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Review

Emerging roles of extracellular vesicles in mediating RNA virus infection

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ABSTRACT

The sudden outbreak of COVID-19 has once again shrouded people in the enormous threat of RNA virus. Extracellular vesicles (EVs), eukaryotic cells-derived small bi-layer vesicles mainly consisting of exosomes and microvesicles, share many properties with RNA viruses including structure, size, generation, and uptake. Emerging evidence has implicated the involvement of EVs in the pathogenesis of infectious diseases induced by RNA viruses. EVs can transfer viral receptors (e.g., ACE2 and CD9) to recipient cells to facilitate viral infection, directly transport infectious viral particles to adjacent cells for virus spreading, and mask viruses with a host structure to escape immune surveillance. Here, we examine the current status of EVs to summarize their roles in mediating RNA virus infection, together with a comprehensive discussion of the underlying mechanisms.

1. Introduction

The sudden outbreak of severe acute respiratory syndrome coronavirus 2- (SARS-CoV-2) infected disease (COVID-19), once again, warns us of the astonishing destructive power of RNA viruses [1]. RNA viruses are a complex group of viruses whose genome consists of RNA [2]. RNA viruses, such as Retroviridae, Coronaviridae, Flaviviridae, and Orthomyxoviridae, are characterized by the outstanding evolutionary capacity, high mutation rates, large population sizes, fast replication ability, frequent recombination, and strong potential of host shifts [3]. With these features, RNA viruses pose significant economic and health costs to humans, animals, plants, and our ecosystems [4]. For example, since the 21st century, there have been three global outbreaks caused by coronaviruses, including the severe acute respiratory syndrome (SARS) that broke out in 2003, the Middle East respiratory syndrome (MERS) in 2012, and COVID-19. The importance of understanding the infection process of RNA viruses and the underlying mechanisms in the design and development of efficient therapeutic strategies for infectious diseases has found wide acceptance from general public to academic community.

In recent decades, extracellular vesicles (EVs) have emerged as a novel intercellular communicator which is strongly associated with various pathological processes [5–7]. EVs are small bi-layer-enclosed vesicles (50 nm-4 μm) that are released from virtually all types of eukaryotic cells [5]. EVs achieve their function through horizontally transferring their bioactive cargos from cell to cell in homeostatic conditions [8]. Growing evidence has implicated the involvement of EVs in viral infection via mediating viral spreading, modulating immunity, and manipulating microenvironment [9]. In this review, we summarize current knowledge in EV biogenesis, composition, function, and provide a comprehensive discussion for the roles of EVs in mediating the infection of RNA virus, especially SARS-CoV-2, together with the underlying mechanisms.

2. EVs

EVs were firstly reported in 1983 by two independent groups [10,11]. Emerging evidence has implicated the production of EVs as a universal cellular process. EVs can be observed in cell culture medium and in all tested biological fluids including blood, sputum, bronchoalveolar lavage fluid (BALF), urine, cerebral spinal fluid, breast milk, and ascites [5]. With comprehensive investigations in recent decades, the biogenesis, composition, and functions of EVs have begun to be understood.

2.1. The biogenesis of EVs

Based on their distinct generation processes, EVs can be divided into various sub-groups [5]. Among all sub-groups, exosomes and microvesicles (MVs) are the two that have gained most attention (Fig. 1) [5]. Exosomes are the smallest type of EVs (50–150 nm) whose biogenesis

