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Infection, Genetics and Evolution 85 (2020) 104422

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

The role of extracellular vesicles in COVID-19 virus infection

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ARTICLE INFO

Keywords:
COVID-19 virus
Viral infection
Extracellular vesicles
Exosomes

ABSTRACT

Extracellular vesicles releasing from various types of cells contribute to intercellular communication via delivering bio-molecules like nucleic acids, proteins, and lipids to recipient cells. Exosomes are 30–120 nm extracellular vesicles that participate in several pathological conditions. Virus-infected cells release exosomes that are implicated in infection through transferring viral components such as viral-derived miRNAs and proteins. As well, exosomes contain receptors for viruses that make recipient cells susceptible to virus entry. Since December 2019, SARS-CoV-2 (COVID-19) infection has become a worldwide urgent public health concern. There is currently no vaccine or specific antiviral treatment existing for COVID-19 virus infection. Hence, it is critical to find a safe and effective therapeutic tool to patients with severe COVID-19 virus infection. Extracellular vesicles may contribute to spread this virus as they transfer such receptors as CD9 and ACE2, which make recipient cells susceptible to virus docking. Upon entry, COVID-19 virus may be directed into the exosomal pathway, and its component is packaged into exosomes for secretion. Exosome-based strategies for the treatment of COVID-19 virus infection may include following items: inhibition of exosome biogenesis and uptake, exosome-therapy, exosome-based drug delivery system, and exosome-based vaccine. Mesenchymal stem cells can suppress non-productive inflammation and improve/repair lung cells including endothelial and alveolar cells, which damaged by COVID-19 virus infection. Understanding molecular mechanisms behind extracellular vesicles related COVID-19 virus infection may provide us with an avenue to identify its entry, replication, spreading, and infection to overcome its adverse effects.

1. Introduction

Many types of eukaryotic cells release extracellular vesicles (EVs) for the cell-to-cell communication. EVs contain numerous bio-molecules like proteins, miRNAs, mRNAs, Long non-coding RNAs (long ncRNAs, lncRNA), DNA strands, lipids, and carbohydrates from parental cells, which deliver them to target calls and reprogram the fate, function, and morphology of target cells (Kowal et al., 2014; Statello et al., 2018). The secretion of EVs was initially designated as a tool for removing unwanted compounds from the cells (Pan et al., 1985). Nonetheless, we currently know that EVs are more than just waste transporters, and the significant interest in the EVs field is now

Abbreviations: Abs, Apoptotic Bodies; ACE2, Angiotensin-converting Enzyme 2; ACLF, Acute-on-chronic Liver Failure; APN, Aminopeptidase N; BAL, Bronchoalveolar lavage; COVID-19, Coronavirus Disease 2019; CMV, Cytomegalovirus; DC, Dendritic Cells; DPP4, Dipeptidyl Peptidase 4; dUTPase, deoxy-uridine triphosphatase; EBV, Epstein-Barr Virus; ECMO, Extracorporeal Membrane Oxygenation; ESCRT, Endosomal Sorting Complex Required for Transport; EVs, Extracellular Vesicles; HSV-1, Herpes Simplex Virus 1; ILVs, Intraluminal Vesicles; ISEV, International Society of Extracellular Vesicles; LIMK, LIM kinase; KSHV, Kaposi's Sarcoma-associated Herpesvirus; LMP-1, Latent Membrane Protein 1; MSCs, Mesenchymal stem cells; MVB, Multivescular Body; MVs, Microvesicles; nSMase, Neutral Sphingomyelinase; MYLK, Myosin Light Chain Kinase; PBC, Primary Biliary Cirrhosis; PBMNCs, Peripheral Blood Mononuclear Cells; PA, Phosphatidic Acid; ROCK, Rho-associated protein kinases; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; STING, Stimulator of INF Genes; TIM-1, T-cell Immunoglobulin and Mucin Domain 1; TMPRSS2, TTSP Family Members Like Transmembrane Protease Serine Type 2; TTSP, Type II Transmembrane Serine Protease

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https://doi.org/10.1016/j.meegid.2020.104422
Received 9 May 2020; Received in revised form 10 June 2020; Accepted 11 June 2020
Available online 13 June 2020
1567-1348/ Published by Elsevier B.V.

engrossed on their ability to exchange bio-molecules between cells (Kowal et al., 2014). EVs play pivotal roles in the progression of different pathological conditions (Yuana et al., 2013). For example, in infectious diseases and cancer, EVs promote pathogenesis of diseases (Fleming et al., 2014; Han et al., 2019a). EVs from infected cells contain virus particles that induce virus infection in healthy cells and modulate immune responses of the host (Fleming et al., 2014). In December 2019, a novel coronavirus infectious disease characterized by acute respiratory impairment as a result of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-2019) broke out in Wuhan city of Hubei province in China. Up to now, no treatments have been reported for COVID-19 infection. Although symptomatic and compassionate care, even with mechanical ventilation or extracorporeal membrane oxygenation (ECMO), are strongly recommended for rescue patients, however, older individuals or patients suffering from diabetes and heart disease remain to be at high risk for adverse outcomes. Understanding molecular mechanisms behind the entry, replication, spreading, and infection of coronavirus may provide us with a tool to overcome COVID-19 infection. Regarding EVs play pivotal roles in spreading and increasing the adverse effect of viruses and potential application of EVs in preventing virus infection, we aimed to review and discuss the function of EVs in coronavirus infection. In this review, we discuss EVs biogenesis and their key roles in different virus infection. Further, we focus on coronaviruses, especially on COVID-19 virus.

2. Extracellular vesicles

EVs represent an vital way of intercellular communication by serving as carriers for transfer among cells of biomolecules (Patil and Rhee, 2019). They are present in several biofluids including blood, Bronchoalveolar lavage (BAL), saliva, urine, milk, cerebrospinal, ascetic, and amniotic fluid (Kowal et al., 2014; Rezaie et al., 2019). According to guidelines of the international society of extracellular vesicles (ISEV), the term EVs encompasses three types of vesicles namely exosomes, microvesicles (MVs), and apoptotic bodies (ABs) (Théry et al., 2018b). This categorize arise based on their origin and size of diameter, therefore, each subclass of EVs represents specific physicochemical properties with pivotal roles in normal and pathological conditions. The biochemical composition of EVs from various cells is different; however, ISEV has defined guidelines for EVs isolation, characterization, and confirmation. In this section, we describe exosomes biogenesis and MVs shedding as these vesicles have pivotal roles in spreading viruses and pathological condition.

