinesins primarily transport cellular components toward the cell periphery, the specific orientation of the microtubule-organizing center (MTOC) may allow kinesin-dependent movement to be crucial for viral access to the nucleus (Dodding and Way 2011; Lou et al. 2023). Second, kinesins may promote the repositioning of intracellular organelles, thereby creating an environment conducive to viral replication (Strunze et al. 2011). Third, kinesins are essential in the transport of newly assembled viral particles from the assembly sites to the plasma membrane, where virions are subsequently released (Jouvenet et al. 2004).

Kinesins and influenza viruses

Recent studies have shown that influenza virus infection increases the expression of several kinesin proteins. Furthermore, inhibiting kinesin activity has been demonstrated to suppress influenza virus propagation both *in vivo* and *in vitro* (Ramos-Nascimento et al. 2017; Cho et al. 2020; Kim et al. 2021; Jeon et al. 2022). These findings indicate that influenza viruses utilize the kinesin-microtubule transport system to facilitate their intracellular movement, thereby enhancing viral replication within host cells (Greber and Way 2006; Simpson and Yamauchi 2020) (Table 1).

KIF11

Kinesin family member 11 (KIF11), also known as kinesin-5 Eg5, is a motor protein that utilizes ATP for microtubule-dependent plus-end motility. It plays a critical role in cell cycle regulation by forming mitotic spindles and extending microtubules (Kapitein et al. 2005). Recent research by Kim et al. demonstrated that treating influenza-infected MDCK or HEK293 cells with KIF11-specific inhibitors, K858 and Monastrol, significantly reduces cytopathic effects (CPEs), such as cell rounding and the formation of syncytia and inclusion bodies in the nucleus caused by the virus (Kim et al. 2021). These results are corroborated by a corresponding decrease in virus replication within host cells, validated by flow cytometry and western blot analyses. Additionally, the export of viral ribonucleoprotein (vRNP) from the host nucleus is suppressed by these inhibitors, as evaluated by confocal microscopy. The precise mechanisms by which KIF11 influences influenza virus propagation remain unclear. It is hypothesized that KIF11 may directly interact with viral components or rearrange intracellular organelles during viral replication to create a favorable environment for the virus, warranting further investigation.

KIF18A

Kinesin family member 18A (KIF18A) that belongs to kinesin-8 is an intracellular motor protein characterized by its ATP-driven, microtubule-dependent motility toward the microtubule plus-end (Mayr et al. 2007). KIF18A is primarily involved in regulating chromosome dynamics during mitosis by controlling chromosome congression, suppressing centromere movements, and maintaining spindle microtubule oscillation (Malaby et al. 2019). However, the involvement of KIF18A in the viral