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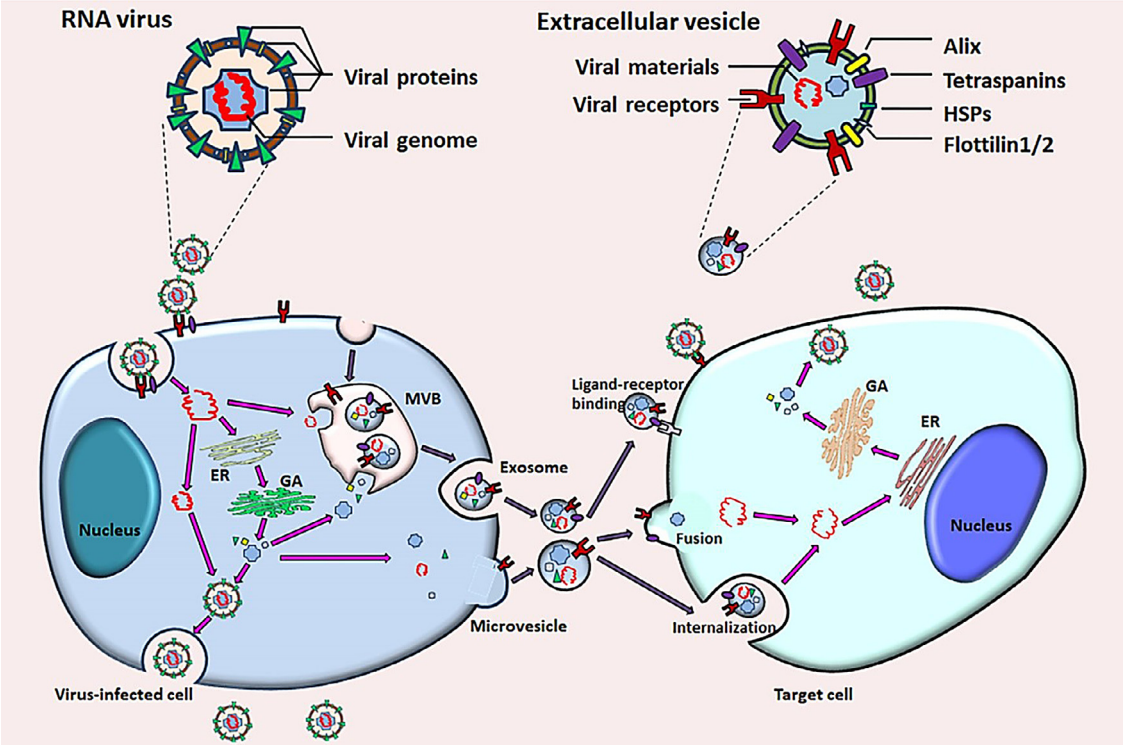

Fig. 1. Biogenesis of EVs in virus-infected cells and EV-mediated viral transmission. Viruses generally enter host cells by either direct fusion or endocytosis. After entry, viruses release their genomes for viral protein synthesis. In virus-infected cells, the biogenesis of exosomes originates from the formation and maturation of MVBs. ILVs within MVBs are released into extracellular milieu, and those released ILVs are referred to as exosomes. MVs are generated via the direct outward budding of the plasma membrane. During EV (exosome/MV) generation process, viral genomes and translated viral products can be sorted into EVs and released into intercellular space. EVs reach their target cells via three different ways: endocytosis-mediated internalization, direct-fusion of membrane, and ligand-receptor interaction. Those EVs can transfer viral receptors to recipient cells to make the latter more susceptible to infection and deliver viral materials to their targets to facilitate viral transmission. EV: Extracellular vesicle; MVB: Multivesicular body; ER: Endoplasmic reticulum; GA: Golgi apparatus; ILV: Intraluminal vesicle; MV: Microvesicle.

initiates from early endosomes (EE) [12]. EEs mature into multivesicular bodies (MVBs) that generate intraluminal vesicles (ILVs) through inward budding of cell membrane. MVBs then fuse with plasma membrane to release ILVs into extracellular milieu. These released ILVs are referred to as exosomes. Therefore, exosomes are enriched with endosomal molecules, including tetraspanins (CD9, CD63, CD81, and CD82), heat shock proteins (Hsc70, and Hsp90), ALG-2-interacting protein X (Alix), tumor susceptibility gene 101 (Tsg101), and major histocompatibility complex (MHC) classes I and II, that can be used as exosome markers [5]. MVs, whose diameters are 100–2000 nm, are generated through direct outward budding from the plasma membrane [5]. Thus, MVs can be validated by plasma membrane components like selectins, integrins, CD40 ligand, flotillin-2, and adenosine diphosphate ribosylation factor 6 (ARF6). Interestingly, unlike exosomes that are generally secreted in a continuous manner, some reports claimed that MVs may be released under stimulation [13]. Besides exosomes and MVs, there are other types of EVs such as apoptotic bodies and extracellular mitochondrial particles (mito-particles) [5,14]. Apoptotic bodies are only formed via plasma membrane-blebbing during the systematic breakdown of cells undergoing apoptosis. Moreover, mito-particles are a unique type of EVs that transfer entire functional mitochondria among cells [15]. Dislike exosomes and MVs, these EVs are either generated in specific conditions or in lack of information for their biogenesis and function. Therefore, they are not included in this review.