2.1. Exosomes biogenesis

Exosomes are the smallest subclass of EVs with 30–120 nm diameter originating from the endosomal pathway where inward budding of multivescular bodies (MVBs) membrane creates intraluminal vesicles (ILVs) inside MVBs. Upon fusion of MVBs with the plasma membrane, ILVs are secreted into the extracellular milieu as exosomes (Jabbari et al., 2019) (Fig. 1). Using transmission electron microscopy, exosomes seem cup-shaped particles and, however, via cryoEM appear the spherical vesicles demonstrating the real morphology of exosomes (Patil and Rhee, 2019). The term exosome (which must not be confused with the exosome complex located inside cytoplasm and is implicated in RNA degradation (Wasmuth et al., 2014) was initially used for vesicles derived from MVBs (Johnstone et al., 1987). MVBs are 400–1000 nm late endosomes containing ILVs and located at the cytoplasm. Different molecules located on the MVB's membrane participate in the inward budding of MVB's membrane and sorting of proteins into ILVs (Fig. 1). One of the protein complexes located on MVB's membrane leading to the generation of ILVs is Endosomal Sorting Complex Required for Transport (ESCRT) machinery. ESCRT-dependent machinery mediates membrane remodeling and scission in various processes like cytokinesis (Abdyazdani et al., 2017; Hurley, 2015), which consists of four complexes such as ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III and appendix molecules that segregate ubiquitylated proteins and sorts them inside ILVs. Exosomes biogenesis occur sequentially in a multistep event, initially ESCRT-0 identifies cargo, and then sorted into nascent ILVs, in following, MVB's membrane invaginated by the collaboration of ESCRT-0, I and -II, and then vesicle maturation and neck contraction mediated by ESCRT-III, and finally the vacuolar ATPase Vps4 facilitates membrane scission and ILVs formation (Kowal et al., 2014; Patil and Rhee, 2019). Some the ESCRT-machinery related molecules such as Alix (an accessory protein) and Tsg101 (a ESCRT-I component) are released within exosomes and most widely considered as exosomal markers (Hurley, 2015; Jeppesen et al., 2019). Furthermore, ESCRT-independent mechanisms have been reported to produce exosomes. For example, ceramide, a cone-shape lipid, mediates exosome biogenesis. Neutral sphingomyelinase (nSMase) catalyzes the formation of ceramide from sphingomyelin on the surface of the endosomal membrane. Then, ceramides mediate a spontaneous inward curvature on MVB's membrane, leading to the production of ILVs. Besides, tetraspanins like CD63, CD9, CD81, and also other molecules such as Tsg101 (Edgar et al., 2014; Tukmechi et al., 2014; Van Niel et al., 2011), syndecan-syntenin-ALIX complex (Friand et al., 2015; Roucourt et al., 2015), VCAM-1, and α4 integrin (Nazarenko et al., 2010; Theos et al., 2006), phosphatidic acid (PA) (Ghossoub et al., 2014) have been confirmed to play the pivotal roles in exosome loading and biogenesis. It is worth to note that ESCRT-dependent and ESCRT-independent mechanisms may synergically or alternatively act on a MVB and also various types of MVBs may be generated inside cells. Exosomes cargo is provided by components from Golgi apparatus, endocytosis, and the cytoplasm. Several processes including ESCRT-dependent pathway, ESCRT-independent pathway, and RISC/Ago2 complex are involved in protein and miRNA sorting into exosomes. Some molecules are present on exosomes as they originally are the composition of the endosomal pathway, and some molecule may be packaged into exosomes randomly. However, the exact underlying mechanisms in exosome loading process remain still unclear. Three possible fates for MVBs inside cell have been suggested as: the secretion pathway, the degradation pathway, and the back-fusion pathway (Kowal et al., 2014; Rezaie et al., 2019) (Fig. 1). In the secretion pathway, MVBs fuse with the plasma membrane, and then ILVs release onto the extracellular milieu as exosomes. In the degradation pathway, MVBs fuse with lysosomes for hydrolyze cargo and recycling and/or inactive biomolecules. In the back-fusion pathway, MVBs/exosomes fuse with the plasma membrane for recycling some receptors and biomolecules on the plasma membrane. Intracellular trafficking of MVBs is facilitated by various types of Rab proteins that preferentially move MVBs within different pathways and participate in the fusion of MVBs with the plasma membrane in collaboration with SNARE proteins. (See Fig. 2.)

2.2. Microvesicles biogenesis

MVs, shedding vesicles, budding directly from the plasma membrane, have size between 100 and 1000 nm in diameter that participate in intracellular communication (Camussi et al., 2010) (Fig. 1). The density of MVs is between 1.02 and 1.22 g/mL and they are characterized by common markers like selectins, integrins, CD40 ligand, flotillin-2, and adenosine diphosphate ribosylation factor 6 in their surface (Patil and Rhee, 2019). Many cells produce MVs transferring various biomolecules, which play the important role in physiological and pathological conditions. MVs may be released upon a stimulus, but then exosomes can constitutively be produced or following a stimulus (Muralidharan-Chari et al., 2010) and theirproduction is resembling the abscission stage in the cytokinesis process as well as the virus outward projection from the virus-infected cells (Camussi et al., 2010). The key role of Rho-associated protein kinases (ROCK) in the formation of MVs has been reported (Li et al., 2012). Li et al. reported that ROCK1 and ROCK2 activate LIM kinase (LIMK) and myosin light chain kinase

