Review

Herpesvirus acts with the cytoskeleton and promotes cancer progression

Yingfen Wu[1,2,3], Fang Wei[2], Le Tang[2], Qianjin Liao[2,4], Hui Wang[4], Lei Shi[2], Zhaojian Gong[2], Wenling Zhang[2], Ming Zhou[1,2,3], Bo Xiang[1,2,3], Xu Wu[1,2,3], Xiaoling Li[1,2,3], Yong Li[2,5], Guiyuan Li[1,2,3], Wei Xiong[1,2,3], Zhaoyang Zeng[1,2,3], Fang Xiong[1,2✉], Can Guo[1,2,3✉]

1. NHC Key Laboratory of Carcinogenesis, Xiangya Hospital, Central South University, Changsha, Hunan, China
2. The Key Laboratory of Carcinogenesis and Cancer Invasion of the Chinese Ministry of Education, Cancer Research Institute, Central South University, Changsha, Hunan, China
3. Hunan Key Laboratory of Nonresolving Inflammation and Cancer, Disease Genome Research Center, the Third Xiangya Hospital, Central South University, Changsha, Hunan, China
4. Hunan Key Laboratory of Translational Radiation Oncology, Hunan Cancer Hospital and the Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan, China.
5. Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA

✉ Corresponding authors: xiongf@csu.edu.cn; guocde@csu.edu.cn; Tel.: 86-731-8480-5446;

Abstract

The cytoskeleton is a complex fibrous reticular structure composed of microfilaments, microtubules and intermediate filaments. These components coordinate morphology support and intracellular transport that is involved in a variety of cell activities, such as cell proliferation, migration and differentiation. In addition, the cytoskeleton also plays an important role in viral infection. During an infection by a Herpesvirus, the virus utilizes microfilaments to enter cells and travel to the nucleus by microtubules; the viral DNA replicates with the help of host microfilaments; and the virus particles start assembling with a capsid in the cytoplasm before egress. The cytoskeleton changes in cells infected with Herpesvirus are made to either counteract or obey the virus, thereby promote cell transforming into cancerous ones. This article aims to clarify the interaction between the virus and cytoskeleton components in the process of Herpesvirus infection and the molecular motor, cytoskeleton-associated proteins and drugs that play an important role in the process of a Herpesvirus infection and carcinogenesis process.

Key words: Herpesvirus; cytoskeleton; drugs; infection; cancer

Introduction

Herpesvirus and its life cycle

Herpesviruses are a family of enveloped double-stranded linear DNA viruses that contain subfamilies that are classified as alpha, beta, and gamma herpesviruses [1]. Members of the alpha herpesvirus subfamily include the human pathogens herpes simplex virus (HSV), and varicella-zoster virus (VZV), as well as the animal pathogens pseudorabies virus (PRV), bovine herpesvirus, and Marek's disease virus, which proliferate rapidly and cause cytopathic effects [2]. The beta herpesvirus subfamily includes, human and mouse cytomegalovirus (HCMV and MCMV, respectively), with a long growth cycle, and infection by these viruses enlarges cells [3]. The gamma herpesvirus subfamily contains the lymphotropic Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV), whose target cells are mainly lymphoid cells that cause lymphoproliferation [4] Human gamma herpesvirus is closely related to the occurrence of some malignant tumors, such as EBV associated with Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma (NPC) [5-15], HHV-8/KSHV and Kaposi's sarcoma (KS) (the most common tumor in AIDS patients) [16], primary effusion lymphoma(PEL) [17]

and multicentric Castleman disease(MCD) [18]. The virions of herpesviruses are made of DNA genome and an outside protein aceous capsid. Several proteins surrounding the capsid are called the tegument. There are multiple viral glycoproteins surrounding the tegument in an envelope.