2.2. *The contents and their packing mechanisms of EVs*

Basically, EVs contain various types of functionally relevant biomolecules including proteins & peptides (e.g., endosome-associated proteins, membrane proteins, lipid raft proteins, etc.), nucleic acids (e.g., DNA, mRNA, and non-coding RNA), and lipids [5]. The contents of EVs are significantly influenced by the generation mechanisms, the cellular origins, and the pathophysiological states of parent cells. As we discussed above, MVs and exosomes contain different types of membrane proteins due to distinct biosynthetic pathways [5]. Furthermore, EVs inherit many cell type-specific molecules from their parent cells. For example, neural-derived EVs (NDEVs) specifically express L1CAM neural adhesion protein which can be used to isolate NDEVs from plasma via immunoabsorption-based strategy [16]. Similarly, EVs derived from different types of lung cells can be also separated by the surface proteins, such as caveolin-1 for lung epithelial cells and Ly-6 G/Ly-6C for macrophages [17]. Besides, EV cargos can change along with the transition of parent cell phenotypes. Post lipopolysaccharide (LPS) stimulation, EVs derived from microglia and macrophages contain higher levels of pro-inflammatory factors including Tissue necrosis factor-alpha (TNF-α) and miR-23/146 [18,19]. Therefore, the profiles of EVs contents change in a dynamic manner, which significantly influences the biological function of EVs.

Mounting studies have demonstrated that EVs utilize complex mechanisms to load their cargos. It was thought previously that bioactive molecules in the cytosol are passively encapsulated in the generation process of EVs. However, this hypothesis has been challenged since the high-throughput analyses suggested distinct protein and nucleic acid profiles of EVs, compared with that of their parent cells [20]. Recent research reported that the cargo loading of EVs also requires active machineries. For instance, proteins can be sorted into exosomes via both endosomal sorting complexes required for transport (ESCRT)-dependent and independent mechanisms [21]. ESCRT-related molecules syndecans and syntenin interact with LYPX9(n)L motif-containing proteins such as CD63 and Alix [22]. These proteins are sorted toward

Table 1
The involvement of virus infected cell-derived EVs in viral infection.

Virus	Loading molecules	Pro-/Anti-viral	Detailed function	References
HIV	CCR5	Pro-viral	Viral receptor	[41]
	CXCR4	Pro-viral	Viral receptor	[42]
	Tim4	Pro-viral	Receptor for viral PtdSer	[43]
	CD4	Anti-viral	Viral receptor for gp120	[45]
	Nef	Pro-viral	T cell apoptotic inducer	[48]
	TAR miRNA	Pro-viral	Viral promoter activator	[49]
HTLV1	Tax-mRNA	Pro-viral	Pro-inflammatory cytokine production inducer	[51]
SARS-CoV-2	ACE2	Pro-viral	Viral receptor	[57]
MER-CoV	CD9	Pro-viral	S protein cleavage	[58]
SARS-CoV	Spike protein	Pro-viral	Viral production	[60]
HCV	Envelope proteins and viral RNA	Pro-viral	Viral transmission	[72]
	Ago2-miR122-HSP90	Pro-viral	Viral production	[74]
IAV	CD9, CD81, ICAM1, annexin A3	Pro-viral	Viral evasion and spreading	[77]
	miR-17–5p	Pro-viral	Anti-viral Mx1 inhibition	[81]
	Cytokines, COMMD Proteins	Anti-viral	Immune response inducer	[82]
HAV	Viral RNA	Pro-viral	Viral production	[84]
EV71	miR-146a	Pro-viral	Interferon response inhibition	[85]
EBOV	Viral RNA	Pro-viral	Viral production	[86]
	TLRs, RLRs	Pro-viral	Viral receptor	[87]

MVBs when ESCRT-mediated vesicular budding takes place. The ESCRT-independent sorting involves tetraspanins and lipid raft that bind to CD10, premelanosome protein (PMEL), Epstein Barr virus (EBV) protein, the latent membrane protein 1 (LMP1), MHC class II proteins, and many other proteins to load these molecules into exosomes [23–26]. Additionally, the sorting of RNAs into exosomes can be mediated by various RNA-binding proteins including hnRNPA2B1, SYNCRIP, and Ago2 that recognize specific RNA motifs [27–29].

