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REVIEW

SPECIAL ISSUE: CELL BIOLOGY OF HOST–PATHOGEN INTERACTIONS

The diverse roles and dynamic rearrangement of vimentin during viral infection

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ABSTRACT

Epidemics caused by viral infections pose a significant global threat. Cytoskeletal vimentin is a major intermediate filament (IF) protein, and is involved in numerous functions, including cell signaling, epithelial–mesenchymal transition, intracellular organization and cell migration. Vimentin has important roles for the life cycle of particular viruses; it can act as a co-receptor to enable effective virus invasion and guide efficient transport of the virus to the replication site. Furthermore, vimentin has been shown to rearrange into cage-like structures that facilitate virus replication, and to recruit viral components to the location of assembly and egress. Surprisingly, vimentin can also inhibit virus entry or egress, as well as participate in host-cell defense. Although vimentin can facilitate viral infection, how this function is regulated is still poorly understood. In particular, information is lacking on its interaction sites, regulation of expression, post-translational modifications and cooperation with other host factors. This Review recapitulates the different functions of vimentin in the virus life cycle and discusses how they influence host-cell tropism, virulence of the pathogens and the consequent pathological outcomes. These insights into vimentin–virus interactions emphasize the importance of cytoskeletal functions in viral cell biology and their potential for the identification of novel antiviral targets.

KEY WORDS: Vimentin, Intermediate filaments, Virus infection, Virus binding, Virus entry, Virus trafficking, Virus replication, Virus assembly, Virus egress

Introduction

Increasingly frequent outbreaks of viral diseases have prompted active research efforts into the cell and molecular biology of different viruses. As obligate intracellular parasites, viruses hijack the host-cell machinery for invasion, replication and dissemination (Eisenreich et al., 2019). Their pathogenesis during infection is dependent on the interaction between, on one hand, specific effector molecules on the virus particles and, on the other hand, characteristic receptors and facilitating molecules on the host cell. Intermediate filaments (IFs) are a main component of the cytoskeleton, and are distinguished by their medium size (10-nm diameter), compared to actin filaments (F-actin; 7 nm) and microtubules (MTs; 24 nm) (Franke et al., 1978). IFs are classified into six types based on their sequence similarities and protein structure (reviewed in Lowery et al., 2015). Vimentin is a member of the type III IF proteins, mainly expressed in cells of mesenchymal origin (Capetanaki et al., 1983) (Box 1). Vimentin filaments serve as a scaffold for organelle anchorage, cytoskeletal interactions and mechanics, and signal transduction (reviewed in Ivaska et al., 2007, Lowery et al., 2015). There is mounting evidence from numerous reports demonstrating that vimentin filaments are important for viral infection (reviewed in Dohner and Sodeik, 2005, Foo and Chee, 2015, Denes et al., 2018, Zhang et al., 2019, Ramos et al., 2020, Wen et al., 2020). In this Review, we highlight the diverse roles and the dynamic characteristics of vimentin, and its role at each stage of infection, including virus entry, trafficking, replication, assembly and egress. We also present recent findings on how vimentin-induced processes, such as virus-related carcinogenesis, abnormal cell cycle and defense responses, may trigger a self-perpetuating disease cycle with fatal consequences. Finally, we investigate promising avenues for further research in vimentin and viral infections, and discuss their ramifications.

Vimentin in virus binding and entry

Viruses exploit specific cell surface receptors to identify and infect their target cells (Fig. 1A). However, because of the sparse distribution and low interaction affinity of specific receptors, numerous viruses bind to non-specific attachment factors or require co-receptors to allow for stepwise entry (Marsh and Helenius, 2006; Brandenburg and Zhuang, 2007). An efficient way to treat infectious diseases is to block pathogen entry, which is a critical target strategy when developing therapies to inhibit the spread of viruses (reviewed in Mazzon et al., 2019). In this section, we focus on how cell surface vimentin (CSV), a soluble form of vimentin that localizes at the cell surface (Box 1), influences the binding and entry of virus particles in the host cell.

Vimentin as a cell surface co-receptor for virus binding

CSV has been reported to act as a co-receptor that facilitates the binding and entry process of numerous viruses (Fig. 1A; Table 1). For instance, vimentin has been shown to interact with the third hypervariable region (V3 loop) of the viral protein gp120 of the human immunodeficiency virus (HIV) before the viral capsid fuses with the host membrane (Thomas et al., 1996; Weiss, 1993) (Table 2). A similar phenomenon was observed in the severe acute respiratory syndrome coronavirus (SARS-CoV) infection, which caused outbreaks of atypical pneumonia with high morbidity and mortality in 2003 (Groneberg et al., 2003; Peiris et al., 2003). CSV functions as a co-receptor for the binding of the SARS-CoV spike protein to the host receptor angiotensin-converting enzyme 2 (ACE2) (Yu et al., 2016) (Table 2). Anti-vimentin antibodies successfully blocked the uptake of SARS-CoV virus-like particles (VLPs), and its neutralization efficiency (43.4%) was surprisingly

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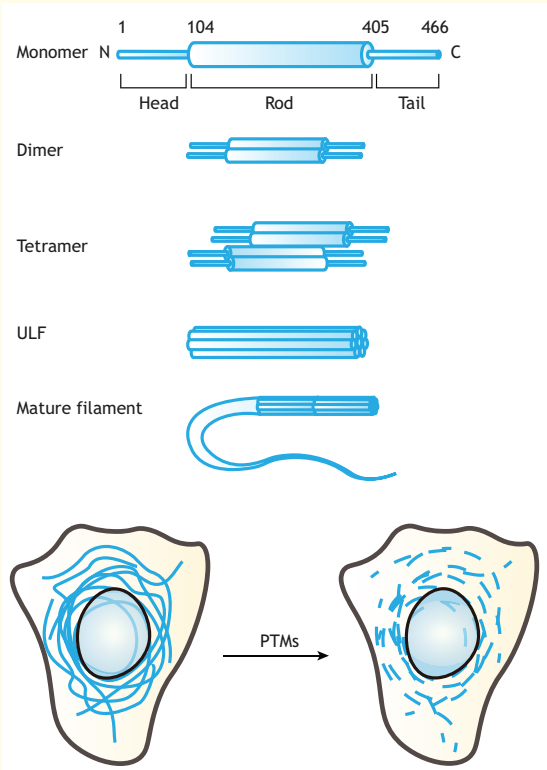
Box 1. Brief overview over vimentin and its biology

Vimentin monomers contain a nonhelical amino (N)-terminal head, a conserved central α-helical rod and a carboxy (C)-terminal tail domain; these monomers can undergo homodimerization and consequent antiparallel association between two dimers to form a soluble tetramer, which are considered as the structural units for vimentin polymerization (top portion of figure). Further lateral assembly of eight tetramers make a unit length filament (ULF), which is followed by longitudinal annealing and radial compaction to form insoluble mature vimentin filaments (reviewed in Fuchs and Weber, 1994, Lowery et al., 2015, Herrmann and Aebi, 2016). Vimentin filaments normally surround the nucleus and extend throughout the cytoplasm to provide a scaffold for cellular components (reviewed in Danielsson et al., 2018) (lower portion of figure). However, soluble forms of vimentin are found on the cell surface and in the extracellular environment; there, vimentin can act as a cellular receptor and intercellular crosstalk messenger to participate in pathophysiological processes, such as inflammation and cell senescence (Mor-Vaknin et al., 2003; Yang et al., 2016, reviewed in Danielsson et al., 2018; Ramos et al., 2020).