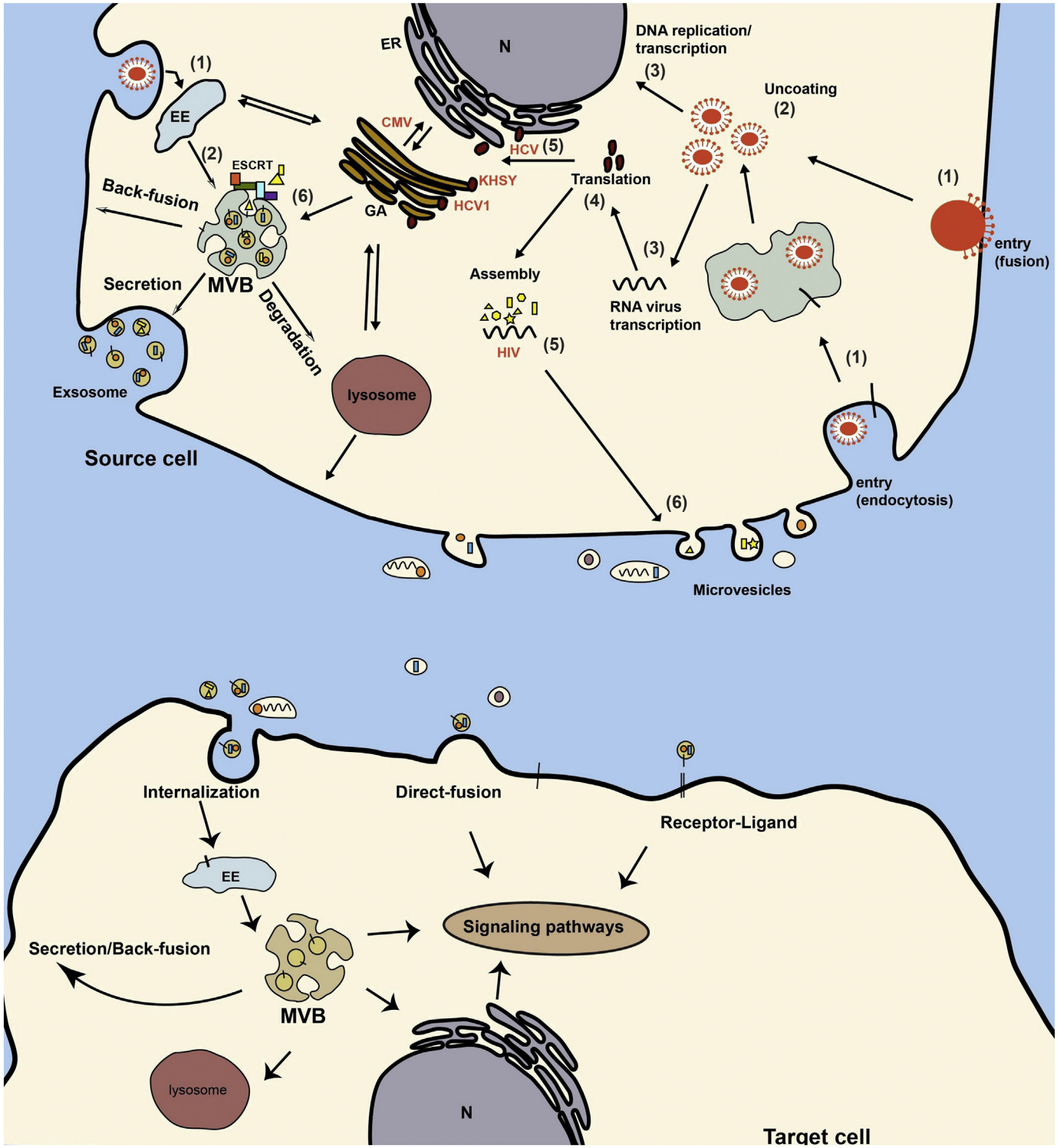

Fig. 1. Biogenesis of exosomes and microvesicles (MVs) in virus-infected cells. Exosomes originating from multivesicular bodies (MVBs) located in the cytoplasm, while MVs shedding from the plasma membrane of cells. Exosomes/MVs can reach to target cells by the three possible ways including internalization, direct-fusion, and receptor-ligand interaction. Viruses can entry onto host cells via direct fusion and endocytosis (1). After entry, viruses may be uncoated or/and sorted into MVBs/exosomes (2) and viral component can be directed into nucleus or/and translated into proteins (3). Translated products may assemble (5) or /and enter EE and GA; and finally are sorted into MVBs/exosomes (6). Alternatively, after assembly, viral components may be directed into MVs (6). CMV: Cytomegalovirus; EBV: Epstein–Barr virus; EE: early endosomes; ER: Endoplasmic Reticulum; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HSV1: Herpes simplex virus; KSHV: Kaposi's sarcoma-associated herpesvirus.

(MYLK) in the downstream pathway, which in turn phosphorylate cofilin and myosin respectively, consequently, these events promote elongation of actin filaments along the plasma membrane and induce contraction of filaments. Overall, this event induces formation of an actin complex like a ring, which is vital for the shedding of MVs from the plasma membrane (Li et al., 2012). In tumor cells, LIMK is abundantly expressed, which correlates with an increased production of MVs in these cells (Davila et al., 2003; Davila et al., 2007). MVs can change

function and fate of target cells through delivering different biomolecules to target cells.

EVs have been shown to influence target cells through three possible ways including receptor-ligand interaction, direct fusion, and internalization; even if detailed mechanisms are uncertain (Fig. 1). In the receptor-ligand interaction pathway, receptors located on the surface of the exosomes interact with ligands located on the target cells and vice versa, inducing downstream signaling pathways. EVs may bind to heparan sulphate, a proteoglycan located on the cell surface (Christianson et al., 2013), as well as lectins (Barrès et al., 2010), integrins (Hoshino et al., 2015), and even tetraspanins (Mulcahy et al., 2014). Thus, it seems that different receptors and ligands mediate different EVs-cell interaction (Morelli et al., 2004; Tian et al., 2014)In the direct fusion pathway, EVs directly fuse with the plasma membrane of recipient cells, thus, cargo directly is delivered into the cytoplasm. The miRNA and mRNA cargo of EVs must deliver to the cytoplasm to elicit its function and it seems that direct fusion pathway could represent the most rapid way to deliver exosomal cargo. Montecalvo et al. showed that miRNAs and luciferin are delivered to the cytoplasm of the recipient cell by this pathway (Montecalvo et al., 2012). The third pathway is internalization, which encompasses clathrin-dependent (Tian et al., 2014), caveolae-dependent (Verdera et al., 2017), phagocytosis (Verdera et al., 2017), and macropinocytosis (Feng et al., 2010). As EVs are heterogeneous both in size and surface composition, it is not unclear which mechanisms dominantly involved in internalization of EVs. Collectively, EVs are heterogeneous and can influence various cells by different ways, thus the delivery way of EVs cargo may be dependent on the type of EVs and recipient cell. In addition, the quantitative contribution of a pathway compared to the other pathways is not clear.

3. Extracellular vesicles and virus

EVs can transfer virus component including proteins, genomic molecules (Nolte et al., 2016), and receptors from infected cells to healthy cells that make healthy cell more susceptible to infection (Fig. 2). Table 1 summarized the viral components of EVs released from infected cells. EVs and viruses share common properties in their structure, size, generation, even in uptake. For instance, ESCRT machinery is involved in both EVs and viruses generation and both EVs and viruses use the same way to reach to the recipient cells. Besides, viral infection may affect exosomes loading mechanism of infected cells, so that proteins and nucleic acids content of EVs are changed after infection (Fig. 2). This means that infected cells release altered EVs independent of viral related content. Thus, these altered EVs may also modulate the immune response of the host, with respect to EVs released from non-infected cells. However, EVs may negatively regulate the spreading of virus infection, thereby inducing immune system responses against viruses. In this section, we discuss the key role of EVs in different virus spreading and suppressing.

3.1. HIV-1 virus

Among viruses, HIV-1 is the most common and pathogenic strain of the viruses that have been widely studied. HIV-1 encompasses two copies of noncovalently linked and positive-sense single-stranded RNA encapsulated by a conical capsid composed of lentiviruses typical protein p24 (Lu et al., 2011). EVs transfer HIV proteins to target cells and contribute in the spreading of infection by making target cells susceptible to HIV infection. For instance, HIV protein Nef is sorted into EVs (Ali et al., 2010; Raymond et al., 2011) and when these EVs delivered to latent HIV-1 cells, these cells were activated and were more vulnerable to HIV infection (Arenaccio et al., 2015). Nef has the potential to block the formation of $CD4^+$ EVs from T cells, which, in turn inhibits recognition of circulating virus by circulating CD4 (de Carvalho et al., 2014). Besides, EVs containing Nef were capable of inducing senescence or death in $CD4^+$ T lymphocytes (Arenaccio et al., 2014; Lenassi et al., 2010). EVs bearing Nef from macrophages mediated degradation of MHC-I and $CD4^+$ via beta-COP-dependent pathway in T cells,