2.3. The functions of EVs

After being released into the extracellular space, EVs can fuse with the plasma membrane of target cells, be internalized by recipient cells via endocytosis or phagocytosis, or bind to target cells through ligand/receptor interactions [5,30]. These vesicles then modulate the biological processes of recipient cells by either transferring functional biomolecules or regulating the activities of membrane receptors and their downstream signal cascades [5,8,30]. Since MVs and exosomes are often released concomitantly, exhibit similar morphological features, and share membrane markers, it is sometimes difficult to discriminate the roles of these two sub-groups of EVs [31]. Therefore, the functions of MVs and exosomes are often examined as a whole.

The complex contents of EVs determine their diverse biological functions. To date, the roles of EVs in various physiological (e.g., embryo development [32], adult neurogenesis [33], hematopoiesis [34]) and pathological (e.g., cancer [6], neurological disorders [5], renal disease [35], metabolic disease [7]) processes have been systematically summarized. All these works demonstrate the importance to carefully look into the involvement of EVs in RNA virus infection, a key academic and clinical issue, especially in the COVID-19 crisis [36,37].

3. EVs and RNA virus infection

With the expansion of our understanding of exosomes, more and more attention has been paid to the role of exosomes in various physiological and pathological processes, especially in viral infection. Here, we summarize the positive/negative roles of EVs in the infection of various RNA virus (Table 1).

3.1. Retroviridae

Retroviruses are a group of double-stranded RNA viruses having the capacity to integrate into host genome [38]. Among all members of *Retroviridae* family, human immunodeficiency virus (HIV) is the most famous one. We have demonstrated that the infection of HIV significantly accelerates the releasing rate of EVs from parent cells, especially immune responsible cells like macrophages and microglia [39]. More importantly, HIV propagation and release in human cells can be suppressed by blocking exosome secretion using neutral sphingomyelinase-2 (nSMase2) inhibitor GW4869 [40], further suggesting the involvement of EVs in HIV infection. Currently, two main mechanisms for EV-mediated HIV infection have been revealed.

First, EVs regulate virus entry into cells by expressing viral receptors. On one hand, EVs transfer viral receptors to recipient cells and make the latter more susceptible to infection. EVs can transfer CCR5, a chemokine receptor that is central to the transmission and propagation of HIV, from CCR5-expressing cells (e.g., ovary cells and peripheral blood mononuclear cells, etc.) to CCR5-null ones [41]. Similarly, EVs derived from platelet and megakaryocyte deliver HIV co-receptors CXCR4 to CXCR4-null cells to facilitate HIV infection [42]. Moreover, EVs isolated from human breast milk and plasma may enhance HIV entry into immune cells via transferring T cell immunoglobulin and mucin protein 4 (TIM4), a receptor for phosphatidylserine (PtdSer) on virus envelope [43]. It is also possible that HIV may bind to EVs and get internalized into target cells together with EVs. This premise is validated by blocking exosomal proteins tetraspanins via specific antibodies, which abrogates the positive effects of EVs on HIV entry into target cells [44]. On the other hand, EVs with HIV receptor may also hinder the interaction between virus and cells. de Carvalho found that $CD4^+$ *T* cells secrete EVs that contain HIV receptor CD4. GP120 on the HIV envelope can bind with these $CD4^+$ EVs, rescuing more T cells from infection [45]. The ectopic expression of Nef, a HIV accessory protein, results in the reduction of CD4 expression on EVs, which promotes HIV infection. Although these observations were obtained in vitro, the same situation may also take place *in vivo*.

Second, EVs can directly transfer viral materials to target cells to accelerate HIV infection. Ali et al. detected Nef protein in EVs derived from Jurkat cells, a cell line of T-lymphocyte, suggesting Nef can be selectively loaded into EVs [46,47]. Nef in EVs further activate latent HIV in infected $CD4^+$ *T* lymphocytes, implying a novel mechanism for HIV reactivation in latent reservoirs [48]. Additionally, EVs also enhance virus production via delivering viral nucleic acids to target cells. Exosomes derived from HIV-infected T cells contain a large number of viral microRNAs (miRNAs) including trans-activation response element (TAR) miRNA [49]. TAR contains hairpin dynamic structure that enhances trans-activation of the viral promoter, up-regulates viral RNA

production, and induces virus replication. Exosomal TAR miRNAs confer a protective phenotype to recipient cells under stress conditions by down-regulating Bim and Cdk9 expression, thus, in turn, sustains the virus generation [50].