Vimentin is highly dynamic and rapidly responds to physiological stimuli through constant exchange between its soluble and polymerized forms, which dictates the structural and mechanical properties of cellular organelles and the cell (reviewed in Snider and Omary, 2014, Ramos et al., 2020; Perez-Sala et al., 2015). Importantly, various post-translational modifications (PTMs), mainly phosphorylation, can regulate the solubility and disassembly of vimentin filaments (Bouamrani et al., 2010, reviewed in Snider and Omary, 2014; Ramos et al., 2020) (lower portion of figure). For example, vimentin can be phosphorylated by protein kinase C (PKC), calmodulin-dependent protein kinase II (CaMKII) and Rho-associated protein kinase (ROCK; ROCK1 and ROCK2) (Geisler et al., 1989; Ando et al., 1991; Goto et al., 1998); phosphorylation then enables the involvement of vimentin in diverse biological processes, such as cytoskeletal cross-linking, intracellular organization, cell cycle and cell differentiation (Olson and Capetanaki, 1989; Robert et al., 2014, reviewed in Shi et al., 2016; Danielsson et al., 2018). Despite its importance, the regulation of vimentin is relatively poorly understood in the context of viral infection, as compared to that of filamentous actin (F-actin) and microtubules (MTs) (reviewed in Greber and Way, 2006, Radtke et al., 2006, Naghavi and Walsh, 2017, Walsh and Naghavi, 2019).



comparable with that of the anti-ACE2 antibody (51.6%) (Yu et al., 2016). CSV also binds to the nucleocapsid protein (NP) of the porcine reproductive and respiratory syndrome virus (PRRSV, also known as Betaarterivirus suid 1) to form a receptor complex with the cellular receptors heparan sulfate, sialoadhesin and vimentin, and promotes virus binding and receptor-mediated endocytosis (Neumann et al., 2005; Kim et al., 2006; Wang et al., 2011) (Table 2). CSV has also been identified to be involved in the adsorption of the flavivirus Dengue virus type 2 (DENV-2) into vascular endothelial cells, through a still partly unknown molecular mechanism (Yang et al., 2016).

Different viruses interact with CSV by binding to its distinct domains (Fig. 1C; Box 1). For example, the VP1 protein of enterovirus 71 (EV71) has been shown to interact with amino acids (aa) 1–56 of vimentin, located in its head region, to promote its binding to host cells (Du et al., 2014) (Table 2). Furthermore, the envelope protein domain III (EDIII) of DENV-2 interacts with the central rod domain of CSV (Yang et al., 2016) (Table 2). Several residues in the vimentin rod domain have been predicted to participate in this interaction based on the modeling of its 3D structure, including Asp53, Phe85, Glu82, Gly30 and His29 of DENV-2 EDIII, and Try291, Leu380, Glu288, Tyr383, Leu284 and Met391 of vimentin (Yang et al., 2016). The identification of these relevant functional residues opens up the possibility of developing molecular therapies targeting CSV. During the infection of Japanese encephalitis virus (JEV), another deadly flavivirus, the envelope proteins interact with the head and tail domains of CSV to bind to and enter the target cells (Solomon, 2004; Das et al., 2011; Liang et al., 2011) (Table 2). Hence, the lack of a conserved or shared molecular mechanism for viral entry results from the variability of the domains of vimentin to which virus binds, and might allow the binding of different viruses to vimentin.

Viral infection can also modulate the expression level of CSV. SARS-CoV VLPs and VP1 of EV71 increase the expression of CSV, which in turn will boost virus entry (Yu et al., 2016; Wang et al., 2020). In comparison, DENV-2 infection has no impact on CSV expression (Yang et al., 2016). Somewhat surprisingly, the expression levels of CSV decreased to half in PRRSV-infected MARC-145 cells when compared to uninfected cells at 48 h post infection (hpi), but were restored to the same level as in uninfected cells at 72 hpi, which indicates that the change of CSV expression may vary over the course of the infection (Kim et al., 2006). The possible reason for this is that endocytosis of PRRSV reduces the level of CSV, so that it returns to its pre-infection levels due to the recovery of cells at later stages of infection (Kim et al., 2006). These results indicate that infections with different viruses lead to specific effects on the CSV depending on the corresponding entry mechanisms, many of which still remain to be discovered.

CSV and cell tropism of viruses

Cell tropism of viruses refers to the ability of different viruses, or different strains of same virus, to efficiently infect specific cell types (McFadden et al., 2009). In addition, the dependence of viruses for CSV affects how viral particles enter the host cells. Among the family of JEVs, different strains show variable vimentin dependence. The depletion or knockdown of vimentin reduced the levels of viral particles that were able to bind to the host cell surface and subsequently produce new viral particles for RP-9 (a virulent JEV variant), although the same was not observed for RP-2 ms (a JEV attenuated variant with lower pathogenicity) (Liang et al., 2011). RP-2 ms becomes dependent on vimentin only when glycosaminoglycans (the major cell surface receptors for RP-2 ms) are blocked, indicating that there is a

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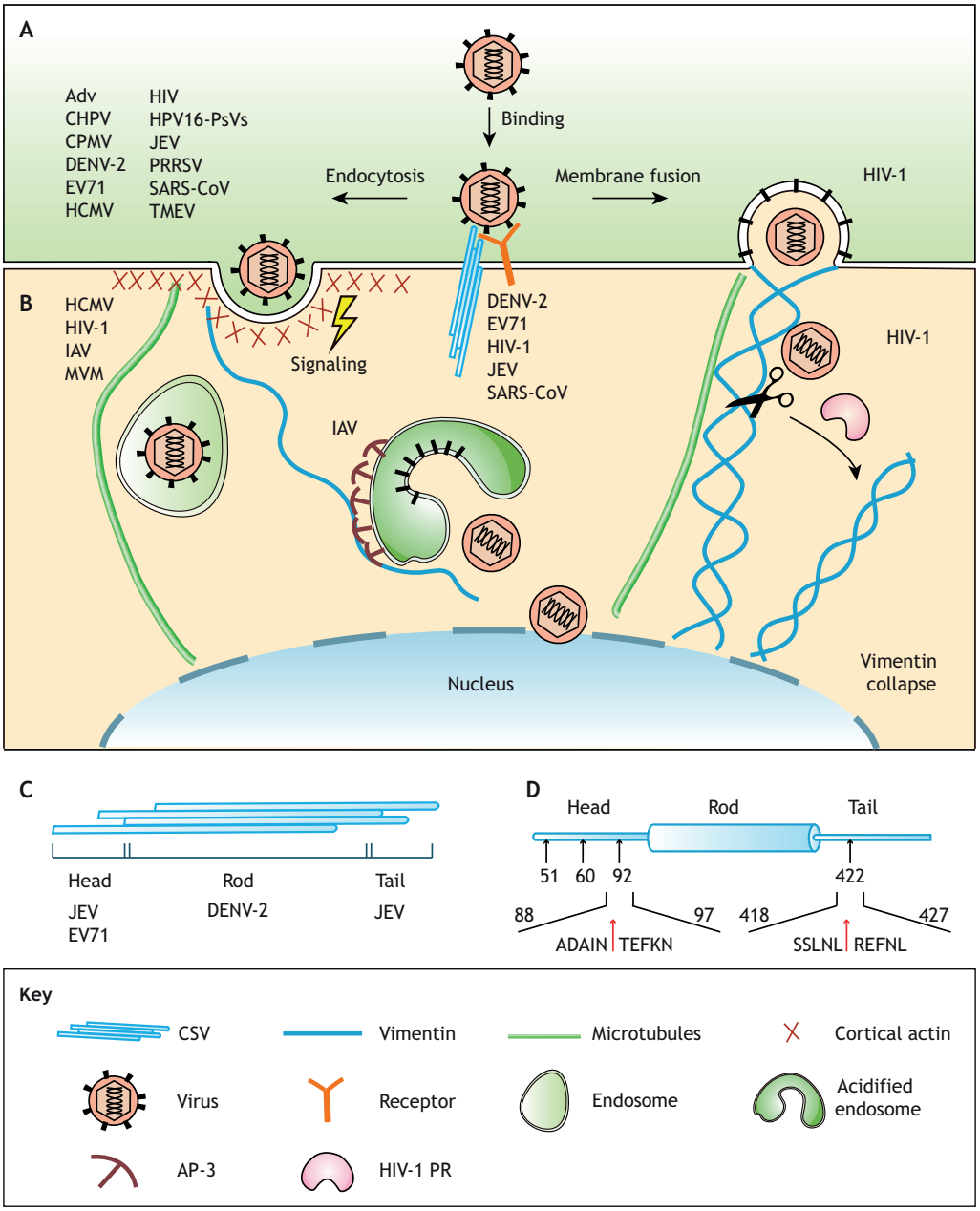