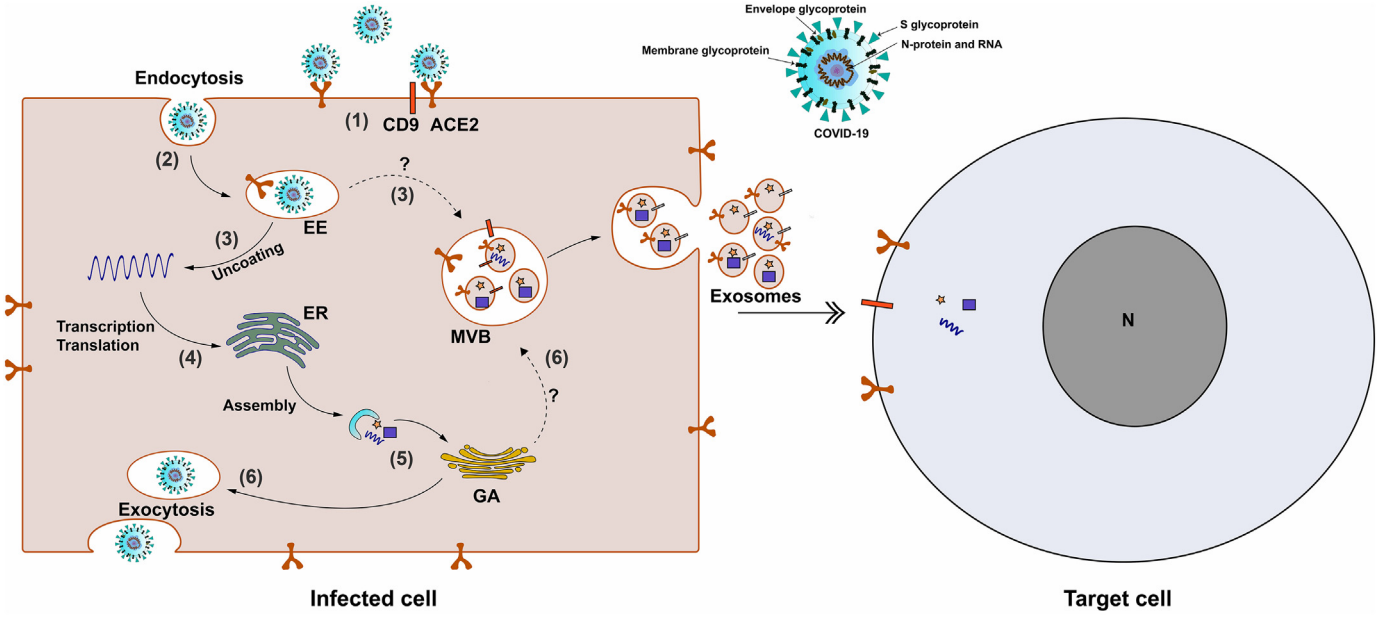

Fig. 2. The coronavirus disease 19 (COVID-19) life cycle in human lung cells. COVID-19 entry into cells when S protein binds to ACE2 receptor (1). After docking, the S protein conformation is changed, which facilitates virus entry into the endosomal pathway (2). Then, COVID-19 virus releases RNA into the cell or/and COVID-19 virus components may be directed into MVBs/exosomes (3). Virus RNA is translated into viral replicas polyproteins pp1a and 1ab, which are then cleaved into viral components by viral proteinases. Viral proteins and RNA are subsequently assembled into virions in the endoplasmic reticulum and Golgi (4 and 5) and then released out of the cell via exocytosis or directed into exosomes (6). Upon entry, COVID-19 virus may be directed into the exosomal pathway, and its component is sorted into exosomes for secretion and spreading (steps 3 and 6). Extracellular vesicles (exosomes and microvesicles) may contribute to spread this virus as they transfer such receptors as CD9 and ACE2, which make recipient cells susceptible for virus docking. ACE2, angiotensin-converting enzyme 2; EE, early endosome; ER, endoplasmic reticulum; GA, Golgi apparatus; MVB, multivesicular body; N, nucleus.

Table 1
The viral components of EVs released from infected cells.

Virus	Loading molecules	Mechanism of action	Reference
HIV-1 virus	Nef protein	Proviral	Ali et al., 2010; Raymond et al., 2011; Arenaccio et al., 2015; (de Carvalho et al., 2014; Arenaccio et al., 2014; Lenassi et al., 2010; Schaefer et al., 2008; Xu et al., 2009;
	$CCR5^+$	Proviral	Mack et al., 2000;
	CXCR4	Proviral	Rozmyslowicz et al., 2003
	TAR	Proviral	He et al., 2010; Narayanan et al., 2013.
	APOBEC3G	Antiviral	Khatua et al., 2009;
	cGAMP	Antiviral	Bridgeman et al., 2015; Gentili et al., 2015;
	miRNA-99	Antiviral	Bernard et al., 2014
	miRNA-88	Antiviral	Bernard et al., 2014
HCV	E1 protein	Proviral	Ramakrishnaiah et al., 2013; Longatti et al., 2015
	E2 protein	Proviral	Ramakrishnaiah et al., 2013; Longatti et al., 2015
	Ago2-miR122-HSP90	Proviral	Bukong et al., 2014; Wilson et al., 2011
EBV	LMP-1	Proviral	Hurwitz et al., 2017; Verweij et al., 2011; Nanbo et al., 2013; Meckes et al., 2010
	Host protein galectin-9	Proviral	Meckes et al., 2010; Klibi et al., 2009;
	HIFα	Proviral	Aga et al., 2014;
	IFI16	Proviral	Ansari et al., 2013
	dUTPase	Antiviral	Ariza et al., 2013
	miR-BHRF1-cluster	Proviral	Xia et al., 2008
	miR-BART-1 cluster	Proviral	Pegtel et al., 2010;
	miR-BART-2 cluster	Proviral	Haneklaus et al., 2012; Choi et al., 2013; Choi and Lee, 2017
	Non-coding RNAs	Proviral	Zhao et al., 2019; Ahmed et al., 2014;
KSHV[a]	Lactate dehydrogenase	Proviral	Meckes et al., 2013;
	IL-1	Proviral	Singh et al., 2013;
	IFI16	Proviral	Singh et al., 2013;
	Viral miRNAs	Antiviral	Chugh et al., 2013
	mitochondrial DNA	Antiviral	Jeon et al., 2019
HSV-1[b]	miR-H28	Antiviral	Han et al., 2016
	miR-H29	Antiviral	Han et al., 2016
	STING protein	Antiviral	Kalamvoki et al., 2014
CMV	lectin	Proviral	Plazolles et al., 2011
	DC-SIGN	Proviral	Plazolles et al., 2011
	IFI16	Antiviral	Lo Cigno et al., 2015
	Glycoprotein B	Antiviral	Walker et al., 2009
Coronavirus	CD9	Proviral	Earnest et al., 2017; Jabbari et al., 2019;
	ACE2	Proviral	Wan et al., 2020; Owczarek et al., 2018;
	Spike S protein	Proviral	Kuate et al., 2007
	SGTM	Proviral	Kuate et al., 2007

[a] Kaposi's sarcoma-associated herpesvirus.
[b] Herpes simplex virus-1.