The life cycle from herpesvirus entering the host to egress is a complex process in terms of space and time. First, herpesviruses enter cells by fusion with the plasma membrane or are endocytosed to the cell to eventually fuse within an intracellular vesicle or clathrin endocytosis pathways [19]. During this process, viral glycoproteins (gB, gH/gL, gD) and host cell surface receptors play key roles [20].However, except HSV, HSV is preferentially taken up into glioma cells through an endosomal pathway rather than through fusion with the cell surface[21].The herpesvirus enters the cell and releases the viral capsid. Once the virus capsids enter the cytoplasm, the tegument proteins fall from the capsid, bind with the microfilaments and reach the centrioles and nuclei that are retrograding along the plus-end of the microtubules [22]. After the virus enters the nucleus, the virus begins DNA replication and macromolecular synthesis. When those actions are completed, the virus particles are packaged into mature viruses with capsids before release to the extracellular space. The virus life cycle in a host cell cannot proceed without the help of the intracellular cytoskeleton.

Cytoskeleton components and related proteins

The cytoskeleton is a complex intracellular network that consists of three components: microfilaments, microtubules and intermediate filaments [23-25]. Microfilaments are composed of actin filaments, and there are two forms of actin *in vivo*: G-actin and F-actin (i.e., the actin monomer and actin monomers assembled in fibrous actin). Actin has ATPase activity because of an ATP binding site in the inner side of the monomer. Actin monomers bind with ATP and initiate microfilaments assembly. Most of the microfilaments in the cell are concentrated in the cytoplasmic area and cross-linked with the microfilament-binding proteins to form a cell cortex involved in phagocytosis and other processes. Microfilaments also form stress fibers in focal adhesions, pseudopods and microvilli. The functioning of the microfilament network depends on a combination of microfilament-binding proteins, including fascin, cofilin and other proteins [26]. In addition, the molecular motor myosin, especially myosin V (MyoV) and MyoVI, specifically binds to

the filaments and utilizes energy generated by the hydrolysis of ATP to transport cargo along microfilaments [27-29].

Other important components of the cytoskeleton are microtubules (MTs). Microtubules are hollow tubular structures composed of alpha- and beta-tubulin heterodimers. Alpha- and beta-tubulin heterodimers form fibrils through nucleation, and then those fibrils form microtubules by elongation in the microtubule organizing center (MTOC)[30]. Due to the different speeds of microtubules extension at both ends (the faster end called the plus end, the other is the minus end), thus making microtubules be in a polar state [31]. This polarity keeps microtubules in a dynamic state. The dynamics and distribution of microtubules are influenced by various factors, including GTP hydrolysis, posttranslational modifications of tubulin subunits, and microtubule-associated proteins [32]. Microtubule-associated proteins (MAPs) are a class of proteins that are present along with the assembly of microtubules and are classified as MAP1, MAP2, MAP3, MAP4, tau, and others. Those proteins which have one or several microtubule-binding domains can stabilize microtubules as well as regulate microtubule network distribution and function. The targeted transports between microtubules to microtubules and membrane vesicles are regulated by two types of molecular motors: the plus end motor, kinesins, which is the transport toward the outer cell periphery. Kinesin consists of a motor domain in the shape of a sphere and a rod-shaped structure that contains ATP-binding sites and microtubule-binding sites [33]. The minus end steering motor, dynein, transports from the outer edge of the cell to the center. Dynein is the largest and fastest moving member of motor proteins [33-35].

The intermediate filament (IF) is also one of the components of the cytoskeleton. The IF is a rope-like structure with a highly conserved alpha spiral rod region in it. IFs are largely responsible for providing mechanical integrity for a cell, and they provide a scaffold for proteins involved in polarized trafficking [36]. Several well-known examples include keratins, neuro filaments, vimentin, desmins, and lamin A/C. In the process of virus infection, the role played by the intermediate filaments is less clear than other components of the cytoskeleton, in consist of impacts of virus infection.