Fig. 1. Vimentin-associated early stages of virus infection – binding, entry and intracellular trafficking. (A) Stepwise entry of animal viruses. Binding is the first step in viral infection, which involves specific cell surface receptors that cooperate with attachment factors or co-receptors, such as cell surface vimentin (CSV). Then, receptor-mediated endocytosis or membrane fusion facilitate the entry of the virus. (B) Trafficking of animal viruses. Vimentin filaments may cooperate with MTs to guide virus-containing vesicles efficiently and accurately transport them to the replication site, which in the case of the HCMV, HIV-1, IAV and the MVM is the nucleus. In IAV, the AP-3 interacts with vimentin to facilitate the release of the viral genome from the acidified endosome. After HIV-1 entry, vimentin cleavage by the HIV-1 protease (PR, indicated with scissors) could induce the collapse of the vimentin network to the perinuclear area, which is presumed to allow nuclear translocation of the virus. (C) Distinct interaction domains of CSV. EV71 interacts with the N-terminus of CSV, Dengue virus type 2 (DENV-2) interacts with the rod domain of CSV, and Japanese encephalitis virus (JEV) interacts with the head and tail domains of CSV. (D) Cleavage sites of vimentin targeted by HIV-1 PR. These sites are indicated by black arrows, and the red arrows represent the specific site of the cleavage in the aa sequence. The first site is localized in the C-terminal tail domain (aa 422) and the other three secondary sites are in the N-terminal head domain (aa 51, 60 and 92). The full names of the viruses presented in the figure can be found in a footnote in Table 1.

complementary role as a co-receptor for vimentin (Su et al., 2001; Liang et al., 2011). A similar phenomenon also occurs in human cytomegalovirus (HCMV) infection; absence of vimentin impairs the onset of HCMV infection (Miller and Hertel, 2009; Roy et al., 2020). Intriguingly, in vimentin-null mouse embryonic fibroblast (MEF) cells, AD169 (a CMV strain produced in human fibroblasts with narrow cell tropism) infection was initially delayed and recovered later on, whereas for TB40/E (a CMV strain produced in endothelial cells with broad cell tropism), infection was constantly abortive (Plotkin et al., 1975; Sinzger et al., 2008; Miller and Hertel, 2009). Taken together, these results indicate that the varied dependency on vimentin might result in different tissue tropism and pathological outcomes of virus infection.

Vimentin also turns non-permissive cell lines into hosts that are susceptible to virus infection. For example, PRRSV has a highly restricted cell tropism for the African green monkey kidney cell line MA-104 and its derivatives, MARC-145 and CL-2621 (Duan et al., 1997), but delivery of recombinant simian vimentin from susceptible MARC-145 cells into insusceptible cells, such as BHK-21 (baby hamster kidney) cells and CRFK (Crandell Rees feline kidney) cells, enables a successful infection by PRRSV (Kim et al., 2006). In contrast, NP of PRRSV naturally interacts with CSV and leads to the infection of MARC-145 cells, but not BHK-21 or CRFK cells, even though all three cell lines express vimentin (Kim et al., 2006; Shi et al., 2015). In western blot assays, the bands of vimentin from these cell lines were slightly different, probably due to phosphorylation (Kim et al., 2006), suggesting that the strict cell tropism of PRRSV might be related to various post-translational modifications (PTMs) of vimentin in different cells.

In this context, it is interesting to note that plant viruses can utilize CSV to enter mammalian cells. Anti-vimentin antibodies partially blocked the binding of the plant *picornavirales* comovirus cowpea mosaic virus (CPMV) to human epithelial cells, suggesting that vimentin is involved in the internalization of CPMV in different

Table 1. Summary of viruses known to interact with vimentin at different steps of the viral life cycle

Steps in viral life cycle	Virus	Reference(s)
Entry	Adv	Belin and Boulanger 1985
	CHPV	Kavathekar et al. 2020
	CPMV	Koudelka et al. 2009, Steinmetz et al. 2011
	DENV-2	Yang et al. 2016
	EV71	Du et al. 2014
	HCMV	Miller and Hertel, 2009
	HIV	Thomas et al. 1996
	HPV16-PsVs	Schäfer et al. 2017
	JEV	Das et al. 2011, Liang et al. 2011
	PRRSV	Kim et al. 2006, Shi et al. 2015
	SARS-CoV	Yu et al. 2016
	TMEV	Nedellec et al. 1998
Intracellular trafficking	HCMV	Miller and Hertel, 2009
	HIV-1	Thomas et al. 1996
	IAV	Wu and Panté 2016
	MVM	Fay and Panté 2013
Replication	ASFV	Stefanovic et al. 2005
	Ad2 and Ad5	Defer et al. 1990
	ARV	Chiu et al. 2016
	CVB3	Matilainen 2016, Turkki et al. 2020
	DENV-2	Kanlaya et al. 2010, Lei et al. 2013, Teo and Chu 2014
	FV3	Murti et al. 1988
	FMDV	Gladue et al. 2013, Ma et al. 2020
	HBV	Huang et al. 2013
	HCV	Nitahara-Kasahara et al. 2009
	HIV-1	Fernández-Ortega et al. 2016
	IAV	Huang et al. 2019
	IBV	Emmott et al. 2010
	IBDV	Zheng et al. 2008
	PRRSV	Song et al. 2016, Chang et al. 2018
	TGEV	Zhang et al. 2015
	VV	Risco et al. 2002
	ZIKV	Pagani et al. 2017
Assembly and Egress	BTV	Bhattacharya et al. 2007
	DENV-2	Kanlaya et al. 2010
	FMDV	Gladue et al. 2013
	HIV-1	Wang et al. 2016
	TMEV	Nedellec et al. 1998

