



# Exosomes and COVID-19: challenges and opportunities

Ghader Babaei<sup>1</sup> · Nasrin Zare<sup>1</sup> · Aynaz Mihanfar<sup>1</sup> · Mohammad Hassan Khadem Ansari<sup>1</sup>

Received: 31 July 2021 / Accepted: 24 November 2021 / Published online: 13 January 2022  
© The Author(s), under exclusive licence to Springer-Verlag London Ltd., part of Springer Nature 2021

## Abstract

Coronavirus disease 2019 or COVID-19, starting from Wuhan, China, in December 2019, is a pandemic situation affecting millions worldwide and has exerted a huge burden on healthcare infrastructure. Therefore, there is an urgent need to understand the molecular mechanisms underlying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and design novel effective therapeutic strategies for combating this pandemic. In this regard, special attention has been paid to the exosomes. These nanoparticles are extracellular vesicles with critical function in the pathogenesis of several diseases including viral sepsis. Therefore, they may be involved in the pathogenesis of COVID-19 infection and also may be a way for transferring viral components and infecting other neighbor cells. Exosomes also can be considered as a therapeutic strategy for treating COVID-19 patients or used as a carrier for delivering effective therapeutic agents. Therefore, in this review, we discussed the biogenesis and contents of exosomes, their function in viral infection, and their potential as a therapeutic candidate in treating COVID-19.

**Keywords** COVID-19 · Exosomes · Drug delivery · COVID-19 transmission

## Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ARDS	Acute respiratory distress syndrome
MVs	Microvesicles
ABs	Apoptotic bodies
ACE-2	Angiotensin-converting enzyme-2
AT2	Type II alveolar cells
TNF	Tumor necrosis factor
IL	Interleukins
G-CSF	Granulocyte colony-stimulating factor
MCP-1/CCL2	Monocyte chemoattractant protein-1
MIP	Macrophage Inflammatory Proteins
IP-10	Interferon gamma-induced protein 10
NK	Natural killer

PD-1	Programmed cell death protein 1
NKG2A	Natural killer group 2A
Tim-3	T-cell immunoglobulin mucin-3
HLA-E	Histocompatibility antigen alpha chain E
IFN	Interferon
Th1	T helper 1 cells
MVB	Multivesicular bodies
TfR	Transferrin receptors
LBPA	Lyosbisphosphatidic acid
TGN	Trans- Golgi network
DAG	Diacylglycerol

## Introduction

Coronavirus disease 2019 or COVID-19, which is caused by a novel virus from the coronavirus family, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started at Wuhan city of China in December 2019, affected approximately 50 million people worldwide (Fauci et al. 2020). This pandemic is resulting in the adverse effects on the people's social life, economy, and more importantly exerting a huge pressure on the healthcare infrastructure (Velavan and Meyer 2020). Cytokine storm-induced by SARS-CoV-2 infection is demonstrated to lead to acute respiratory distress syndrome (ARDS), as well as eventual failure in the multiple vital organs. In approximately 80% of patients affected by COVID-19, no mild symptoms, which are limited to the

✉ Aynaz Mihanfar  
Mihanfar.aynaz@umsu.ac.ir

✉ Mohammad Hassan Khadem Ansari  
ansari\_mh@umsu.ac.ir

Ghader Babaei  
babaei.gh@umsu.ac.ir

Nasrin Zare  
N.zare1533@gmail.com

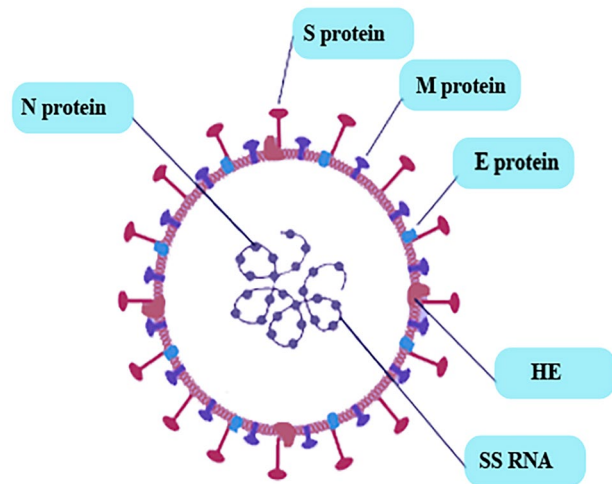
<sup>1</sup> Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