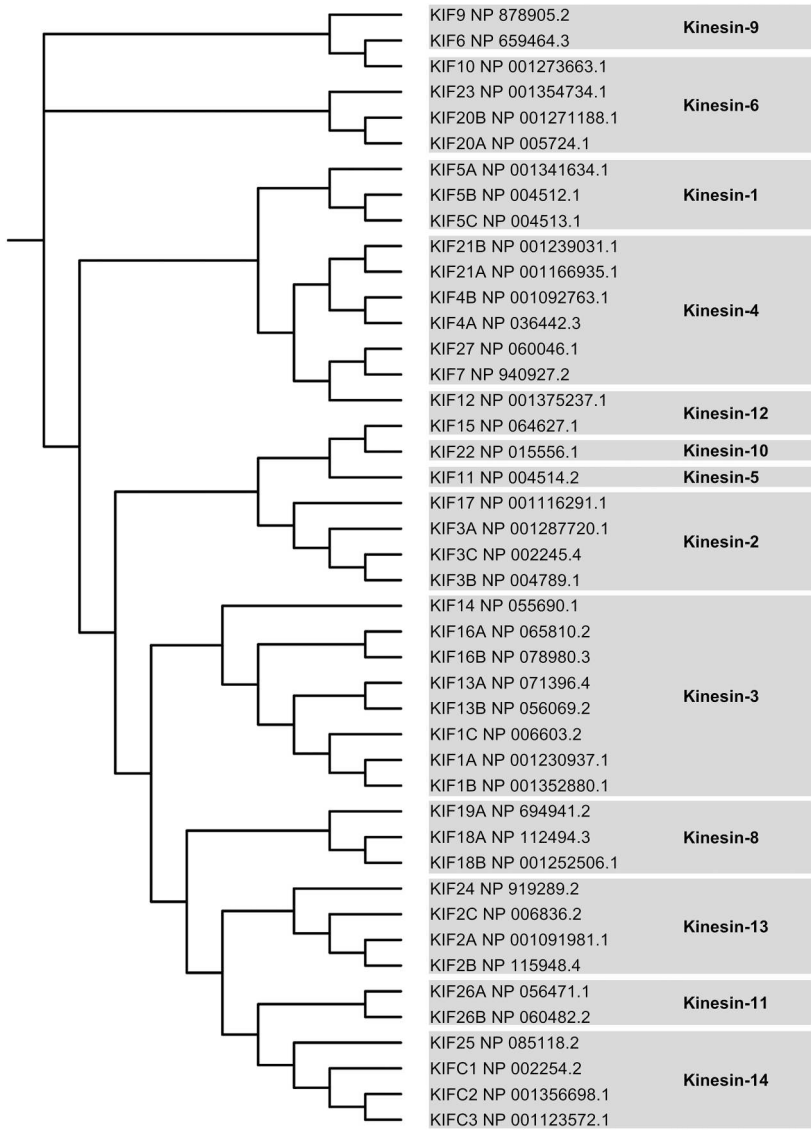

Figure 1. Phylogenetic analysis of kinesin superfamily proteins. Based on the nomenclature established by Lawrence et al. (2004), KIFs (kinesin-related proteins) were classified into their respective families (Lawrence et al. 2004). A guided phylogenetic tree was constructed using pairwise sequence alignment through Clustal software. The input sequences were obtained from the RefSeq protein database at the National Center for Biotechnology Information (NCBI).

life cycle remains underexplored. Recent research by Cho et al. has highlighted the role of KIF18A during the entry and egress stages of virus infections (Cho et al. 2020). This study reports that KIF18A expression increases following influenza virus infection. Treatment of infected cells with BTB-1, a small molecule inhibitor of KIF18A, results in a marked reduction in CPEs, alongside lower rates of intracellular virus replication and reduced virus egress. Additionally, suppressing KIF18A expression via small interfering RNA (siRNA) significantly curtails virus propagation, while its overexpression enhances viral spread. These effects are mechanistically supported, as the KIF18A inhibitor successfully blocks viral infection-induced activation of the MAPK-AKP pathway and RanBP3, a cofactor of chromosome region maintenance 1/exportin1/Exp1/Xpo1 (CRM1), which is crucial for vRNP export. Furthermore, treatment with the KIF18A inhibitor substantially lowers morbidity and mortality in mice infected with the influenza virus, underscoring KIF18A's role in multiple phases of the viral replication cycle and its potential as an antiviral target. Future studies using single-virus tracking techniques, such as super-resolution microscopy(Jeong and Kim 2022), could further clarify the direct interactions between KIF18A and viral components throughout the influenza replication cycle.

KIF20A

Kinesin family member 20A (KIF20A), also known as mitotic kinesin-like protein 2 (MKLP2), is a motor

protein that utilizes ATP for microtubule-dependent, plus-end-directed motility (She et al. 2020). KIF20A plays a crucial role in regulating cellular processes during mitosis and cytokinesis, promoting chromosome segregation and cleavage furrow formation (Wu et al. 2019). It assists in the proper distribution of cellular compartments through its interaction with microtubules. Recent studies highlight the importance of KIF20A activity in the replication of the influenza virus (Jeon et al. 2022). This study reveals that KIF20A expression is significantly correlated with influenza virus replication. Overexpression of KIF20A in HEK293 cells substantially enhances virus replication. Treatment with the KIF20A-specific inhibitor paprotrain, either before or during virus infection, has been shown to effectively reduce virus replication. However, inhibition of KIF20A after viral entry does not significantly affect viral activity, indicating that KIF20A plays a role in the early stage of viral infection. These findings underscore the critical function of KIF20A in the early stages of influenza virus infection. Furthermore, *in vivo* studies demonstrate that KIF20A inhibition significantly reduces both morbidity and mortality in mice infected with the influenza virus, accompanied by decreased viral titers in the lungs. Complementary research has identified Polo-like kinase 1 (Plk1) as an upstream regulator of KIF20A, also influencing influenza A virus (IAV) replication and propagation (Hirata et al. 2014; Pohl et al. 2017). Knockdown of Plk1 in A549 cells significantly decreases IAV production, a finding supported by reduced viral production in human lung cells treated with a specific Plk1 inhibitor. Together, these findings suggest a pivotal role for KIF20A in influenza virus replication. Given that KIF20A is highly expressed in various cancers, it has been considered a novel target in anti-cancer treatments (Zhang et al. 2016; Shen et al. 2019; Jin et al. 2023). Therefore, the KIF20A inhibitors previously developed for cancer therapy may also hold potential for antiviral therapy, warranting further investigation.