The purpose of this paper is to elucidate the role of the cytoskeleton and associated proteins in the process of herpesvirus infection and the effects on the cytoskeleton after cell infection with the herpesvirus, thereby promoting tumor development [37-39].

# The Interaction between Herpesvirus and the Cytoskeleton during Virus Infection

Microfilaments Interact with Herpesvirus during Infection

Once herpes virions make contact with cells, they encounter the cortical actin meshwork lining the cytosolic side of the plasma membrane, and the actin molecules connected to the cell surface receptors. Virion glycoproteins bind to specific host cell receptors during an infection (Figure 1). Ultimately, the envelope and plasma membrane fuses, delivering the capsid and tegument into the cytosol [40].

Viruses regulate the morphology and dynamics of microfilaments in cells by interacting with the surface receptors of cells. Binding of HSV-1 gD to the surface receptor nectin-1 stimulates Rho GTPase signaling or induces Cdc42 signaling [41-44], which in turn alter them or phology of cortical actin [45]. KSHV interacts with the cell surface receptors ephrin A2 receptor (EphA2R) and α3β1, αVβ, αVβ5 integrins, which results in simultaneous induction of FAK, Src, PI3-K, Rho-GTPase signal and adaptor molecules that play critical roles in actin dynamics [46-49]. A dynamic actin cytoskeleton is necessary for viral entry, intracellular migration, and virion release [50-52]. When virus egress, the tegument protein VP22 of HSV-1 interacts with non-muscle myosin IIA (NMIIA), have implications for virions as they enter the extracellular environment [53-58]. Also, the KSHV gB mediates entry through association with the α3β1 integrin receptor and activates Rac1, Cdc42 and RhoA, then induces the formation of actin stress fibers and filopodia [59].

The impact on microfilaments not just happened on the surface, but also in the cytoplasm. Transport from the cell periphery to nucleusis mediated by microtubules and the molecular motor dynein. However, actin rearrangement and actin stress fibers are associated with viral spread. U$_S$3, which is a conserved alpha herpesviral serine/threonine kinase, leads to PKA-dependent S188 RhoA phosphorylation, which is one of the hallmarks of suppressed RhoA signaling, U$_S$3-mediated actin rearrangements, actin stress fiber breakdown and protrusion formation, as well as increased viral spread [60]. Actin stress fibers may also be affected by KSHV Kaposin B protein, and
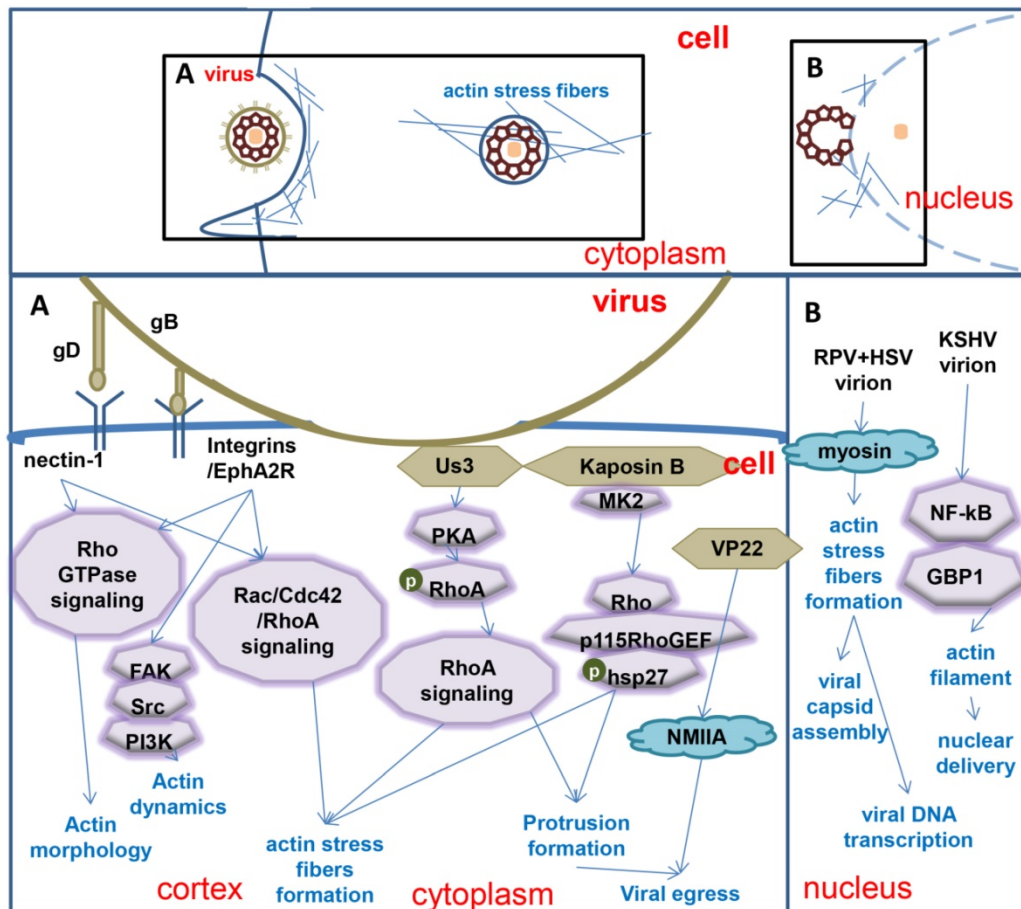
Figure 1. Model of herpesvirus entry, DNA replication and egress with the help of microfilaments. A. The activity arises in cortex and cytoplasm when a herpesvirus enters and egresses. B. The activity occurs in the nuclear periphery and inside.