Importantly, these aforementioned roles of EVs are not only for the infection of HIV, but also for that of other retroviruses. For example, viral Tax-mRNA can be selectively sorted into exosomes released from cells infected with Human T cell lymphotropic virus type 1 (HTLV-1) [51]. These studies suggest that EVs may be widely involved in retrovirus replication and infection, which needs to be addressed in future investigations.

3.2. Coronaviridae

Coronaviruses are a family of viruses enveloping positive-strand RNAs that encode a standard set of four structural proteins: the spike (S) glycoprotein, envelope (E) glycoprotein, membrane (M) protein, and nucleocapsid (N) protein [52]. The culprit of the COVID-19 epidemic, SARS-CoV-2, belongs to this family. SARS-CoV-2 infects cells via targeting angiotensin converting enzyme 2 (ACE2) receptor, a type I integral membrane protein of renin-angiotensin systems that regulates cardiac and kidney functions [53,54]. The interaction of SARS-CoV-2 S protein with ACE2 recruits transmembrane protease serine 2 (TMPRSS2) for ACE2 cleavage, further enhancing viral entry [54,55]. The involvement of EVs in SARS-CoV-2 infection was firstly implied by the study that explored the therapeutic effects of antimalarial drugs, Chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) against COVID-19 [56]. Results suggest that the anti-viral effects of these drugs are likely via blocking exosome release, endocytosis, and phagolysosomal fusion. Current evidence indicates that EVs may facilitate the infection of SARS-CoV-2 using similar strategy to that of HIV through transferring host molecules or viral materials.

First, EVs carry host proteins that make recipient cells more susceptible to SARS-CoV-2 infection. ACE2 has been identified in exosomes and can be transferred among cells via exosomes [57]. Consequently, EVs recipient cells can be decorated with ACE2 even without ACE2 expression. Moreover, EVs may also mediate cell entry of SARS-CoV-2 through CD9, an EV-enriched tetraspanins, since CD9 and TMPRSS2 work together in cleaving the S protein of MERS coronavirus to facilitate a quick viral entry [58].

Second, EVs may promote the spreading of SARS-CoV-2 particles or components. In exosomes isolated from BALF of patients with coronavirus infection, N proteins can be detected, implying the possibility for the existence of SARS-CoV-2 particles in EVs [59]. Furthermore, S proteins of SARS coronavirus can also be loaded into exosomes by ectopically expressing these proteins intracellularly [60]. Similar mechanisms may be utilized by SARS-CoV-2 to enhance viral entry. Furthermore, SARS-CoV-2 may evade from immune recognition and enter target cells together with EVs,. This speculation requires more studies to verify in the future.

Besides, there are other pathways for viral entry that are under the regulation of EVs. For instance, both SARS-CoV-2 and EVs may utilize dynamin/caveolin-1-dependent endocytosis in the internalization process [61]. Whether or not EVs facilitate SARS-CoV-2 infection via enhancing endocytosis of target cells is an interesting question to be answered. Therefore, although our knowledge about the roles of EVs in the infection of coronaviruses in general and SARS-CoV-2 in particular remains limited, numerous studies on other types of RNA virus can guide our research to a deeper dimension to defeat the COVID-19 crisis in a near future.