Kinesins and other viruses

Kinesins are critical host factors that regulate the replication of various pathogens, in addition to influenza viruses. For example, kinesin family member 5 (KIF5), a plus-end directed kinesin, mediates the endocytic trafficking of HSV and classical swine fever virus (SFV) through a microtubule-dependent process (DuRaine et al. 2018; Pegg et al. 2021; Lou et al. 2023). Recent advancements in microscopy, including single-virus tracking techniques, allow for direct visualization of viral transport and interactions with host cellular components. Using multi-channel super-resolution and live TIRF microscopy, Scherer et al. demonstrated that HSV proteins recruit kinesin family member 1A (KIF1A) to facilitate viral transport (Scherer et al. 2020). Additionally, kinesin family members 3A (KIF3A) and 3B (KIF3B) are involved in the assembly and egress of enveloped viruses such as HIV and Kaposi's sarcoma-associated herpesvirus (KSHV) (Yamazaki et al. 1995; Sathish et al. 2009; Gaudin et al. 2012). Silencing KIF3A in HIV-infected macrophages impairs the egress of new virions, leading to the accumulation of viral components within cells. Furthermore, KIF1A, which is primarily known for its role in neuronal development, also facilitates the transport of herpes simplex virus-2 (HSV-2) (Koshizuka et al. 2005).

Upstream regulators of KIF20A, such as Plk1 and Aurora Kinase B (AurKB), play significant roles in various virus-host interactions. Plk1 enhances hepatitis B virus (HBV) replication (Diab et al. 2017), and its inhibition has been shown to eliminate the virus in CD4+ T cell reservoirs (Zhou et al. 2020). Additionally, AurKB expression increases in cells infected with dengue virus (DENV) or hepatitis C virus (HCV) (Madejon et al. 2015; Pérez-Olais et al. 2019). RhoA-associated coiled-coil-containing protein kinase 1 (ROCK1), which regulates the phosphorylation of KIF20A, has been found to enhance the recruitment of HIV components to viral assembly sites. Disrupting the KIF20A-ROCK1 interaction impairs HIV replication and reduces viral infectivity (Wen et al. 2014) (Table 1).

Since kinesins and their upstream regulators are essential for the replication of a diverse range of viruses – including influenza virus, HSV, SFV, KSHV, HBV, DENV, HCV, and HIV – they represent promising antiviral targets. However, kinesins are also involved in critical cellular processes, such as microtubule dynamics, spindle formation, and organelle transport. Therefore, further research is needed to elucidate the mechanisms by which kinesins interact with viruses and influence their life cycle, with the goal of developing novel kinesin-based antiviral therapies.

Dynein and viruses

Dynein, a minus-end directed motor protein associated with microtubules, is often considered the directional counterpart of kinesin (Reck-Peterson et al. 2018). This large protein complex is composed of heavy, intermediate, light intermediate, and light chains. The heavy chain provides structural support, with a motor domain at the N-terminus and a cargo-binding domain at the C-terminus. The other chains contribute to cargo binding at the C-terminal of the heavy chain and interact with dynactin and cargo adaptors to facilitate retrograde transport.

Table 1. Kinesins in interactions with viruses.

Kinesins	Viruses	References
Kinesin-1		
KIF5A	HSV-1	(Lou et al. 2023) (DuRaine et al. 2018)
KIF5B	HSV-1, SFV, HIV	(Pegg et al. 2021) (Lou et al. 2023) (Malikov et al. 2015) (Lukic et al. 2014)
KIF5C	HSV-1	(DuRaine et al. 2018)
Kinesin-2		
KIF3A	HIV, KSHV	(Gaudin et al. 2012) (Sathish et al. 2009)
Kinesin-3		
KIF1A	HSV-2	(Koshizuka et al. 2005)
KIF13	IAV	(Ramos-Nascimento et al. 2017)
Kinesin-5		
KIF11	ZIKA, IAV	(Liu et al. 2021) (Kim et al. 2021)
Kinesin-6		
KIF20A	IAV, HBV*, HIV*, HCV*, DENV*	(Jeon et al. 2022) (Zhou et al. 2020)* (Pérez-Olais et al. 2019)* (Pohl et al. 2017)* (Diab et al. 2017)* (Madejon et al. 2015)* (Wen et al. 2014)* (Hirata et al. 2014)*
KIF20B	HSVs	(Georges et al. 2019)
Kinesin-8		
KIF18A	IAV	(Cho et al. 2020)

HIV, Human immunodeficiency virus; HSV, Herpes simplex virus; IAV, Influenza A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; KSHV, Kaposi's sarcoma-associated herpesvirus; SFV, Simian virus; DENV, Dengue virus.
*Interaction with adaptor, downstream, or upstream molecules of kinesins.