KSHV Kaposin B protein can cause alterations in endothelial cell physiology, including the formation of long parallel actin stress fibers that depend on Kaposin B-mediated activation of a noncanonical signaling pathway that includes the stress-inducible kinase MK2, hsp27, p115 Rho GEF and Rho.

The activity of the virus in the nucleus is related to actin (Figure 1). The nuclear Herpesvirus capsid motility is active, directed, and uses nuclear filamentous actin to transport capsids through the nucleoplasm [27, 28]. And the movement of capsid along the actin filaments to perinuclear area may be driven (at least partly) by myosin [27, 28]. The appearance of nuclear actin filaments is associated with viral capsid assembly, and the appearance of nuclear actin filaments prior to assembly of the viral capsid is essential for the formation of viral capsid assembly sites. Transcription of the virus is also necessary for the formation of actin filaments [27]. Infection of neurons with PRV and HSV-1, which are alpha-herpesviruses, led to the formation of actin filaments in the nucleus, whereas uninfected nuclei did not contain actin filaments. The advances along actin filaments of PRV and HSV-1 viruses occurred in a myosin-dependent manner [27]. However, Jens B. Bosse found that herpesvirus nuclear capsid motility is not dependent on F-actin [61]. During infection with human cytomegalovirus (HCMV), viral DNA synthesis occurs at the periphery of replication compartments. Within the nuclear interior, and then, the assembled capsids must reach the inner nuclear membrane for translocation to the cytoplasm (nuclear egress). Actin filaments (F-actin) play an important role during the processes that facilitate movement of HCMV capsids to the inner nuclear membrane during nuclear egress. Actin is localizing along the RC periphery and between the RC periphery and the nuclear rim [62]. KSHV infection could increase both the transcription and protein levels of guanylate-binding protein 1 (GBP1) at the early stages of primary infection by activating the NF-κB pathway. However GBP1 significantly inhibited KSHV infection by inhibiting the nuclear delivery of KSHV virions through disrupting actin filament formation with its GTPase activity and dimerization [63].