therefore suppressed cytotoxic immune responses of T cells (Schaefer et al., 2008). In addition to T cells, Nef^+ EVs could suppress the adaptive immune response by inhibiting the production of IgA and IgG in B cells, thus promoting the evasion of the humoral immune response (Xu et al., 2009). EVs released from HIV-1 infected cells transfer viral receptors to target cells and make these cells more susceptible to infection. For instance, EVs released from $CCR5^+$ ovary cells and peripheral blood mononuclear cells (PBMNCs) transfer CCR5 to CCR5 null cells and induce HIV-1 infection (Mack et al., 2000). Similarly, EVs derived from platelet and megakaryocyte contain HIV co-receptors CXCR4 that deliver it to the CXCR4-null cell and make them susceptible for X4-HIV (Rozmyslowicz et al., 2003). These data indicate virus receptors transferred by EVs may make cells susceptible to HIV infection in vitro; however, the in vivo response of this mechanism remains unclear. EVs can transfer viral nucleic acids and participate in the spreading infection via facilitating the generation of a virus in infected cells. Narayanan et al. reported that HIV-infected cells produced EVs contain transactivation response element (TAR) RNA (Narayanan et al., 2013). TAR is a stem-loop shaped molecule that located at the 5′ tail of HIV transcripts, which, in infected cells, interact with the Tat protein and up-regulates viral RNA production. The TAR-RNA molecule may be processed into miRNAs and suppressed a Bcl-2 interacting protein, which causes resistance against apoptosis, therefore, sustains the virus production (He et al., 2010; Narayanan et al., 2013).

However, antiviral function for EVs derived from infected cells has been reported. Khatua et al. declared that EVs produced by infected cells contain APOBEC3G molecules, the host antiviral proteins. APOBEC3G, a cytidine deaminase, inhibits viral replication by altering the cytosine residues to uracil in the minus strand of the viral DNA during reverse transcription. It seems that packaging APOBEC3G within EVs is more effective because the viral protein Vif (an opposing protein) is not packaged within EVs (Khatua et al., 2009). Another antiviral soluble host factors is cGAMP that are sorted into EVs of infected cells and activates antiviral response through interferon and innate immune responses (Bridgeman et al., 2015; Gentili et al., 2015). Two HIV miRNAs namely miRNA-99 and miRNA-88 induce endosomal TLR8 and NFkB signaling pathway, which consequently induces TNFα release from bystander macrophages, and thereby recalls immune response against HIV (Bernard et al., 2014).

3.2. Hepatitis C virus

Hepatitis C virus (HCV) is an enveloped 55–65 nm particles containing positive-sense single-stranded RNA (Ferri et al., 2015). It was previously thought that this virus is accumulated inside the cytoplasm and the endoplasmic reticulum (ER), however, this virus is encapsulated into MVBs/exosomes in a Hrs-dependent manner and released via the exosomal secretory pathway (Tamai et al., 2012). Further scrutiny investigation confirmed that HCV envelope proteins E1 and E2, as well as viral RNA are sorted into exosomes (Ramakrishnaiah et al., 2013). Using cells deficient structural proteins, Longatti et al. found that exosomes from those cells, which did not express any virions could infect other cells (Longatti et al., 2015), and they conclude that at least for HCV, exosomes are the key tool for the infection in recipient cells. EV-mediated infection is more advantageous for HCV virus because EVs mask the HCV virus with a host structure, thus, avoid immune

responses and increase infection via host receptors, suitable for viral docking (Bukong et al., 2014). EVs from HCV-infected patients transfer replication element viral RNA in complex with Ago2-miR122-HSP90 that promotes HCV reproduction via interaction with the 5′UTR of HCV RNA (Bukong et al., 2014; Wilson et al., 2011).

3.3. Herpesviruses

3.3.1. Epstein-Barr virus

Herpesviruses are DNA viruses that cause infections and certain diseases in both animals and humans (Sehrawat et al., 2018). Such DNA viruses as Epstein-Barr virus (EBV) engage EVs for spreading and affect target cell function. EVs derived from EBV-infected cells contain Latent Membrane Protein 1 (LMP-1) (Flanagan et al., 2003), which mimics CD40 signaling and promotes B lymphocytes proliferation and facilitates class-switch recombination independent of T cell (Rastelli et al., 2008). CD63 molecules mediate sorting of LMP-1 within EVs and have been revealed to suppress constitutive NF-kB activation (Hurwitz et al., 2017; Verweij et al., 2011). Researches have shown that EVs bearing LMP-1 from EBV-infected cells regulate different signaling pathways. For instance, these EVs increased expression of adhesion molecules like ICAM-1 in target cells (Nanbo et al., 2013) and activated Akt and ERK signaling pathways in target cells. They also are enriched with EGFR that prompt the expression of the EGFR in healthy epithelial cells (Meckes et al., 2010). In this case, it is not surprising that activation of growth signaling pathways in target cells play the pivotal roles in tumorigenesis. Oncogenic proteins and viral miRNAs cargo of these EVs regulate the expression of genes in the surrounding tissue, which in turn, induce immune-surveillance and then inhibit immune cells and protect transformed cells in tumor environment. EBV-infected cells secrete EVs transferring host proteins, which may affect viral infectivity. EVs from EBV-infected nasopharyngeal carcinoma cells contain the host protein galectin-9 (Meckes et al., 2010) that interacts with the T-cell immunoglobulin and mucin domain 1 (TIM-1) on T cell membrane and causes apoptosis in T cells. Besides, these EVs induced apoptosis in EBV-specific $CD4^+$ cells population (Klibi et al., 2009). EBV-infected cancer cells release EVs containing HIFα, which promotes pathogenesis of cancer (Aga et al., 2014). Ansari et al. found that EBV-infected Raji cells package γ-interferon-inducible protein 16 (IFI16) into EVs (Ansari et al., 2013). This protein is responsible for the identifying EBV genome by the innate immune system. Probably, IFI16 secretion by EVs contributes to evasion the recognition of the innate immune response. However, it may be proposed that infected cells expel this factor as garbage out of cells. In contrast, EBV-infected Raji cells produce EVs having deoxy-uridine triphosphatase (dUTPase) (Ariza et al., 2013) that promote NF-kB activation and cytokine production in PBMCs and dendritic cells (DCs). In this regard, it was suggested that EBV-encoded dUTPase may modulate the cellular microenvironment and induce immune responses.

EVs from EBV-infected cells have been shown to deliver viral miRNAs to target cells. EBV miRNAs family consists of three clusters named the BHRF1-cluster, the BART-1 cluster, and the BART-2 cluster, which modulate the immune system of the host (Piedade and Azevedo-Pereira, 2016). For example, BHRF1 has the potential to suppress the expression of CXCL11, the IFN-inducible T-cell attracting chemokine (Xia et al., 2008). Viral miR-BART15 regulates production of the NLRP3 inflammasome and IL-1β (Haneklaus et al., 2012) and inhibits BRUCE and TAX1BP1, thus promotes apoptosis (Choi et al., 2013; Choi and Lee, 2017). EVs contain the viral miRNA BHRF 1, which could repress CXCL11 and inhibit the immune response of the host cells (Pegtel et al., 2010). EVs from EBV-infected gastric cancer cells are enriched with miR-BART15-3p that induce apoptosis in immune system cells (Choi et al., 2013). EBV-infected cells also transfer non-coding RNAs such as EBER1 and EBER2 (Zhao et al., 2019), which contribute to viral-associated cancer via inhibiting apoptosis (Ahmed et al., 2014). The mechanisms involved in sorting of viral miRNAs into EVs have not been fully explained and maybe virus-dependent. Nevertheless, EVs from Burkitt's lymphoma cell line stimulate B cells, thereby promote proliferation, development, and class-switch recombination in B cells, participating in antiviral responses (Gutzeit et al., 2014). Besides, EVs from EBV-transformed B cells preferentially connect with B cells via the interaction of the EBV-encoded glycoprotein gp350 with the CD21 receptor on B cells. Interestingly, inhibition EVs uptake by destroying this interaction repressed EBV infection in healthy B cells, proposing a defensive function for EVs in EBV spreading (Vallhov et al., 2011). These results show the viral content of EVs from EBV-infected cells have both beneficial and detrimental to the host's immune response, however, further scrutiny is essential to elucidate the exact role of these EVs.