Dynein plays an essential role in the positioning of the Golgi apparatus, nucleus, and small organelles (Roberts et al. 2013). Notably, dynein has been shown to regulate various stages of the viral lifecycle, including the transport of viral genomes to the peri-nuclear region and the facilitation of viral egress (Tati and Alisaraie 2022).

Dynein and influenza viruses

Multiple studies have indicated that influenza viruses exploit dynein for the intracellular transport of viral components. Following viral endocytosis, hemagglutinin (HA)-mediated fusion with late endosomes facilitates the release of the M1 protein and the vRNP complex. In this context, histone deacetylase 6 (HDAC6) co-localizes with M1-positive vesicles at the fusion site (Husain and Cheung 2014). This co-localization is associated with viral unanchored ubiquitin, a post-translational modification involving the attachment of ubiquitin molecules to viral proteins. Unlike ubiquitin chains that target proteins for degradation, unanchored ubiquitin plays a role in various cellular processes, including protein trafficking and viral replication. Upon influenza virus infection, unanchored ubiquitin may be involved in facilitating the release of viral components from endosomes or

Table 2. Dynein and its related factors in interactions with viruses.

Viruses	Dynein/Dynein-related host factors	Stage	References
IAV			
	RAB11A	Viral transport	(Bhagwat et al. 2020) (Amorim et al. 2011) (Avilov et al. 2012) (Eisfeld et al. 2011)
	HDAC6	Viral uncoating	(Banerjee et al. 2014)
HSV-1			
	RP3 Tctex1	Viral transport	(Douglas et al. 2004)
PV			
	Dynein	Viral transport	(Florin et al. 2006) (Finnen et al. 2003)
HIV			
	DLC1	Viral entry	(Fontenot et al. 2007)
	DHC	Viral uncoating	(Pawlica and Berthoux 2014)
EV			
	DLC	Viral assembly	(Kubota et al. 2009)

IAV, Influenza A virus; HSV, Herpes simplex virus; PV, Papillomavirus; HIV, Human immunodeficiency virus; EV, Ebola virus; DLC, Dynein light chain; DHC, Dynein heavy chain.

regulating the interaction between HDAC6 and viral proteins (Wang et al. 2022). The presence of HDAC6 in the M1-HDAC6 complex prompts the recruitment of dynein and myosin II, which exert the mechanical force required to disassemble the viral shell. Additionally, dynein is involved in transporting viral RNA from late endosomes to the cytoplasm, a critical step for the replication of viral genetic material (Banerjee et al. 2014; Eisfeld et al. 2015). Dynein plays a crucial role in the influenza virus uncoating process, as ciliobrevin, a cytoplasmic dynein inhibitor, can impede viral uncoating (Artcibasova et al. 2023). Furthermore, dynein is required for the intracellular movement of vRNP, which is essential for influenza virus replication (Chou et al. 2013; Lakdawala et al. 2014). The dynein cofactor RAB11A initiates the nuclear re-import of viral RNA through direct interaction with PB, a polymerase subunit (Amorim et al. 2011; Eisfeld et al. 2011; Avilov et al. 2012; Bhagwat et al. 2020). Moreover, single-virus tracking technology has demonstrated that influenza viruses are co-localized with dynein and myosin, traveling on actin filaments and microtubules, respectively (Zhang et al. 2018). Overall, the essential role of dynein in influenza virus replication is supported by both molecular biology and bioimaging techniques. Further investigation into the mechanisms underlying the interaction between influenza viruses and dynein could provide valuable insights for identifying novel antiviral targets (Table 2).