Interaction between Microtubules and Virus Infection

Viruses must enter the nucleus when viruses need to copy and package their DNA. During adsorption into the nucleus, viruses avoid in the cytoplasm of viscous liquid and many organelles, as well as rely on the transport system of host cells, which is a time-saving method. Microtubules, which are one of the cytoskeletal components, play an important role in viral transport [64]. The MTOC assembled by microtubules is located beside the nucleus and is very convenient and effective for virus to enter the nucleus along microtubules. In addition, with the help of molecular motors, orientation driven transport through kinesins and dyneins, regulates the transport of microtubules, which makes MT the "highways" of microtubule transportation [65]. Viruses retrograde transport along microtubule minus ends towards microtubule-organizing center [66].

The Interaction between Microtubules and Viruses in Cytoplasm

Twenty-three capsid proteins on the surface of the virus are exposed to the cytoplasm when the virus enters the cell, or the virus is assembled. Endothelial capsid proteins such as proteins pUS3, pUL36, pUL37, ICP0, pUL14, pUL16, and pUL21 recruit dynein, dynactin, kinesin-1 and kinesin-2. The capsid proteins which are covered by coat proteins including vhs, pUL11, ICP4, ICP34.5, VP11/12, VP13/14, VP16, VP22 and pUS11, then combine with microtubule motor molecules. Viruses bind to different molecules in the cytoplasm through their own proteins that carry viruses either to the nucleus or membrane [67]. The outer HSV capsid protein, VP26, interacts with the dynein light chains RP3 and Tctex1 [68].The HSV-1 UL34 protein (a primary envelope component) interacts with the dynein intermediate chain [69]. Some outer tegument proteins, such as VP13/14, VP16, and VP22, were lost during viral entry process and did not move with capsids to the nucleus [70]. But inner tegument proteins VP1/2 and UL37 still associate with capsids as they enter into neurons, subsequently, they transport into the nucleus and then dock at the nuclear rim [70]. And inner tegument proteins promote capsid transport along microtubules by interacting with the dynein/dynactin complex [71]. HSV inner tegument proteins UL36 (VP1/2) and UL37 make the movement of capsids more efficient in vitro [71]. The interaction of the UL36p (VP1/2) with the dynein/dynactin microtubule motor complex during retroviral herpes virus pseudorabies virus (PRV) infection promotes retrograde microtubule trafficking of the PRV capsid, also plays an important role in promoting nerve invasion and pathogenesis [72, 73]. Microtubule trafficking of the viral capsid from the periphery of the cell to the nucleus is essential for viral replication. Viruses travel along the negative direction of microtubules toward the microtubule organization center near nucleus [66]. HSV-1 capsids colocalized with cytoplasmic dynein while in transit from the plasma membrane to the nucleus, so dose PRV and EBV [74-76]. HHV8

modulates microtubule dynamics via RhoA-GTP-diaphanous 2 signaling and utilizes the dynein motors to deliver its DNA to the nucleus [59].

The stability and dynamics of microtubules are regulated by virus during the transport from the edge of the host cell to the nucleus. Soluble TAT or ectopic expression of HIV-1 TAT promoted KSHV oncogene Orf-K1 induced cell proliferation, as well as microtubule formation by targeting IκBα to activate the NF-κB pathway with the mediation of miR-891a-5p to induce abnormal angiogenesis, which is a main feature of aggressive AIDS-related Kaposi's sarcoma (AIDS-KS) [77]. Herpes simplex virus particles that have entered primary human cells exploit a dynamic specialized plus end–tracking proteins (+TIP) complex, comprised of end-binding protein 1 (EB1), cytoplasmic linker protein 170 (CLIP-170), and dynactin-1(DCTN1), to initiate retrograde transport [78]. The microtubule cytoskeleton undergoes a rapid and transient increase induced by EBV replication as well [79].