3.3. Flaviviridae

Flaviviridae viruses are a group of enveloped viruses including Zika virus (ZIKV), Hepatitis C virus (HCV), dengue virus (DENV), Japanese encephalitis virus (JEV), West Nile virus (WNV), and tick-borne encephalitis virus (TBEV) that contain a single-strand RNA genome of positive polarity [62]. Initially discovered in 1947, ZIKV has been demonstrated to cross the placental barrier (PB), and ZIKV infection has been suggested to cause brain abnormalities such as microcephalic fetuses [63,64]. Upon infection with ZIKV, ZIKV infection permissive Hofbauer cells (macrophages of the placenta) are recruited and amplify ZIKV replication [65,66]. EVs derived from the activated macrophages are internalized by human trophoblast cells via an active clathrin-dependent endocytic process, leading to pro-inflammatory cytokine production by the placenta [67]. Further study suggested that ZIKV-infected macrophages-derived EVs induced NLRP3 inflammasome activation, caspase-1 hyperactivity, and interleukin-1β (IL-1β) secretion, therefore causing host innate immunity in multiple organs [68]. Besides, EVs also mediate ZIKV infection and spreading across neural cells once ZIKV reaches the central nervous system (CNS). We found that ZIKV enters astrocytes with significantly higher efficiency than other types of cells in the brain and induces the biogenesis of EVs of infected cells [40]. The inhibition of EV release by GW4869 blocks ZIKV propagation and release in human fetal astrocytes [40,69]. Similar results were reported in primary culture of murine cortical neurons, in which an increase in exosome biogenesis was recorded post ZIKV infection [70]. The expression and activity of nSMase2 were also induced by ZIKV infection. The silencing of nSMase2 or the treatment of GW4869 both reduced the exosome-mediated viral transmission rate and burden. The studies conducted by us and other groups suggest that exosomes facilitate the transmission of ZIKV although the underlying mechanisms remain to be unveiled.

Besides, EVs are involved in the infection of other *Flaviviridae* viruses. For example, HCV can be encapsulated into MVBs/exosomes in a Hrs-dependent manner and released via the exosomal secretory pathway [71]. More detailed studies confirmed the sorting of HCV envelope proteins and viral RNA into exosomes [72]. Due to the same size, density, and sedimentation characteristics between EVs and infectious HCV particles, Longatti et al. utilized Huh7 cells that contain HCV subgenomic replicon (SGR) encoding the viral nonstructural proteins [73]. In this way, they successfully demonstrated that HCV RNA can be transferred from HCV SGR to plasmacytoid dendritic cells (pDCs) by EVs, in a virion-independent manner. Furthermore, EVs can also mask HCV with a host structure to escape immune surveillance and increase infection efficiency [74]. EVs from sera of chronic HCV-infected patients transfer replication-competent viral RNAs that interact with Ago2, HSP90, and miR-122, to promote HCV reproduction.

Taken together, EVs are widely associated with the infection of *Flaviviridae* viruses highly likely through transporting viral regulatory elements and modulating innate immune responses.

3.4. Orthomyxoviridae

The family *Orthomyxoviridae* comprises the genus *Influenzavirus* which contains two species A and B and an unnamed genus that contains influenza C virus [75]. Influenza A virus (IAV) infects the nasal and tracheal airways, and then spreads throughout the upper and lower respiratory tract, causing outbreaks of acute respiratory tract infections and seasonal epidemics [75,76]. In the infection process, EVs may provide shelter for host and viral proteins and genome, facilitate IAV's escape from immune surveillance, and favor viral entry into the recipient cells [76]. High-throughput analysis has discovered that IAV integrates with exosomal proteins or markers such as annexin A3, CD9, CD81, and ICAM1, which may protect IAV and promote viral spreading [77]. Furthermore, EVs contain host molecules with positive effects on virus replication during IAV infection [78]. For instance, multiple groups reported that IAV infection significantly shifted the miRNA signatures within circulating exosomes [79,80]. Post IAV infection, EVs derived from lung epithelial cells or isolated from patients' BALF were found to be enriched with miR-17–5p that decreased the expression levels of the antiviral factor Mx1, therefore significantly enhancing IAV replication [81]. In ad-

dition, EVs released from IAV-activated macrophages also contain high levels of proteins with pro- and anti-inflammatory functions, whose effects in IAV infection remain to be further investigated [82].