Adv, Adenovirus; ARV, Avian reovirus; ASFV, African swine fever virus; BTV, Bluetongue virus; CHPV, Chandipura virus; CPMV, Cowpea mosaic virus; CVB3, Coxsackievirus B3; DENV-2, Dengue virus type 2; EV71, Enterovirus 71; FMDV, Foot-and-mouth disease virus; FV3, Frog virus 3; HBV, Hepatitis B virus; HCMV, Human cytomegalovirus; HCV, Hepatitis C virus; HIV-1, Human immunodeficiency virus 1; HPV16-PsVs, Human papillomavirus16 pseudovirions; IAV, Influenza A virus; IBV, Coronavirus infectious bronchitis virus; IBDV, Infectious bursal disease virus; JEV, Japanese encephalitis virus; MVM, Parvovirus minute virus of mice; PRRSV, Porcine reproductive and respiratory syndrome virus; SARS-CoV, Severe acute respiratory syndrome coronavirus; TGEV, Transmissible gastroenteritis virus; TMEV, Theiler's murine encephalomyelitis virus; VV, Vaccinia virus; ZIKV, Zika virus.

species (Koudelka et al., 2009). Furthermore, the tropism of CPMV for CSV allows it to efficiently penetrate tumor cells, and thus this virus has the potential to become a biocompatible platform for cancer therapy, acting as a nanoparticle for targeted delivery (Beatty and Lewis, 2019). Theiler's murine encephalomyelitis virus (TMEV), an animal picornavirus that is structurally related to CPMV, also interacts with vimentin in order to enter animal cells (Nedellec et al., 1998; Lin et al., 2000; Koudelka et al., 2009). This similar tropism for vimentin provides new insight into the relationship between plant and animal picorna-like viruses.

Inhibition of virus entry by vimentin

Although there are numerous examples where CSV is required for virus binding and entry, it can also interfere with the internalization of viral particles. In stark contrast to what has been observed for SARS-CoV and DENV-2 (Yang et al., 2016), knocking down CSV with siRNA significantly increased the binding and internalization of human papillomavirus 16 pseudovirions (HPV16-PsVs) (Schäfer et al., 2017). Here, vimentin deters the entry of HPV16-PsVs, possibly through steric hindrance to prevent virus–receptor interaction (Schäfer et al., 2017), indicating that vimentin may exert diverse effects on virus entry, which need further elucidation.

Together, these studies have uncovered a dual role for CSV in the process of virus entry. CSV can act as a co-receptor or an attachment factor to facilitate virus binding and entry, suggesting that vimentin has the potential to be a broad-spectrum antiviral target; however, CSV can also impede virus internalization through steric hindrance. Therefore, it will be important to confirm the specific interaction sites between different viruses and vimentin. Moreover, the various PTMs of vimentin and specific viral proteins may synergistically determine the difference in cell tropism and pathology between different types of viral infection. In addition to virus entry, vimentin is also involved in virus intracellular trafficking as discussed next.

The role of vimentin in virus intracellular trafficking

After their uptake into the host cell through endocytosis or membrane fusion, viruses typically hijack the host cytoskeleton for further trafficking (reviewed in Yamauchi and Helenius, 2013) (Fig. 1B). In order to avoid being recycled back to the plasma membrane and expelled into the extracellular environment or degraded in lysosomes, viruses utilize endosome acidification to trigger the release of the viral genome at their replication sites (cytoplasmic or nuclear) (Staring et al., 2018). Numerous studies have revealed the role of vimentin in the subcellular positioning of endosomes and lysosomes (reviewed in Margiotta and Bucci, 2016), as well as the transportation of viral-containing vesicles (Miller and Hertel, 2009; Wu and Panté, 2016), as discussed below (Table 1).

Vimentin is important for the distribution and acidification of endosomes

The viral RNA and proteins of the Influenza A virus (IAV) are normally released from acidified endosomes. This RNA then associates with the nucleoprotein and polymerase to form a viral ribonucleoprotein complex (vRNP) that is transported into the cell nucleus for replication (Matsuoka et al., 2013). Depletion of vimentin leads to defects in endo-lysosomal Cl^- channels, which may be controlled by the adaptor complex 3 (AP-3; a protein complex that mediates intracellular membrane trafficking), impairing the acidification of endocytic organelles (Peden et al., 2004; Styers et al., 2004; Margiotta and Bucci, 2016; Wu and Panté, 2016). As a result, in the IAV H3N2 strain, a large amount of viral particles are trapped in late endosomes (LEs), impairing release of vRNPs into the cytoplasm or their import into the nucleus. These data indicate that vimentin promotes IAV infection by facilitating AP-3-mediated acidification of endosomes (Styers et al., 2004; Wu and Panté, 2016) (Fig. 1B).

Mislocalization of LEs owing to the lack of vimentin is also related to a low trafficking efficiency of virus-containing vesicles toward the nucleus in HCMV-infected cells (Miller and Hertel, 2009). Moreover, in vimentin-null MEF cells infected with the parvovirus minute virus of mice (MVM), the distribution of virus-containing vesicles becomes spread throughout the cytoplasm

Table 2. Summary of viral proteins that associate with vimentin during viral infection

Virus species	Viral protein	Host cell	Proposed or established role	Reference
ARV	P17	Vero cells	Regulates the cell cycle	Chiu et al. 2016
BTV	VP2	Vero cells	Contributes to virus egress	Bhattacharya et al. 2007
DENV-2	E	ECV304	Contributes to virus entry	Yang et al. 2016
	NS4A	Huh-7 cells	Regulates the construction of viral replication complexes	Teo and Chu 2014
EBV	LMP1	NPC cells	Regulates signal transduction and cell transformation	Meckes et al. 2013
EV71	VP1	U251 cells	Contributes to virus entry	Du et al. 2014
FMDV	2C	MCF-10A	Contributes to virus replication	Gladue et al. 2013
	3A	FBK cells	Negatively regulates virus replication	Ma et al. 2020
HCV	C	Huh-7 cells	Regulates the degradation of the core protein	Nitahara-Kasahara et al. 2009
HIV-1	PR	EAC cells	Cleaves vimentin and induces the collapse of vimentin into a perinuclear aggregate	Shoeman et al. 1990
		Hela cells		
Hika cells		Honer et al. 1991		
SW13 cells		Shoeman et al. 2001		
Vif	Hela cells	Induces the collapse of vimentin into a perinuclear aggregate	Karczewski and Strebel 1996	
gp120	E7C3 cells	Contributes to virus entry	Thomas et al. 1996	
IAV	vRNPs	A549 cells	Regulates vRNP translocation	Huang et al. 2019
JEV	E	BHK-21 cells	Contributes to virus entry	Liang et al. 2011
PRRSV	NP	MARC-145	Contributes to virus entry	Kim et al. 2006
NSP2	Vero cells	Contributes to virus replication	Song et al. 2016	
SARS-CoV	S	Vero E6 cells	Contributes to virus entry	Yu et al. 2016
TGEV	NP	ST cells	Contributes to virus replication	Zhang et al. 2015