The Interaction between Microtubules and Virus during Viral Egress

The virus capsids reach the cell periphery along the plus-end of the microtubule. Microtubule-mediated anterograde transport of herpes simplex virus (HSV) is crucial for the spread and transmission of the virus [80]. Kinesin-3 interacts with the viral membrane protein pUs9 during viral transport of the virus capsid in the early stages of infection with pseudorabies virus (PrV), and this interaction is attenuated when the virus reaches the neuronal axons [81]. KIF1A is a microtubule dependent kinesin-3 motor involved in axonal sorting and transport. Viral particles are co-transported with KIF1A in the axons of primary rat superior cervical ganglion neurons and overexpression or disruption of KIF1A function increases and reduces anterograde capsid transport, respectively. Us9 and KIF1A interact early during infection with the aid of additional viral protein(s) but they exhibit diminished binding at later stages when capsids typically stall in axons [81]. MT-binding protein dystonin (BPAG1) promotes trafficking of the virus from the centrosome to the cells along the positive end of the microtubule when there is a Herpes Simplex Virus 1 infection [82]. Dystonin (BPAG1) is also recruited by the capsid-binding protein pUL37 to the HSV-1 capsid to promote viral egress from the cytoplasm [83]. It has been shown that HDAC6 promotes assembly of IAV along microtubules to the plasma membrane by promoting microtubule acetylation [84]. HDAC6 in tumor cells appears to increase replication of oncolytic herpes simplex virus type 1 (oHSV) and alter the trafficking of post-entry oncolytic viral particles (OVs) from the nucleus to lysosomes [21]. The majority of HSV-containing organelles attached to the microtubules have a simple, minimal reconstitution of microtubule-mediated anterograde traffic that facilitates and complements molecular analysis of the HSV egress *in vivo* [80].

The Interaction between Intermediate Filaments and Virus during Infection

Egress from the nucleus requires herpesvirus capsids to traverse the inner nuclear membrane, an intermediate filaments meshwork composed of lamins and lamin-associated polypeptides [85]. MCMV egress from nuclear via its M50/p35 and M53/p38 proteins. M50 was inserted into the inner nuclear membrane (INM) and concentrated into distinct sites by M53. M50 then recruited cellular protein kinase C (PKC) [86-88], which phosphorylated lamins, thereby destabilizing the nuclear lamina layer [89]. The HSV-1 UL31 and UL34, M50 and M53 homologs in HSV and PRV, could bind lamin A/C in vitro, and caused lamin conformational changes in the nuclear [90-92]. PKC was also recruited to the nuclear rim depending on the presence of UL31 and UL34 [93]. Emerin, an INM protein that binds directly to lamin A/C, was also phosphorylated and delocalized during HSV infection, contributing to the egress of viral capsids from the nucleus [94].

### Cytoskeleton Components during the Late Stage of Infection

In a latent infection, the virus has a very strong relationship with the cytoskeleton. Infection of most cells by herpesviruses causes a dramatic rearrangement of actin filaments and microtubules. HSV-infected cells showed a reorganization of actin filaments and a continuous decrease of F-actin [95]. Actin stress fibers dissociate by the viral Us3 serine/threonine kinase during alpha herpesvirus infection [96-99]. In consistent with actin filaments, the microtubule cytoskeleton undergoes a rapid and transient increase induced by EBV lysis and replication [100]. BGLF4, which is an EBV-encoded kinase that phosphorylates serine residues 25 and 38 of stathmin during mitosis, contributes to alterations in cellular MT dynamics during the EBV lytic cycle in EBV-harboring NPC [101]. The EBV-encoded protein LMP1 oncogene plays an important role in microtubules. LMP1 promotes microtubule degradation through ERK-mediated down-regulation of Op18/stathmin signaling in nasopharyngeal carcinoma cell [102]. LMP1 upregulates Cdc42 kinase activity, and oncoprotein 18/stathmin (Op18/stathmin) phosphorylation promotes microtubule

polymerization during mitosis, which leads to nasopharyngeal carcinogenesis [103]. LMP1 down-regulates the expression of RASSF1A, which is a protein that stabilizes microtubules depending on the activation of intracellular signaling of NF-κB, and this downregulation may facilitate transformation of premalignant nasopharyngeal epithelial cells into cancer cells [104-107]. In addition, LMP1 interacts with FGD4 to activate Cdc42 and thereby leading to actin cytoskeleton rearrangement and increased motility of NPC cells [108-110]. EBV-encoded miRNAs [111] such as BART6-3p [112] and BART-10-3p [113] regulate microfilaments through downstream target genes.