3.3.2. Kaposi's sarcoma-associated herpesvirus (KSHV)

Kaposi's sarcoma-associated herpesvirus (KSHV) is a gamma herpesvirus like EBV and the infectious cause of cancer. EVs derived from KSHV-infected cells, in contrast with EBV, do not contain such viral proteins (Meckes et al., 2013; Singh et al., 2013). However, host biomolecules may be loaded into EVs and these molecules modulate immune responses. For instance, KSHV infection may alter the metabolism toward glycolytic metabolism in infected B cells. Meckes et al. showed that KSHV-infected cells produced EVs enriched with lactate dehydrogenase, a glycolytic metabolism enzyme, that reprogrammed metabolism in target cells (Meckes et al., 2013), increasing viral permanence. Furthermore, EVs from KSHV-infected cells have immunosuppressive molecules such as cleaved IL-1 and IFI16 that are essential for KSHV latency. These EVs contribute to extracellular elimination of the host innate immune responses (Singh et al., 2013). In a study by Chugh et al., it was demonstrated that EVs from KSHV infected cells transferred miRNA, which supported the progress of malignancies, like primary effusion lymphoma (Chugh et al., 2013). However, recently Jeon et al. showed that KSHV-infected cells secrete EVs carrying mitochondrial DNA, which could initiate antiviral responses (Jeon et al., 2019).

3.3.3. Herpes simplex virus 1 (HSV-1)

HSV-1 proteins can alter cargo of EVs derived from infected cells. The viral glycoprotein B downregulates the expression of HLA-DR molecules at the plasma membrane of infected cells by diverting these molecules into the exosomes (Temme et al., 2010). Furthermore, EVs from HSV-1 infected cells have viral miRNAs, which are involved in latency regulation (Naqvi et al., 2018). Han et al. found that viral miRNAs like miR-H28 and miR-H29 are encapsulated into EVs from the HSV-1 infected cells. Further experiment showed that abnormal expression of these miRNAs in transfected cells resulted in a decrease in the expression of viral gene products and also inhibited the spread from infected cells to healthy cells (Han et al., 2016). Authors indicated that HSV-1 regulates its own replication and spread. However, there exists evidence that HSV1-infected cells release EVs enriched with a stimulator of INF genes (STING) protein that inhibits the viral spread and augmented host cell survival (Kalamvoki et al., 2014).

3.3.4. Cytomegalovirus (CMV)

Cytomegalovirus (CMV)-infected cells have been shown to release EVs that suppress antiviral responses of the host and then increase viral infectivity (Plazolles et al., 2011). CMV infection increased the release of EVs containing lectin and DC-specific intercellular adhesion molecule-3 grabbing non-integrin proteins (DC-SIGN), which are required for virus uptake. These vesicles had potential to promote myeloid DCs infection, indicating a fall in antiviral responses (Plazolles et al., 2011). Unlike such herpesvirus as the EBV and KSHV, production of IFI16 inhibits CMV virus spread, because it is an anti-replication element for CMV (Lo Cigno et al., 2015). In CMV infection, endothelial cells secrete EVs containing glycoprotein B that activate $CD4^+$ T cells, thus, not only promote adaptive immune responses but also support maintain T cells population specific for the CMV (Walker et al., 2009). Furthermore,

virus resistant cells produce EVs with distinct miRNAs and mRNAs cargo that induce resistance in recipient cells upon deliver to them. For instance, primary human placental trophoblasts are resistant to CMV and HSV-1 viruses infection and their EVs induce resistance against these viruses in non-placental recipient cells (Delorme-Axford et al., 2013).

4. Coronavirus

Coronaviruses are enveloped, spherical or pleomorphic viruses, have single-strand positive-sense RNA genome with the longest among the RNA viruses (Belouzard et al., 2012). They refer to a wide virus family leading cause of common cold and severe infection like severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS)(de Groot et al., 2013; Drosten et al., 2003; Kuiken et al., 2003). According to literature, 6 coronavirus species are recognized to cause human respiratory diseases (Su et al., 2016). In December 2019, a novel coronavirus infectious disease characterized by acute respiratory impairment due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan city of Hubei province in China. The WHO identified it on January 12 and named “new novel coronavirus 2019 (2019-nCoV)”, therefore coronavirus 2019 (2019-nCoV) and COVID-19 virus is referred to as 2019-nCoV is a common name, and SARS-CoV-2 is a classification name for this new emerging virus. As of 10 June 2020, more than 7 million cases have been reported across 216 countries and territories, resulting in more than 400,000 deaths and more than 3 million people have recovered (https://covid19.who.int). Common symptoms comprise fever, cough, fatigue, shortness of breath, and loss of smell and taste. While the majority of cases result in mild symptoms, some progress to acute respiratory distress syndrome (ARDS) likely precipitated by a cytokine storm, failure in organs, septic shock, and blood clots. The time from exposure to onset of symptoms is typically around five days, but may range from two to fourteen day (Adhikari et al., 2020; Murthy et al., 2020)