ARV, avian reovirus, P17, non-structural protein p17; BTV, bluetongue virus, VP2, outer capsid protein VP2; DENV-2, dengue virus type 2, E, envelop protein, NS4A, non-structural protein 4A; EBV, Epstein–Barr virus, LMP1, latent membrane protein-1; EV71, enterovirus 71, VP1, capsid protein VP1; FMDV, foot-and-mouth disease virus, 2C, non-structural protein 2C, 3A, non-structural protein 3A; HCV, hepatitis C virus, C, core protein; HIV-1, human immunodeficiency virus 1, PR, protease, Vif, virion infectivity factor protein, gp120, envelop protein gp120; IAV, Influenza A virus, vRNPs, viral ribonucleoprotein complexes; JEV, Japanese encephalitis virus, E, envelop protein; PRRSV, porcine reproductive and respiratory syndrome virus, NP, nucleocapsid protein, NSP2, nonstructural protein 2; SARS-CoV, severe acute respiratory syndrome coronavirus, S, Spike protein; TGEV, transmissible gastroenteritis virus; NP, nucleocapsid protein. Vero cells, African green monkey kidney epithelial cells; ECV304, human urinary bladder carcinoma cells; Huh-7 cells, human hepatocellular carcinoma cells; NPC cells, neural progenitor cells; U251 cells, human glioblastoma astrocytoma cells; MCF-10A, human breast epithelial cells; FBK cells, primary fetal bovine kidney cells; EAC cells, Ehrlich ascites carcinoma; HeLa cells, Henrietta's cervical cancer cells; Hika cells, human skin fibroblasts; SW13 cells, human adrenal adenocarcinoma cells; E7C3 cells, mouse melanoma cell line K 1735-M2 stably transfected the with HPV16 E7; A549 cells, adenocarcinomic human alveolar basal epithelial cells; BHK-21 cells, baby hamster kidney fibroblasts; MARC-145, African green monkey kidney cells; ST cells, swine testicular cells.

instead of the typical perinuclear accumulation (Fay and Panté, 2013). A similar phenomenon was observed in SW13 cells transfected with pNL-A1 (a plasmid encoding all HIV-1 proteins except for *gag* and *pol* products, the core structural polyprotein and the reverse transcriptase, respectively) (Karczewski and Strebel, 1996). Without vimentin, the virion infectivity factor (Vif) of HIV-1 locates diffusely in cytoplasm, nucleus and nuclear membrane instead of in the perinuclear area (Karczewski and Strebel, 1996). These results suggest that vimentin guides the efficient transport of viruses to the replication site by ensuring the normal distribution of endosomes.

Vimentin roles in nuclear translocation

In addition to the essential role of vimentin in cellular cargo transportation, the rearrangement of vimentin filaments, triggered by viral components, also contributes to the trafficking of viral particles. For example, in mouse fibroblast cells infected with MVM, vimentin filaments rearrange and accumulate at the nuclear periphery at 2 hpi. This rearrangement occurs in MVM-infected cells, but not in cells incubated with non-infectious viral empty capsids (devoid of viral DNA), suggesting that the release of the virus from the endosomes to the cytoplasm triggers the rearrangement of vimentin (Fay and Panté, 2013). HIV-1 RNA needs to be reverse transcribed, then imported into the nucleus and integrated into the host genome for replication (Craigie and Bushman, 2012). Pretreatment with anti-vimentin serum reduced the amount of *gag* RNA from HIV-1 pseudovirions (particles that cannot replicate, but do enter the nucleus) in the nuclei of monocytes, and inhibited nuclear translocation of HIV-1 DNA in monocytes and CD4+ T cells infected with the live virus (Thomas et al., 1996). Using a single-round challenge system of HIV-1 pseudovirions, the number of cells that successfully integrate HIV genes were shown to be significantly reduced in vimentin-knockdown MT4 cells (Fernández-Ortega et al., 2016). These results indicate that vimentin is essential for HIV-1 nuclear translocation. Furthermore, viral proteins can interact with vimentin and alter the vimentin network to facilitate their nuclear translocation. Previous studies have revealed that the association of HIV-1 Vif with vimentin resulted in the collapse of vimentin filaments into a perinuclear aggregate, and chemical treatment with demecolcine (a drug that promotes the collapse of vimentin filaments towards the cell nucleus) was not able to restore the colocalization pattern (Karczewski and Strebel, 1996) (Table 2). Apart from Vif, HIV-1 protease (PR) can cleave four sites in the vimentin sequence, also inducing the collapse of vimentin filaments to a juxtanuclear localization, which facilitates nuclear translocation of HIV-1 (Shoeman et al., 1990, 2001; Honer et al., 1991) (Fig. 1D) (Table 2). Importantly, vimentin contains a protein kinase C (PKC) phosphorylation site at one of its cleavage sites (Tozser et al., 1999). The phosphorylation of vimentin by PKC prevents HIV-1 PR-mediated proteolysis within the head domain (Tozser et al., 1999). The findings discussed above suggest that the rearrangement of vimentin might promote the transfer of HIV-1 from the cell membrane to the nucleus.

A recent study found that IAV subtype H7N9 infection upregulates miR-1290, a host microRNA that targets and downregulates the expression of vimentin mRNA by binding to a specific site in the 3′ untranslated region (UTR) of the vimentin

gene; this may lead to increased levels of vRNPs in the cell nucleus and enhanced viral polymerase activity (Huang et al., 2019) (Table 2). miR-1290 is only found in human and ferret lung cells, but not in mouse or chicken cells (Huang et al., 2019), suggesting that IAV-induced downregulation of vimentin through miR-1290 is host specific. Moreover, human vimentin can interact with vRNPs through the binding of the polymerase subunit PB2 to regulate vRNP translocation (Huang et al., 2019). There are several lines of evidence showing that IAV adaptation to human cells is dependent on mutations in the three polymerase subunits (PB1, PB2 and PA), which enable efficient viral replication (Manz et al., 2013). These results indicate that the difference in infectivity and replicative ability of the same IAV between species may be related to the differential regulation of vimentin (Huang et al., 2019). In addition, disruption of vimentin expression enhanced viral replication by leading to the retention of vRNP in the nucleus of A549 cells infected with the IAV subtype H7N9, but reduced viral mRNA by interfering with the endosomal distribution in MEFs infected with subtype H3N2 (Wu and Panté, 2016; Huang et al., 2019); this suggests that the viral strain and host cell type greatly affect the function of vimentin during virus trafficking.

Hence, vimentin may control the precise transport of virus to the replication site and the timely release of the viral genome from the endosome by affecting endosome localization and acidification, which is important for efficient virus replication (Wu and Panté, 2016). Since vimentin interacts with the nuclear lamina and the host-cell DNA (Capco et al., 1982), it is tempting to speculate that vimentin increases the speed of viral genome translocation across the nuclear pore complex (Miller and Hertel, 2009). It will be interesting to address in the future how host-specific factors interact with vimentin to interfere with virus trafficking.