Cytoskeletal Drugs and Small-molecular Inhibitor on Viral Infection

Intact cytoskeleton and cytoskeletal dynamic affect viral infection and viral DNA nuclear transport. Studies have shown that cytoskeletal drugs, including the microtubule- inhibiting drugs colchicine, nocodazole or paclitaxel, and the anti-actin filament drug cytochalasin D, do not alter the redistribution, or the abundance of viral proteins or replication complexes increases or decreases, i.e., does not affect viral replication in the cells during viral replication [114]. However, Latrunculin A, which a F-actin-inhibiting drug, stalled nuclear capsids and induced actin rods to form in the nucleus. Immobile capsids accumulated around actin rods, and capsid motility stopped because latrunculin-induced actin rods nonspecifically bind nuclear capsids [61]. Viral particles are colocalized with microtubules and dynein proteins *in vivo*. The DNA trafficking was reduced by an inhibitor of the dynein motor and overexpression of dynamitin [115-123]. The co-localization of the microtubules and the viral capsid can also be disrupted by the microtubule drug nocodazole [59]. Nocodazole induces the expression of virus proteins, in addition to disrupting the co-localization of the microtubules and the viral capsid. Microtubule drugs affect the interaction of microtubules and viruses. Treatment with nocodazole, which provokes the depolymerization of microtubules, induces the expression of two EBV lytic cycle proteins, Zta and EA-D, which was mediated by transcriptional upregulation via protein kinase C (PKC).In experiments with the microtubule destabilizing drug nocodazole, viral oncoprotein EBNA3C disrupted the mitotic spindle detection point [124]. Pre-treatment with inhibitors for PKC or its downstream signaling partners p38 mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) abolished the nocodazole-mediated induction of two EBV lytic cycle proteins, Zta and EA-D in EBV-positive NPC cells [125]. DNA transporting of the virus can also be affected by other drugs. Deactivation of Rho GTPases
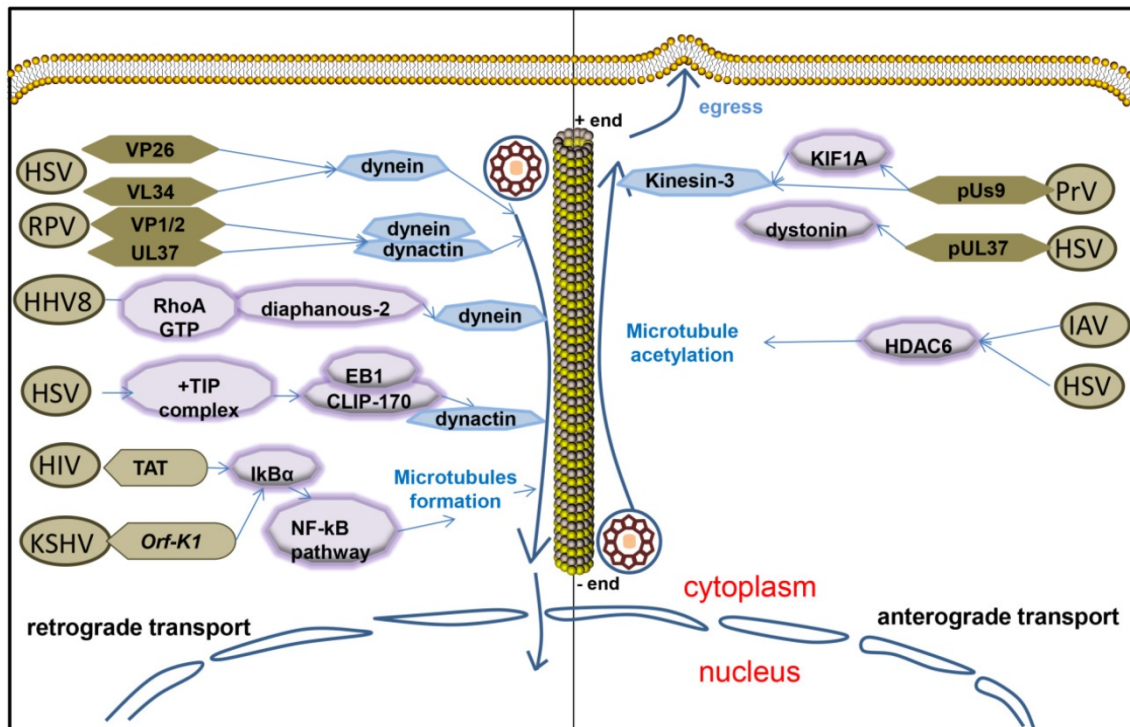
Figure 2. Microtubules interact with herpesvirus during viral infection. Herpesvirus retrograde transports along microtubule by interacting with dynein or dynein/dynactin complex when virus targets nucleus. After egresses from nucleus, herpesvirus anterograde transports along microtubule by interacting with kinesin or acetylating microtubule.