Dynein and other viruses

Similar to influenza viruses, various other viruses also depend on dynein and its adaptor molecules for

efficient replication. For example, the herpes simplex virus type 1 (HSV-1) capsid protein VP26 interacts with the dynein light chains RP3 and Tctex1 during retrograde axonal transport (Douglas et al. 2004). Additionally, the papillomavirus (PV) L2 small capsid protein facilitates the release of the viral genome from endosomes and mediates its transport by attaching to dynein. When the interaction between the L2 small capsid protein and dynein was disrupted by mutation, viral infectivity was significantly impaired (Finnen et al. 2003; Florin et al. 2006). Furthermore, both dynein light chain 1 (DLC1) and dynein heavy chain (DHC) are involved in the entry and egress stages of HIV (Fontenot et al. 2007; Pawlica and Berthoux 2014). In a similar manner, the Ebola virus (EV) VP35 protein interacts with DLC8, another dynein light chain, to enhance viral replication efficiency, as demonstrated through co-immunoprecipitation (co-IP) (Kubota et al. 2009). These findings suggest that various viruses exploit the dynein-mediated intracellular transport system to facilitate their replication. However, due to the multifunctional role of dynein, targeting it with inhibitors may present challenges related to specificity and toxicity. Future studies should therefore focus on developing inhibitors that selectively disrupt viral interactions with dynein while minimizing adverse effects on its essential cellular functions.

Myosin and viruses

Myosins are actin-based molecular motors that promote actin-based motility through ATP hydrolysis. Myosins are composed of heavy and light chains. The heavy chains form the main structural component, including the head domain responsible for ATP hydrolysis and actin binding. The light chains, associated with the neck region of the heavy chain, play a role in the activation of myosins (Akhmanova and Hammer 2010; Hartman and Spudich 2012). Myosin isoforms are determined by a combination of genetic variation and alternative mRNA splicing. Multiple isoforms of myosin are present in humans (Coluccio 2020), and some are involved in viral replication cycles. By modulating the actin cytoskeleton, myosins assist in the transport of viruses (Burckhardt and Greber 2009) and enhance cell–cell contact, which is essential for viral transmission between cells (Mothes et al. 2010).

Myosin and influenza viruses

Influenza viruses exploit myosins for entry into host cells (de Vries et al. 2011) and for the export of vRNPs from the nucleus (Banerjee et al. 2013). This section outlines the involvement of the myosin family in the replication of influenza viruses.

Myosin II

Myosin II, a conventional myosin, consists of two heavy chains, two essential light chains (ELCs), and two regulatory light chains (Hartman and Spudich 2012). Although myosin II primarily facilitates muscle contraction, non-muscle myosin II (NMMII), encoded by the *MYH9*, *MYH10*, and *MYH14* genes, plays critical roles in intracellular trafficking, cell division, cell–cell contact, and actin network formation (Vicente-Manzanares et al. 2009). Influenza virus predominantly enters cells via clathrin-mediated endocytosis (CME), as reported by (Meischel et al. 2020). However, under certain conditions, the virus employs a clathrin-independent entry mechanism that involves NMMII. Influenza virus generates both spherical and filamentous virions; spherical virions mainly use CME for entry, while filamentous virions, likely due to their elongated structure, do not (de Vries et al. 2011). When CME is inhibited, the virus activates macropinocytosis to enter host cells, a process that requires NMMII activity (Rossman et al. 2012). Filamentous virions predominantly rely on NMMII-associated macropinocytosis for host cell entry. Additionally, NMMII facilitates 'viral surfing,' a process where the virus moves toward adjacent cells via the actin–myosin network (Sun and Whittaker 2007). This network is also essential for assembling influenza viral particles (Roberts et al. 2015). Recent studies suggest that myosin IIA, whose heavy chain is encoded by MYH9, plays a crucial role in IAV infections (Chen et al. 2023). In human lung cells lacking MYH9, IAV infectivity is significantly diminished, with reductions in viral binding and entry. Interestingly, overexpression of MYH9 does not affect viral attachment or internalization but does reduce viral infection and vRNP activity. Moreover, MYH9 disrupts vRNP formation by interacting with the viral nucleoprotein (NP), thereby inhibiting viral RNA transcription (Chen et al. 2023) (Table 3).

Myosin VI

Myosin VI, an unconventional myosin found only in higher eukaryotes, localizes in regions enriched with clathrin and the clathrin adapter protein AP-2 in polarized cells, such as epithelial cells. Previous research (Sun and Whittaker 2007) has emphasized the essential role of the myosin VI tail in facilitating the entry of influenza virus into epithelial cells. Specifically, influenza virus infection in polarized cells shows a strong dependence on the actin network, which is absent in non-polarized cells. This reliance is further supported by evidence that disruption of actin filaments in host cells significantly impairs viral internalization. Treatment with cytochalasin D, an inhibitor of actin polymerization, markedly reduces the entry of

Table 3. Myosin and its related factors in interactions with viruses.