The role of vimentin in virus replication

After release of the virus genome at the replication site, viruses utilize the host-cell machinery to form viral factories (also known as viral inclusion or viroplasm) that ensure efficient viral replication and assembly, as well as to protect the newly assembled particles from the host defenses (reviewed in Netherton and Wileman, 2011). The formation of these viral factories is often accompanied by extensive rearrangement of the cytoskeleton and the cell membrane (reviewed in Netherton and Wileman, 2011). However, the mechanisms and function of cytoskeletal rearrangements for the assembly of these elaborate viral factories are still poorly understood.

Vimentin cages facilitate virus replication

Vimentin has been shown to facilitate efficient viral RNA replication and viral protein synthesis by concentrating around the viral factories and form cage-like structures, termed vimentin cages. (Murti et al., 1988; Defer et al., 1990; Teo and Chu, 2014) (Fig. 2A) (Table 1). Confocal microscopy analysis showed that vimentin filaments and the Golgi concentrate in viral factories, where vimentin colocalizes with the core protein p39 of the vaccinia virus (VV) (Ferreira et al., 1994; Risco et al., 2002). For the Zika virus (ZIKV), vimentin surrounds the envelope protein and the double-stranded RNA colocalizes with calreticulin and vimentin at the perinuclear viral factory region (Pagani et al., 2017). Previous studies have also found that vimentin colocalizes with the DENV nonstructural protein 1 (NS1), and the disruption of vimentin reduced the expression of NS1 and the replication of the virus (Kanlaya et al., 2010). Knocking down vimentin leads to a spread of viral factories of DENV-2 and coxsackievirus B3 (CVB3) throughout the cytoplasm, instead of them localizing at the perinuclear region; this suggests that vimentin filaments also serve as a scaffold to recruit viral components for efficient viral replication (Teo and Chu, 2014; Turkki et al., 2020). The NP of the transmissible gastroenteritis virus (TGEV) colocalizes and interacts with vimentin (Zhang et al., 2015) (Table 2). Here, vimentin knockdown significantly decreased cell-associated TGEV, which resulted in a reduction of viral replication (Zhang et al., 2015). By using a multi-round infectivity assay with the replication-competent HIV-1 BRU strain, it has been shown that vimentin knockdown significantly reduces HIV-1 capsid protein (CAp24) levels in infected MT4 cells (Fernández-Ortega et al., 2016). In addition, vimentin depletion also hinders viral RNA expression, as well as synthesis of viral matrix protein during IAV infection (Wu and Panté, 2016). Moreover, disruption of vimentin significantly reduced the viral yield of the foot-and-mouth disease virus (FMDV) and the avian reovirus (ARV) (Gladue et al., 2013; Chiu et al., 2016).

Vimentin also interacts with other host factors to bind viral proteins. For example, the B domain of annexin A2 (ANXA2), a Ca^{2+}-dependent phospholipid binding protein, interacts with vimentin, allowing its binding to the PRRSV NP, as neither vimentin nor ANXA2 can bind to PRRSV individually (Chang et al., 2018). The complex formed by vimentin, ANXA2, the viral nonstructural protein 2 (NSP2) and the NP can further promote the replication of PRRSV (Song et al., 2016; Chang et al., 2018) (Table 2).

Dynamic rearrangement of vimentin during virus replication

The rearrangement of the vimentin network is very dynamic throughout the infection process. Previous work has shown that the first 50 residues of the cytosolic N-terminal of DENV NS4A (N50) protein interact with vimentin in Huh7 cells (Teo and Chu, 2014) (Table 2). Interestingly, the strength of the vimentin–NS4A interaction constantly increased from 24 to 48 hpi, peaking at 48 hpi, before decreasing afterwards (Teo and Chu, 2014). Consistent with this, the vimentin–NS4A complex localizes close to the cell nucleus, assembling the vimentin cage-like structure at 48 hpi, which then moves further away from perinuclear region at 72 hpi (Teo and Chu, 2014). These results suggest that the vimentin–NS4A interaction induces the formation of the vimentin cage in a time-dependent manner during the infection process (Teo and Chu, 2014). Furthermore, inhibition of viral protein synthesis by cycloheximide treatment could prevent vimentin rearrangements, which suggests that these are also triggered by the synthesis of CVB3 viral proteins during its infection (Turkki et al., 2020). Blocking vimentin dynamics with β′-iminodipropionitrile (IDPN) significantly decreased the synthesis of the nonstructural proteins 2A, 3C and 3D of CVB3, which led to attenuation of the cleavage of cellular poly(A)-binding protein (PABP) and Ras GTPase-activating protein-binding protein 1 (G3BP1) (two substrates linked to promotion of apoptosis during infection) (Turkki et al., 2020). In this way, disruption of vimentin reduces caspase activation and prolongs cell survival after CVB3 infection (Rivera and Lloyd, 2008; Turkki et al., 2020). These results suggest that the dynamic rearrangement of vimentin is important for the proper function of nonstructural viral proteins.

The reorganization of vimentin is associated with its dynamic phosphorylation (Fig. 2B). DENV-2 infection induces Rho-associated protein kinase (ROCK) activation and phosphorylation of vimentin at serine 71 (Ser71), which can be blocked by treatment with the ROCK inhibitor Y-27632 (Lei et al., 2013). In addition, the time-dependent pattern of calmodulin-dependent protein kinase II

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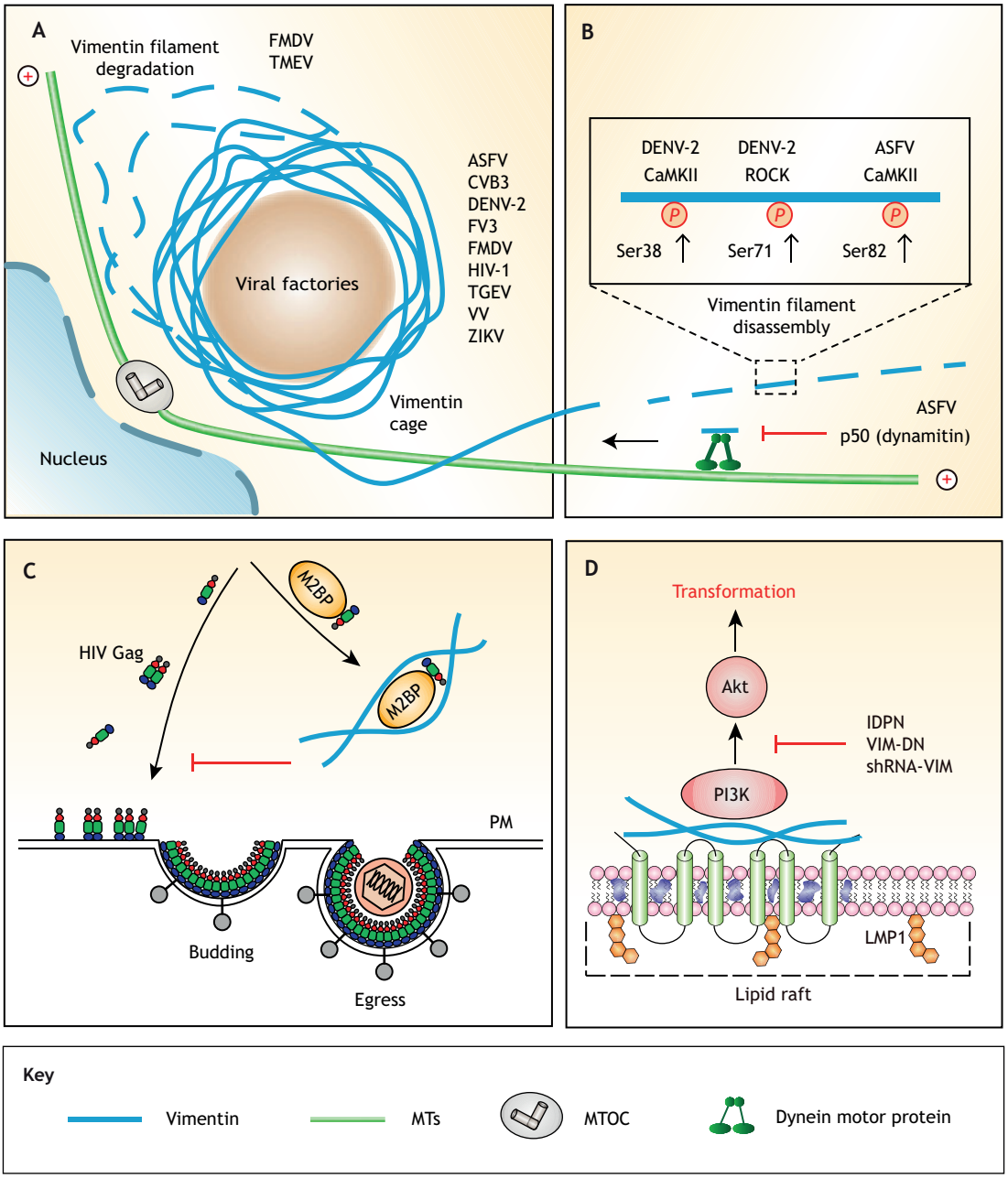