by Clostridium difficile toxin B can significantly reduce the acetylation of microtubules and inhibit the transport of viral DNA to the nucleus, whereas activation of Rho GTPases by Escherichia coli cytotoxic necrotizing factor promotes the nuclear transport of viral DNA [59]. The microtubule inhibitor podofilox can preferentially target microtubule networks in the plasma membrane. Podofilox limits an early step of virus entry at the cell surface to drastically reduce infection by herpes simplex 1, which indicates that microtubules appear to be participating in the post-binding step of virus entry including the pre- and post-penetration events [126]. Currently, there is a small-molecule that has been found to have a good effect on viruses. R10015 is a lead compound that blocks LIMK activity by binding to the ATP-binding pocket. R10015 specifically blocks viral DNA synthesis, nuclear migration, and virion release [127]. Scientists hope that this molecule will provide inspiration for further research on virus suppression.

Conclusions

Each components of the cytoskeleton plays an important role in the course of herpesvirus infection. Microfilaments interact with viral glycoproteins to mediate entry of the viruses when viruses contact the cells. Once viruses enter the cytoplasm, they travel along the minus end of the microtubule with the help of molecular motors, and then reach the microtubule organization center and nucleus at last. In the nucleus periphery, actin mediates the entry of viral DNA into the nucleus. After the replication of the viral DNA is completed, the viral DNA exits the nucleus under the action of the intermediate filaments and proceeds along the positive end of the microtubules toward the edges of the cells. Those cytoskeleton components are not independent of virus infection, but are coordinated with each other to participate in the virus infection. The virus capsid is released into the cytoplasm after fusion of the viral membrane and the host membrane, so it interacts with actin along microtubules to target the nuclear membrane [128]. During those processes, the cytoskeleton interacts with the virus, and the virus also changes the cytoskeleton, which affects the development of some virus-related tumors. However, there are still some questions that have not been answered. For example, how do the interactions between actin and microtubule, the interactions between cytoskeleton components and motor proteins, and the interactions between motor proteins and virus proteins facilitate trafficking within the cell? Atomic force microscopy (AFM) could be used as a tool for high resolution research into the ultrastructure and mechanical properties of tumor cells [129]. Moreover, the mechanism by which the virus affects the development of tumors through the cytoskeleton also requires further exploration.

Competing Interests

The authors have declared that no competing interest exists.

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