Viruses	Myosin/Myosin-related host factors	Stage	References
IAV			
	NMMII	Viral entry	(Rossman et al. 2012)
		Viral export	(Roberts et al. 2015)
	NMHC-IIA	Viral entry	(Chen et al. 2023)
	Myosin VI	Viral entry	(Sun and Whittaker 2007)
HIV-1			
	NMMII	Viral budding	(Yao et al. 2013) (Gladnikoff et al. 2009)
HCMV			
	Myosin Va	Viral transport	(Wilkie et al. 2018)
HSV-1			
	NMHC-IIA	Viral entry	(Arii et al. 2010)
PV			
	NM1	Viral replication	(Sankovski et al. 2018) (Oswald et al. 2017)
SARS-CoV-2			
	NMHC-IIA	Viral entry	(Chen et al. 2021)

HSV, Herpes simplex virus; IAV, Influenza A virus; HCMV, Human cytomegalovirus; PV, Papilloma virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; NMMII; Non-muscle myosin II, NMHC-IIA; Non-muscle heavy chain IIA, NM1; Nuclear myosin 1c.

biotinylated influenza virus, underscoring the critical role of actin filaments in the viral entry process. Furthermore, cells transfected with a plasmid expressing a mutant myosin VI tail domain exhibit a significantly reduced rate of viral infection. This resistance is observed exclusively in polarized cells expressing the mutant tail domain, which contains only the cargo adaptor domain but lacks the wild-type C-terminus specific to polarized cells. This finding suggests that the activity of myosin VI is particularly crucial for influenza virus entry in polarized cells and that the C-terminus of myosin VI plays a key role in this process (Sun and Whittaker 2007). Additionally, myosin VI has been shown to colocalize with influenza virus in both MDCK and HeLa cells. This colocalization, confirmed through spinning disk confocal microscopy in cells infected with influenza virus (Zhang et al. 2018), indicates that influenza virus requires myosin VI and the actin cytoskeleton for internalization into epithelial cells during the early stages of infection. This internalization is essential for viral entry and subsequent replication within the host.

Myosin and other viruses

Myosin activity affects the replication of several viruses beyond influenza. For example, during HIV infection, myosin facilitates viral budding. In infected cells, actin and myosin co-localize and concentrate at the budding site, whereas in non-infected cells, their distribution remains random. Notably, inhibition of myosin light chain kinase (MLCK) leads to a concentration-dependent decrease in HIV release (Yao et al. 2013). Furthermore, the major capsid protein (MCP) of human cytomegalovirus (HCMV) interacts with nuclear myosin Va, promoting MCP transport to the peri-nuclear region to facilitate viral egress. Colocalization of myosin Va with MCP on actin filaments is revealed by fluorescence microscopy, and depletion of myosin Va suppresses viral replication (Wilkie et al. 2018). In the case of HSV-1, non-muscle myosin IIA (NMIIA) interacts with the major tegument protein VP22, which is critical for nuclear egress (Arii et al. 2010). Interestingly, the surface expression of NMIIA is upregulated upon HSV-1 infection, and NMIIA inhibition decreases HSV-1 infectivity in both *in vivo* and *in vitro* studies. Additionally, the E2 protein of PV interacts with nuclear myosin 1c (NM1) during the viral lifecycle (Oswald et al. 2017; Sankovski et al. 2018). A recent study has also identified MYH9 as a potential receptor for SARS-CoV-2; in human cell lines, MYH9 interacts with the viral S protein, and depletion of MYH9 significantly reduces viral entry and infection (Chen et al. 2021) (Table 3). Collectively, myosin activity influences the replication of multiple viruses, facilitating processes such as HIV budding, HCMV capsid transport, HSV-1 nuclear egress, PV lifecycle interaction, and SARS-CoV-2 entry. Therefore, targeting specific myosins or their related pathways could significantly reduce viral replication and infectivity.

Intermediate filaments and virus

Intermediate filaments, integral to the cellular cytoskeleton, are composed of diverse proteins including vimentin, nestin, and keratins (Fay and Pante 2013; Wen et al. 2020). These filaments play pivotal roles in reshaping cell structure and modulating various cellular responses (Park et al. 2023). Although no motor proteins associated with intermediate filaments have been identified, research suggests that these filaments, particularly vimentin, influence cellular responses to viral infections. Unlike microtubules and actin filaments, which primarily facilitate the intracellular trafficking of virus-containing endosomes, intermediate filaments are essential for preserving the structural integrity and organization of the cell, thereby impacting how cells respond to viral challenges.