4.1. Does CVID-19 virus use extracellular vesicles for infection?

The affliction of coronaviruses is mediated by a trimeric spike glycoprotein existing on the virion membrane. Similar to the envelope of HIV or hemagglutinin of influenza species, the spike proteins of coronavirus are one of class I fusion proteins (Whittaker and Millet, 2020). Most coronaviruses also need two triggering agents for fusion including receptor binding and intracellular proteolytic cleavage, following the proteolysis proceeding on receptor-bound viral ligands (Matsuyama and Taguchi, 2009). The coronaviruses receptors are transmembrane glycoprotein, therefor cell containing them show susceptibility to infection (Li et al., 2003; Raj et al., 2013). Coronaviruses may use the host cell protein dipeptidyl peptidase 4 (DPP4, CD26) for entry, so spike glycoprotein on virus interact with DPP4, however, DPP4 polymorphisms negatively affects entry of this virus (Kleine-Weber et al., 2019; Kleine-Weber et al., 2020). As well, aminopeptidase N (APN) has been revealed to serve as a receptor for different coronaviruses including CCoV, HCoV-229E, FeCoV, and TGEV (Cai, 2017) and considered as target for cancer therapy (Zhang and Xu, 2008). APN is present within exosomes from mast cells (Skokos et al., 2001) and glial cells (Potolicchio et al., 2005). Proteases system of coronaviruses is transmembrane-anchored and essential for infection (Bertram et al., 2013) and intracellular connected with the type II transmembrane serine protease (TTSP) family (Bertram et al., 2013; Glowacka et al., 2011). Confirmed that, TTSP family members like transmembrane protease serine type 2 (TMPRSS2) cleaves coronaviruses fusion glycoproteins (S proteins) to form unlocked and fusion-catalyzing structure at the cell surface and mediate a quick entry (Bertram et al., 2013; Glowacka et al., 2011). Several glycoproteins are essential for complete the fusion event (Ivanovic et al., 2013; Magnus et al., 2009). In this regard, several tetraspanins which are enriched in exosomal membrane (Kowal et al., 2014) may participate in coronavirus fusion event (Charrin et al., 2009). It seems that susceptible cells may have the two triggering elements for fusion, receptors and proteases, with a close relationship. Earnest et al. found that the tetraspanin CD9 and TMPRSS2 facilitate MERS-coronavirus entry and robust infection of mouse lungs in vivo (Earnest et al., 2017). Similarly, Ko et al. reported that enhanced CD9 expression had potential to promote lentiviral transduction both speed and efficiency in various cell lines such as HEK293, SH-SY5Y, HeLa, B cells, and T lymphocytes (Böker et al., 2018). CD9 molecules are present within exosome and MVs, and have a pivotal role in exosomes biogenesis and loading cargo (Andreu and Yáñez-Mó, 2014; Bobrie et al., 2012). It is not surprising that exosomes derived from infectious cells may contribute to promoting virus entry by transferring CD9 molecules (Earnest et al., 2017). Following exosome uptake, exosomal cargo are delivered to recipient cells (Jabbari et al., 2019) and promote susceptibility for virus infection. Furthermore, CD9 molecules have been confirmed to play a key role in loading exosomal cargo by the protein-protein interaction network in MVBs membrane (Bebelman et al., 2018), supposing a pivotal role in loading COVID-19 virus proteins. Muthukumar Gunasekaran et al. showed that coronavirus infections increased circulating exosomes containing lung-associated self-antigens as well as viral antigens and 20S proteasome (Gunasekaran et al., 2020). This fact supports the idea that COVID-19 virus infected cells produce exosomes containing virus particles.

Besides, more recently, Zhang et al. suggested that the angiotensin-converting enzyme 2 (ACE2) may serve as receptor for COVID-19 virus (Zhang et al., 2020). ACE2 is a carboxymonopeptidase that catalyze active angiotensin II to angiotensin (Wan et al., 2020; Zhang et al.), representing antagonist of angiotensin and regulating the ACE/Ang II/Ang II type I receptor signaling (Richards and Raizada, 2018). ACE2 plays protective roles against several pulmonary diseases such as acute lung injury, asthma, acute respiratory distress syndrome, pulmonary hypertension, and chronic obstructive pulmonary disease (Jia, 2016). Interestingly, SARS-CoV spike protein has a high affinity to human ACE2, and the COVID-19 virus and SARS-CoV spike proteins share a high degree of homology in structure (Li et al., 2005; Xu et al., 2020). In a recent study by Wan et al., it was reported that COVID-19 virus has much more affinity to human ACE2 rather than SARS-CoV, which promotes infection and spreading capability of COVID-19 (Wan et al., 2020). Further, recently it was confirmed that spike protein cleavage by TMPRSS2 is needed for COVID-19 virus entry and infection via interaction with the ACE2 receptor (Devaux et al., 2020). There is evidence that exosomes transfer ACE2 to receipt cells (Wang et al., 2020), proposing a supportive function for COVID-19 virus internalization and infection. As ACE2 are sorted into exosomes, presumably COVID-19 virus entry inside cells via internalization pathway, consequently its components such as miRNAs and proteins may be packaged into exosomes the same as other viruses discussed above. Owczarek et al. found that coronavirus can be internalized into cells via caveolin-1 dependent endocytosis and the virus components are shedding from the cell membrane by the vesicles in dynamin-dependent mechanism (Owczarek et al., 2018). These data suggest a supportive role for exosomes in spreading viral infection. However, exosomes from infected cells may induce the humoral and cellular immune response of host via transferring viral and self-antigens (Gunasekaran et al., 2017). Although our knowledge about exosomes derived from COVID-19 virus-infected cells is not abundant, however, in our view these results are important for identifying molecular mechanisms involved in virus spread and further open new avenue for design efficient treatment.

4.2. Are extracellular vesicles a target for the treatment of COVID-19 virus infection?

COVID-19 virus infection has become a globally crucial public health concern. Up to now no specific and effective antiviral therapy can be introduced for patients with COVID-19 virus infection. Although

symptomatic and loyal care, even with mechanical ventilation or ECMO, are strongly suggested for severely infected individuals, those with advancing age and co-morbidities including heart disease and diabetes remain to be at high risk for adverse outcomes. Using exosomes as immunogenic factors for the treatment of SARS coronavirus infection has been examined. Kuate et al. reported that exosomes containing the SARS coronavirus spike S protein induced neutralizing antibody titers that were promoted by priming with the SARS coronavirus spike vaccine and then increasing with the useful adenoviral vector vaccine (Kuate et al., 2007). The authors concluded the application of these artificial exosomes for treatment. In support, Kuate et al. packaged the S protein of the SARS coronavirus into exosomes and transmembrane domains of SARS-S were substituted by those of the G protein of vesicular stomatitis virus to produce chimeric protein (SGTM) containing exosomes for using as vaccine against the SARS coronavirus (Kuate et al., 2007).

Thus, exosomes from COVID-19 virus-infected cells may induce immune cells response, however, the pivotal role of these exosomes have not been exactly described. Besides, exosomes from coronavirus may be useful for delivering therapeutic agents (Romagnoli et al., 2015), as they contain specific targeting molecules, ACE2. They may be loaded by drugs or biological modulators that inhibit virus spreading and replication in recipient cells. Exosomes exhibit promising features that make them superior to other routine nano-delivery tools. For instance, exosomes have cell origin, therefore, display more safety and constant property than other delivery systems like liposomes (Malhotra et al., 2016). Exosomes from virus-infected cells contribute to promote virus infection and suppress immune cells responses (Li et al., 2019), therefore inhibition of exosomes/MVs uptake by neighboring cells may be another useful approach to overcome virus spreading (Schneider et al., 2017).

5. Stem cell therapy for COVID-19 virus infection

Stem cells and their derivatives offer great capacity for innovative medical treatments. A growing body of studies demonstrated the beneficial and therapeutic role of stem cell in regenerative medicine (Han et al., 2019b). Mesenchymal stem cells (MSCs), self-renewal cells, represent the hopeful characteristics like regenerative function and also capability to differentiate into various cell lineages that have attractive great interest of researchers in cell-based therapies for numerous diseases (Ahmadi et al., 2017; Han et al., 2019b; Harrell et al., 2019; Keyhanmanesh et al., 2018). MSCs therapy has recently developed from the preclinical experiments to the clinical trial for different disease states. For example, infusions of umbilical cord MSCs considerably enhanced liver function in decompensated liver cirrhosis and primary biliary cirrhosis (PBC) patients (Wang et al., 2013), increased the survival rate in acute-on-chronic liver failure (ACLF) patients (Shi et al., 2012). MSCs could significantly reduce the pathological changes of the lung (Cruz and Rocco, 2020) and inhibit the cell-mediated immune inflammatory response induced by influenza virus in the animal model (Khatri et al., 2018). Li et al. showed that MSCs can lessen acute lung injury in mice caused by H9N2 and H5N1 viruses via falling the secretion of pro-inflammatory chemokines and cytokines as well as inhibiting inflammatory cells influx onto the lungs (Li et al., 2016). Previous studies have revealed that following infection with coronavirus, the quick replication of the virus in the body, and the consequent inflammatory response increases alveolar epithelial and capillary endothelial cells damage, causing diffuse interstitial and alveolar edema, and pulmonary function, and finally acute hypoxic respiratory insufficiency (Channappanavar et al., 2014; Li et al., 2020; Qian et al., 2013).