Fig. 2. Vimentin-associated late stages of virus infection – replication, assembly and egress. (A) Dynamic rearrangement of vimentin during virus replication and assembly. Vimentin filaments surround the viral factories to form a cage-like structure (vimentin cage) next to the MTOC, which ensures the efficient synthesis of the viral components. This vimentin cage can be degraded for the assembly and egress of viral components at later stages of infection. (B) Proposed model for how vimentin filaments are reorganized to the perinuclear area. DENV-2 infection could induce CaMKII activation and phosphorylation of vimentin at Ser38, as well as activation of ROCK and phosphorylation of vimentin at Ser71. ASFV infection could induce CaMKII activation and phosphorylation of vimentin at Ser82. These phosphorylation events may lead to the disassembly of vimentin filaments and their subsequent reassembly in the perinuclear area owing to their interaction with dynein (a minus-end-directed motor protein) and transport along the MTs ('plus' signs indicate the plus-end of MTs). This can be inhibited by overexpression of the dynactin subunit p50 (dynamitin), which disrupts dynein function by dissociating the dynactin complex during ASFV infection. (C) Vimentin-mediated assembly and egress of HIV-1. The appropriate transportation of the HIV-1 structural protein Gag to the PM is essential for the budding and egress of assembled HIV-1 particles. However, the host Mac-2-binding protein (M2BP) can interact with both vimentin and Gag; this may cause Gag to become trapped within the vimentin network, thereby inhibiting the production of HIV-1 virions. The gray structures indicate envelop proteins of HIV-1. (D) Contribution of vimentin to latent membrane protein 1 (LMP1)-mediated signaling and transformation. The LMP1 of the EBV can increase the amount of vimentin in lipid rafts of the PM; this results in the recruitment of the PI3K to these microdomains and the activation of its downstream target protein kinase B (Akt). Akt activation can be inhibited by the disruption of the vimentin network, for instance by treatment with the vimentin-assembly inhibitor β'-iminodipropionitrile (IDPN), use of shRNA or expression of dominant-negative vimentin (VIM-DN). The full names of the viruses shown in this figure can be found in a footnote in Table 1.

(CaMKII) phosphorylation of vimentin at Ser38 correlates with the strength of the vimentin–NS4A interaction (Teo and Chu, 2014). African swine fever virus (ASFV) DNA replication in the cytoplasm leads to the activation of CaMKII and phosphorylation of N-terminal domain of vimentin at Ser82, which can be blocked by the CaMKII inhibitor KN93 (Stefanovic et al., 2005; Netherton

and Wileman, 2013). In addition, overexpression of p50 (also known as dynamitin or DCTN2) inhibits dynein-dependent transport and blocks the recruitment of vimentin to the microtubule-organizing center (MTOC) during ASFV infection (Stefanovic et al., 2005) (Fig. 2B). These results indicate that the phosphorylation of specific sites could regulate vimentin disassembly and allow vimentin to be transported along MTs to locate close to the MTOC, where ASFV DNA replication and virus assembly occur (Stefanovic et al., 2005) (Fig. 2B). Moreover, the formation of a crescent-shaped vimentin cage around the nucleus is accompanied by the formation of the aggresome (an aggregation of misfolded proteins accompanied by the redistribution of vimentin filaments) in CVB3-infected A549 cells, which is dependent on MTs in the early phases of infection (Matilainen, 2016). These results indicate that the recruitment of vimentin into virus replication and assembly sites may depend on MTs, and the mechanism might be similar to what occurs during aggresome formation (Heath et al., 2001; Wileman, 2006; Netherton and Wileman, 2013).

Taken together, the dynamic rearrangement of vimentin and the formation of vimentin cages contribute to the assembly of viral factories. Vimentin cage formation might be dependent on vimentin phosphorylation; the interaction of vimentin with specific viruses induces its phosphorylation at distinct sites, which triggers the dynamic reorganization of vimentin to surround the viral factory in a MT-dependent manner, providing a scaffold to facilitate virus replication (Stefanovic et al., 2005; Lei et al., 2013; Teo and Chu, 2014) (Fig. 2A,B). However, the detailed mechanism and function of vimentin rearrangement during viral infection may vary depending on the type of viruses. Since many host factors regulate the formation of viral factories, it is critical to determine the factors that interact with vimentin in order to control the viral replication process.

The role of vimentin in the assembly and egress of viral particles

Virus assembly sites can be localized in the nucleus, the cytoplasm or the plasma membrane (PM), and need to be precisely regulated for successful virus spread (Novoa et al., 2005). Following their assembly, the egress of newly assembled viral particles is a highly dynamic process that involves the cooperation between host secretory and viral components (reviewed in Ono, 2009, Lindenbach, 2013). A defect in these processes reduces the production of infectious virions and blocks virus transmission to other host cells (reviewed in Ono, 2009).