3.5. Picornaviridae

Picornaviridae are small, non-enveloped, roughly spherical RNA viruses with positive-strand polarity [83]. The picornavirus family contains several human and animal pathogens including poliovirus (PV), hepatitis A virus (HAV), coxsackievirus (CV), human rhinovirus (HRV), and enterovirus 71 (EV71) [83]. In a recent study, Costafreda et al. reported that EVs derived from HAV-infected cells contain viral RNAs that can be delivered to recipient cells [84]. They further identified cholesterol transporter NPC1 and phosphatidylserine receptor HAVCR as the two key receptors that participate in EV-based viral particle delivery. In addition, Fu et al. found that the infection of EV71, a major etiologic agent of hand-foot-and-mouth disease (HFMD), resulted in enhanced EV release and selective sorting of miR-146a into EVs [85]. Those miR-146a enriched EVs mediate EV71 transmission independent of virus-specific receptor via suppressing type I interferon response in the target cells. Taken together, EVs play an important role in the infection of picornaviruses, indicating EVs as a putative target in treating diseases caused by those viruses.

It is worth-noting that besides aforementioned virus families, other RNA viruses can also utilize EVs in their replication and infection processes. For instance, Ebola virus (EBOV) in *Filoviridae* can uncoat their genomes at MVB compartments for productive infection [86]. EVs can also transfer receptors that are recognized by viruses, such as Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), among cells, that may influence virus infection [87]. These studies suggest that EVs may function as a universal mediator in RNA virus replication and infection, which inspires the research of SARS-CoV-2.

4. Conclusions

As key cell-to-cell communicators, EVs have been demonstrated to be an important regulator in the pathogenesis of various diseases [9,37,88]. Both viruses and EVs are nanosize structures that may utilize similar mechanisms in their generation and internalization [9]. To date, a great progress has been made in understanding the involvement of EVs in RNA virus infection. Generally, EVs mediate viral transmission via three main mechanisms. First, EVs carry viral receptors to make recipient cells more susceptible to viral infection. Second, EVs directly transfer infectious viral particles to accelerate viral transmission. Third, EVs act as shelters to protect viruses from degradation or recognition by immune responsible cells. Therefore, EVs have been proposed as a promising therapeutic target in blocking the infection and spreading of RNA virus. This proposal requires comprehensive investigations *in vitro* and *in vivo*, together with strict clinical studies to support its feasibility and efficacy in the future.

Abbreviations

ACE2, Angiotensin-converting enzyme 2; Alix, ALG-2-interacting protein X; ARF6, Adenosine diphosphate ribosylation factor 6; BALF, Bronchoalveolar lavage fluid; COVID-19, Coronavirus disease 2019; CNS, Central nervous system; CQ, Chloroquine; CV, Coxsackievirus; DENV, Dengue virus; E protein, Envelope glycoprotein; EBOV, Ebola virus; EBV, Epstein Barr virus; EEs, Early endosomes; ESCRT, Endosomal sorting complexes required for transport; EV71, Enterovirus 71; EVs, Extracellular vesicles; HAV, Hepatitis A virus; HCQ, Hydroxychloroquine; HCV, Hepatitis C virus; HFMD, Hand-foot-and-mouth disease; HIV, Human immunodeficiency virus; HRV, Human rhinovirus; IAV, Influenza A virus; IL-1β, Interleukin-1β; ILVs, Intraluminal vesicles; JEV, Japanese encephalitis virus; LMP1, Latent membrane protein 1; LPS, Lipopolysaccharide; M protein, Membrane protein; MERS, Middle East respiratory syndrome; MHC, Major histocompatibility complex; miRNA, MicroRNA; MVBs, Multivesicular bodies; MVs, Microvesicles; NDEVs, Neural-derived EVs; N protein, Nucleocapsid protein; nSMase2, Neutral sphingomyelinase-2; PB, Placental barrier; pDCs, Plasmacytoid dendritic cells; PMEL, Premelanosome protein; PtdSer, phosphatidylserine; PV, Poliovirus; RLRs, RIG-I-like receptors; S protein, Spike glycoprotein; SARS, Severe acute respiratory syndrome; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SGR, Subgenomic replicon; TAR, Trans-activation response element; TBEV, Tick-borne encephalitis virus; TIM4, T cell immunoglobulin and mucin protein 4 TLRs: Toll-like receptors; TMPRSS2, Transmembrane protease serine type 2; TNF-α, Tissue necrosis factor-alpha; Tsg101, Tumor susceptibility gene 101; WNV, West Nile virus; ZIKV, Zika virus

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Availability of supporting data

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Authors' contributions

JCZ and XX conceived the manuscript. XX collected references. XX and YW wrote the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interests regarding the publication of this paper.

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