Intermediate filaments and influenza virus

Research has demonstrated that vimentin plays a role in influenza virus replication. Wu et al. described the

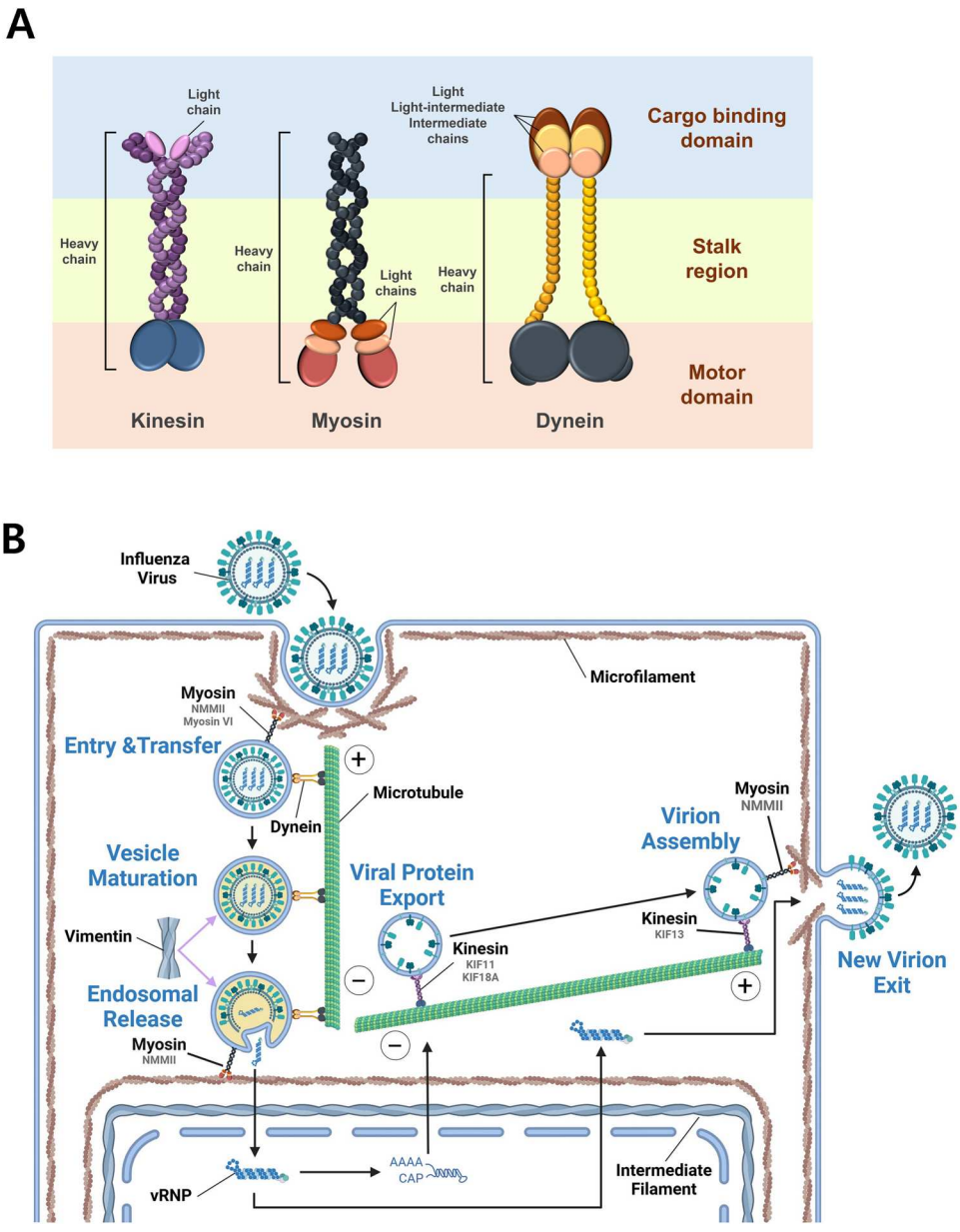

Figure 2. The influenza virus life cycle regulated by the cytoskeleton network. (A) Graphical summary of the motor proteins depicted, showing that kinesin, dynein, and myosin have a motor domain, a stalk region, and a cargo-binding domain. (B) Cytoskeleton components and their associated motor proteins regulate the replication of the influenza virus. Myosin (NMMII, Myosin VI), an actin-based motor protein, and dynein, which moves towards the minus end of microtubules, are involved in viral entry and transport. Vimentin intermediate filaments, along with dynein, facilitate the maturation of vesicles containing virus particles. The endosomal release of the viral genome is controlled by myosin (NMMII), vimentin, and dynein. The nuclear export of vRNA and viral proteins depends on kinesin (KIF11, KIF18A), which moves towards the plus end of microtubules. The assembly and release of new virions require myosin activity. This figure was created using biorender.com.