Vimentin degradation contributes to viral assembly and release

Previous studies have shown that mature bluetongue virus (BTV) particles directly attach to vimentin filaments through their VP2 protein (aa 1–118) (Eaton and Hyatt, 1989; Bhattacharya et al., 2007) (Table 2). Acrylamide treatment significantly reduced the release of both BTV and DENV-2, which may be linked to the resulting disruption of vimentin filaments (Bhattacharya et al., 2007; Kanlaya et al., 2010). Moreover, vimentin cages induced by virus infection were found to degrade at a later stage of infection (Fig. 2A). Electron microscopy studies have revealed that TMEV particles, in a BHK-21 cell line, were wrapped in vimentin cages at 8 hpi, and this network disappears completely at 10 hpi (Nedellec et al., 1998). Consistent with this, vimentin interacts with the FMDV nonstructural protein 2C (Table 2) and forms a cage-like structure around it from 0.5 to 1.5 hpi, which is then degraded between 1.5 and 3 hpi (Gladue et al., 2013). Expression of a dominant-negative vimentin (VIM-DN) (truncated at aa residue 134, whereas the full-length vimentin has 466 aa) did not affect the formation of the vimentin cage, but blocked its degradation and reduced the FMDV titer, suggesting that the degradation of the vimentin cage contributes to virus egress (Gladue et al., 2013). A possible explanation is that the newly synthetized viral proteins need to escape from the vimentin cage to complete viral particle assembly.

Vimentin is involved in host-cell defense

To guard against viral infection, the host cell has developed various strategies to limit viral infection. Among these, the response to interferons (IFNs) and several IFN-stimulated antiviral genes is responsible for eliminating viruses, representing an early host-defense mechanism (Garcia-Sastre, 2017). Vimentin affects the transportation of the HIV-1 structural protein Gag to the PM by interacting with the Mac-2-binding protein (M2BP; an IFN-stimulated product that reduces infectivity and virion production of HIV-1) (Koths et al., 1993; Groschel et al., 2000; Wang et al., 2016) (Fig. 2C). In the absence of M2BP, the HIV-1 structural protein Gag is located at the PM, which is essential for HIV particle assembly (Adamson and Freed, 2007; Wang et al., 2016). Overexpression of M2BP alters the localization of Gag, leading to its diffused distribution in the cytoplasm; overexpression of a dominant-negative vimentin mutant, which induces the collapse of vimentin filaments, leads to the re-localization of Gag to the PM, suggesting that M2BP inhibits HIV-1 Gag trafficking to the PM in a vimentin-dependent manner (Wang et al., 2016) (Fig. 2C). Furthermore, vimentin interacts with Gag only when M2BP is present (Wang et al., 2016). Hence, these results indicate that vimentin can interact with M2BP to mediate host-cell defense during HIV-1 infection.

In conclusion, vimentin cages not only act as a scaffold to promote virus replication and assembly, but can also serve as a barrier to block virus egress. In addition, vimentin could play an antiviral role through its interaction with immune factors (Wang et al., 2016). The effect of vimentin on the release of mature viral particles will further affect the pathological outcomes of viral infection.

Vimentin regulates cell fate and progression of viral infection

Aside from interfering in the viral life cycle, vimentin is also hijacked by viral proteins to regulate various cellular processes. For example, vimentin directly binds the ARV p17 protein to regulate the cell cycle in Vero cells (Huang et al., 2015) (Table 2). ARV infection and p17 transfection upregulate the ataxia telangiectasia mutated (ATM)-checkpoint kinase (Chk)-cell division cycle 25 (Cdc25C) and Tpr–p53–p21 pathways to suppress phosphorylation of vimentin at Ser56 and Ser82, which subsequently cause cells to arrest at G2/M stage (Chiu et al., 2016, 2018). In addition, vimentin is involved in virus-related carcinogenesis. Hepatitis B virus (HBV) and hepatitis C virus (HCV) typically establish persistent infection; these viruses induce EMT in primary human hepatocytes by promoting the increase of vimentin expression, which is linked with mesenchymal characteristics and motile behavior (Ivaska, 2011; Wu et al., 2018), and ultimately causing liver cirrhosis and hepatocellular carcinoma (HCC) (Kim et al., 2003; Tsubota et al., 2010; Bose et al., 2012; Zhai et al., 2014; Navas et al., 2019). A study has shown that HBV X protein (HBx), together with vimentin, downregulates the expression of the long noncoding RNA hDREH (a human ortholog RNA of Dreh, also termed lncRNA-Dreh), which inhibits HCC growth and metastasis *in vitro* and *in vivo* (Huang et al., 2013). Strikingly, in livers of HCV-infected HCC patients, the amount of vimentin in non-cancerous tissue is 10 to 100 times higher than that in cancerous tissue (Tanaka et al., 2004).

The possible reason is that higher expression of vimentin restricts HCV production through the enhancement of proteasomal degradation of the viral protein core (Nitahara-Kasahara et al., 2009) (Table 2), suggesting that vimentin expression might be a molecular mechanism underlying HCV-related carcinogenesis. Moreover, vimentin is involved in the recruitment of key signaling components into the lipid-raft microdomains of the PM that are induced by the latent membrane protein 1 (LMP1) of the Epstein–Barr virus (EBV) (Meckes et al., 2013) (Fig. 2D) (Table 2). LMP1 can increase the levels of vimentin, phosphatidylinositol 3-kinase (PI3K) and its downstream target protein kinase B (Akt family) in lipid rafts, which mediate the transformation and immortalization of the cell (Mainou et al., 2005; Meckes et al., 2013) (Fig. 2D). Disruption of vimentin with IDPN, shRNA or VIM-DN, inhibited LMP1-mediated activation of mitogen-activated protein kinase (MAPK) and the PI3K–Akt pathways (both involved in cell transformation of rodent fibroblasts by LMP1), suggesting that vimentin contributes to LMP1-mediated signaling and cell transformation (Meckes et al., 2013) (Fig. 2D). These results indicate that the dynamic changes in vimentin expression and related signaling pathways could determine cell fate and the progression of diseases caused by viral infections.

Conclusions and future perspectives

Collectively, the studies discussed in this Review suggest that the vimentin network can participate in different steps of the viral life cycle (Table 1), demonstrating that some viruses use similar mechanisms to invade into, traffic through, replicate within and egress from the host cells. Nevertheless, different viruses interact with vimentin through their unique interaction sites (Table 2), allowing for dynamic modifications that are required to complete their own life cycle, which have not yet been fully discovered. Although the vimentin sequence is highly conserved between different species, changes in only a few amino acids could lead to a drastic difference in the ability of a virus to bind to vimentin (Kim et al., 2006), which may account for the strict cell tropism seen in viruses. Therefore, it will be important to understand the full range of viruses that are dependent on vimentin for their infection and dissect their interaction domains, as this might help to exploit new broad antiviral targets.

There are many host factors that coordinate vimentin–virus interactions and regulate viral infection, such as key proteins of the trafficking machinery of vesicular membranes (Wu and Panté, 2016), cytoskeletal elements (Stefanovic et al., 2005), signaling proteins (Meckes et al., 2013), immune factors (Wang et al., 2016), microRNAs (Huang et al., 2019) and lncRNAs (Huang et al., 2013). This may explain why vimentin has such diverse functions during viral infection. Other host cytoskeleton networks, such as F-actin and MTs, can also be affected by viral infections. For instance, many viruses modulate the cortical actin meshwork to enter or egress from target cells (Delorme-Axford and Coyne, 2011; Taylor et al., 2011), or also utilize MTs to translocate throughout the cytoplasm (Niehl et al., 2013; Naghavi and Walsh, 2017) (Fig. 1B). It will be interesting to study how the vimentin network intersects with F-actin and MTs, as well as other IF networks, to regulate viral infection. Furthermore, studying host-specific regulators and their interaction with vimentin will help in the understanding of virus–host coevolution and the different pathological outcomes across species.

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Competing interests

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