The National Health and Medical Commission recently released the “New Coronavirus Infected Pneumonia Diagnosis and Treatment Plan (Trial Version 5)”, which pointed out that the new type of coronavirus severe pneumonia usually has difficulty breathing after one week, and the severe cases quickly progress to acute respiratory distress syndrome, Septic shock and metabolic acidosis that is difficult to correct. It seems that the hallmark of the treatment of COVID-19 virus severe pneumonia is to inhibit the proinflammatory immune response caused by the virus, thereby falling the injury of alveolar epithelial cells as well as capillary endothelial cells, and then reinforcing function of lung cells and also the regeneration of the lung tissue may be achieved using MSCs. In this regard, more recently, a study with identifier number NCT04276987 was recorded that aimed to investigate aerosol inhalation of the exosomes from allogeneic adipose MSCs in the treatment of severe patients with COVID-19 virus pneumonia. We know that exosomes from MSCs are useful factors for treatment of different diseases and suppressed lung inflammation and pathological damage resulting from various types of lung injury. Probably, exosome therapy may be a good tool for treatment or at less for prevent COVID-19 spreading in the host; however, further scrutiny is essential.

6. Challenges and opportunities

Many in vitro studies including cell lines and a limited number of pre-clinical in vivo studies demonstrate that exosomes play pivotal roles in infection diseases. Exosomes have attracted scientists' attentions and revolutionized modern medicine. However, as with numerous experiments on exosomes, although clinical trials, there exist challenges in analyzing the results and conclusions from the results remain elusive as different approaches for EVs isolation and characterization were used by different studies. Some of the studies did not include ISEV guidelines for the EVs characterization and their function, because those experiments had been done before 2014 and 2018 statement of ISEV guidelines of minimal experimental necessities for EVs-based studies (Lötvall et al., 2014; Théry et al., 2018a). Clinical exosomes-based studies are on the rise (https://clinicaltrials.gov), however, there are currently no the USA Food and Drug Administration (FDA)-approved exosome products (https://www.fda.gov/). Thus further scrutiny is necessary. Forthcoming efforts should focus on silencing or eliminating exosomes that selectively encourage diseases, but not benevolent, thus adding novel treatment opportunities to current therapies. Recent studies have shown that it is possible to inhibit the biogenesis and uptake of exosomes (Zheng et al., 2019; Zhou et al., 2017). Some researchers have attempted to examine exosome-inhibitors as research tools for studying exosomes biology; however, others have evaluated the inhibitory potential of such drugs in various disease models (Catalano and O'Driscoll, 2020; Zhou et al., 2017). Most of experiments were done in preclinical, therefore, clinical trials are essential for validation and confirmation. However, the main concern remains about non-targeting effects of exosome-inhibitors on exosomes biogenesis of healthy cells. It seems likely that substantial efforts would still be essential to study inhibitors effects on exosomes release from both healthy and unwell cells as well as to design ways to selectively deliver inhibitors to target cells. Exosome-therapy may be a promising tool for improve infection diseases. Select a popper sour cell to obtain exosomes for suppressing/improving adverse effects of disease is gold standard. The promising function of MSCs-derived exosomes in regenerative medicine has previously been confirmed (Tsiapalis and O'Driscoll, 2020), however, further scrutiny is essential to confirm the usefulness of these exosomes in COVID-19 virus pneumonia. Another interesting approach that exosomes can be used as a therapeutic agent is the drug delivery potential of them (Gnecchi et al., 2006; Lamichhane et al., 2016; Lv et al., 2012). Exosomes can serve as exosome-based nanocarriers that deliver therapeutic agent to target tissues/cells. Exosomes from a safe source such as MSCs may be loaded with optional compounds or genetically engineered for targeting infected tissues/cells, suggesting the exosome-based nanocarriers for treatment of infection diseases. The advent of safe nano-carriers with high efficiency is the core goal of nano-medicine. Thus, the development of exosomes-based nanocarriers has opened a hopeful opportunity for the delivery of therapeutic agents. However, the majority of studies

performed in vitro and animal models, therefore, the safety, specificity, and proficiency of this method in clinical trials remains still more mysterious. Therapeutic anti-viral vaccines in humans have been challenging to implement, despite many different strategies developed for their production and delivery to patients (Hung et al., 2008). These vaccines have not been a strong success so far, and it is surely valuable to consider more effective adjuvant approaches for refining vaccine efficiency. Furthermore, the source of immunostimulatory exosomes for human antiviral vaccines is important and will need further scrutiny (Devhare and Ray, 2017). Overall, exosome research is now in its infancy, therefore, to implement many of the ideas mentioned above, in-depth understanding of EVs (especially exosomes) biology from infected cells are required.

7. Conclusion

The term EVs refers to a wide type of cell-derived vesicles that vary in the biogenesis and biological properties. Among EVs, the key roles of exosomes and MVs in the pathogenesis of diseases have been extensively confirmed. Exosomes from virus-infected cells have been shown to modulate immune cells responses and increase spread and infection of the virus through delivering viral genome and protein particles to healthy cells. In addition, receptors located on exosomes accelerate viral entry and escaping from immune cell recognition. However, some researchers demonstrated that exosomes containing viral component were capable of inducing immune cells responses. In the case of COVID-19 virus, exosomes may contribute to promote spread and infection. Exosomes have receptors for COVID-19 virus entry like CD9 and ACE2, which may be involved in promoting COVID-19 virus infection. Preclinical and clinical application of exosomes for treatment COVID-19 infection could be proposed, which include stem cell-derived exosome therapy, exosome-based drug delivery, inhibition of exosome biogenesis and uptake, and exosome-based vaccine. Using MSCs for tissue regeneration and modulating inflammation has been suggested. There is currently no vaccine or specific antiviral treatment existing for COVID-19 virus infection, thus understanding the exact role of EVs in COVID-19 virus infection increase our knowledge about kinetic of this virus, promoting more effectively prevention and treatment. These findings suggest the following directions for future research on COVID-19 virus kinetic and suppression.

Ethical approval

No ethical approval required.

Sources of funding

Not applicable.

Authors' contribution

M. H., and J. R., collected data, prepared initial draft of the manuscript preparation and edited the manuscript and with equal conceptualization. M. N collected data. Y. P designed the study, edited the final version of manuscript and participated in final conceptualization. All authors read the manuscript and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgment

Not applicable.

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