complex interactions between IAV and intermediate filaments, emphasizing that vimentin depletion impairs late endosome acidification (Wu and Pante 2016), which in turn inhibits IAV genome release. Their study revealed a reduction in viral replication and progeny virus production in vimentin-deficient cells. This observation is further supported by findings that vimentin-deficient cells exhibit enlarged endosomes and impaired endosomal acidification, a process critical for IAV nuclear import. These results suggest that vimentin is essential for influenza virus replication, particularly through its role in endosomal trafficking and acidification.

In a separate study, Huang et al. reported that vimentin may inhibit influenza virus replication by disrupting the fusion of vRNP with the nucleus, thereby delaying nuclear import (Huang et al. 2019). This study also

identified miR-1290, which downregulates vimentin expression, as being upregulated in human cells during influenza virus infection. Inhibition of miR-1290 resulted in reduced influenza virus replication in human cells. Therefore, vimentin appears to be closely associated with the influenza virus life cycle.

Intermediate filaments and other viruses

The interactions between intermediate filaments and various viruses have been well documented. Recent studies have shown that vimentin acts as a co-receptor, enhancing the binding process of SARS-CoV-1 and SARS-CoV-2 to their target, angiotensin-converting enzyme 2 (ACE2) (Yu et al. 2016; Arrindell et al. 2022). Surface vimentin expression is transiently upregulated in SARS-CoV-2-infected Vero E6 and A549 cells, and blocking the accumulation of vimentin on the cell surface by treatment with withaferin A that induces vimentin aggregation *in vitro*, or with anti-vimentin antibodies reduces viral infection (Arrindell et al. 2022). Co-localization microscopy and co-immunoprecipitation (Co-IP) results of vimentin, SARS-CoV-2, and ACE2 provide strong evidence of their interaction, suggesting that vimentin functions as a co-receptor for SARS-CoV-2 infection. Conversely, during human papillomavirus (HPV) infection, surface-expressed vimentin directly binds to HPV particles, hindering their attachment to host cells (Schafer et al. 2017). Additionally, vimentin has been identified as a regulator of the DENV replication complex NS4A, leading to diminished DENV replication (Teo and Chu 2014). DENV infection induces the reorganization of vimentin by altering its phosphorylation levels, and vimentin knockdown using siRNA results in decreased DENV replication. Collectively, these findings illustrate the complex role of vimentin in modulating various phases of the viral life cycle, with both facilitative and inhibitory effects, highlighting the need for further exploration of intermediate filament-virus interactions.

Conclusions and perspectives

This review has outlined the molecular significance of motor proteins in the context of viral infection, with a specific focus on the influenza virus. Viruses exploit host cellular machinery to facilitate their entry and proliferation. For successful replication within the host cell, the viral genome must efficiently enter the host nucleus. The intracellular trafficking system plays a crucial role at various stages of the viral life cycle. Effective viral propagation between host cells is often mediated by the host's molecular export pathways, such as CRM1, which are heavily reliant on the cytoskeletal network. Substantial evidence indicates that microtubule-dependent motor proteins, such as kinesin and dynein, actin-dependent motor myosin, and vimentin intermediate filaments, facilitate viral propagation through specific and direct interactions with viral components, as illustrated in Figure 2.

From a clinical perspective, targeting host factors presents a viable strategy for managing the frequent mutations that result in recurring endemic or pandemic outbreaks. Current vaccines and DAAs provide limited protection due to the high mutation rates of viruses. Drugs that target host factors, however, could offer more durable resistance to viral mutations since both original and mutated viruses depend on similar host mechanisms. Targeting motor proteins represents a promising approach in antiviral drug development. Additionally, repurposing motor protein-targeting drugs, traditionally used in cancer therapy, could bypass some of the major hurdles in new drug development.

In summary, a deeper understanding of the interactions between viral mechanisms and host motor proteins can significantly enhance our knowledge of viral behavior. This insight is crucial not only for comprehending viral dynamics but also for devising effective strategies to mitigate the impact of future pandemics.

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Author contributions

YS contributed to conceptualization and writing. YL contributed to original draft preparation and writing. YC contributed to writing and editing. All authors read and approved the final version of the manuscript.

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