upper respiratory system, are observed (Cao 2020). However, in the elderly or patients suffering from chronic disease including diabetes, lung and heart disorders, ARDS appears and increases mortality rate in these patients (Yang et al. 2020). Except for three medications including remdesivir (as an anti-Ebola virus agent), favipiravir (an anti-influenza virus agent) and camostat mesylate, no effective therapeutic drug has been diagnosed for COVID-19 (Le et al. 2020). Therefore, due to the importance of this pandemic, a huge effort has been made on the designing and introducing novel effective therapeutic options for combating COVID-19 infection. This needs better understanding of molecular mechanisms of virus replication, spreading, and infection.

Approximately all eukaryote cells are able to synthesize and secrete extracellular vesicles (Pegtel and Gould 2019). These small vesicles, which have critical functions in injury, inflammation, and viral infections, are categorized into various subgroups including microvesicles (MVs), exosomes, and apoptotic bodies (ABs) (Théry et al. 2002). These groups have significantly different contents, biogenesis pathways, and function (Théry et al. 2002). Due to substantial function of extracellular vesicle (EV) and exosomes in viral infection, which is mediated by secretion of EVs containing viral particles, hence induction of virus infection in neighbor healthy cells, researchers have focused to understand the roles of EVs, especially exosomes in the pathogenesis of COVID-19 infection and evaluate the possibility of targeting these cellular compartments as a novel therapeutic strategy in COVID-19 (Hassanpour et al. 2020). Given the role of exosomes in the pathogenesis of viral diseases and the potential of these structures in the treatment of many diseases, the purpose of this review is to present the latest studies on the possible role of exosomes in the pathogenesis COVID-19 and the therapeutic potential of exosomes in treatment of patients with COVID-19.

## COVID-19 pathogenesis

SARS-CoV-2 (Belongs to the Betacoronavirus family) is a single-stranded RNA(positive-sense)-enveloped virus with a genome length of 29,881 bp, (Among known RNA viruses, Coronaviruses with a genome length of 26.4–31.7 kb have the largest genome) encoding a total of 9860 amino acids. Studies show that viral proteins encoded by the virus genome are classified into two groups: structural and non-structural proteins. Structural proteins include S, E, M, and N proteins, and non-structural proteins include 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase (Fig. 1) (Mousavizadeh and Ghasemi 2021; Huang et al. 2020b).



**Fig. 1** An overview of the structure of COVID-19

SARS-CoV-2 transmission is achieved by the attachment of virus to the epithelial cell surface present in the oral cavity, as well as surface of mucosal membranes of the otic canal or conjunctiva (Kordzadeh-Kermani et al. 2020). The internalization of SARS-CoV2 is mediated by angiotensin-converting enzyme-2 (ACE-2) protein, which has a high expression level on numerous cells such as esophageal, oral, ileal epithelial cells, urothelial cells of the bladder, kidneys' proximal tubule cells myocardial cells, and more importantly, type II alveolar cells (AT2) (Zou et al. 2020). Following internalization, furin, a cellular enzyme, catalyses a cleavage reaction on the S1/S2 site of the SARS-CoV2 spike protein (Hoffmann et al. 2020), which is an essential step in the virus entrance into the lung cells (Hoffmann et al. 2020). TMPRSS2 primes activated spike protein, and then this protein mediated virus entry to cells via attaching to the ACE-2 receptors. SARS-CoV-2 has a high degree of homology to SARS-CoV, in regard of genetic sequence and the structure of spike protein. Both viruses enter host cells via the same receptor. However, SARS-CoV-2 has approximately tenfold higher affinity for binding to ACE-2, in comparison to SARS-CoV (Wrapp et al. 2020). ACE-2/angiotensin axis plays critical functions in the inflammatory response and signal transductions involved in the tissue injury (Rodrigues Prestes et al. 2017). Viral replication leads to decrease in the expression levels of ACE-2, which eventually results in the suppression of angiotensin II breakdown into angiotensin. Disruption in the ACE-2/angiotensin signaling is responsible for the manifestation of major clinical characteristics of COVID-19 infection including vasoconstriction, hypokalemia, and development of ARDS (Gheblawi et al., 2020; Pal and Bhansali 2020). The severity of COVID-19 has a strongly positive correlation with the tissue levels of inflammatory mediators including tumor necrosis factor (TNF)- $\alpha$ ,

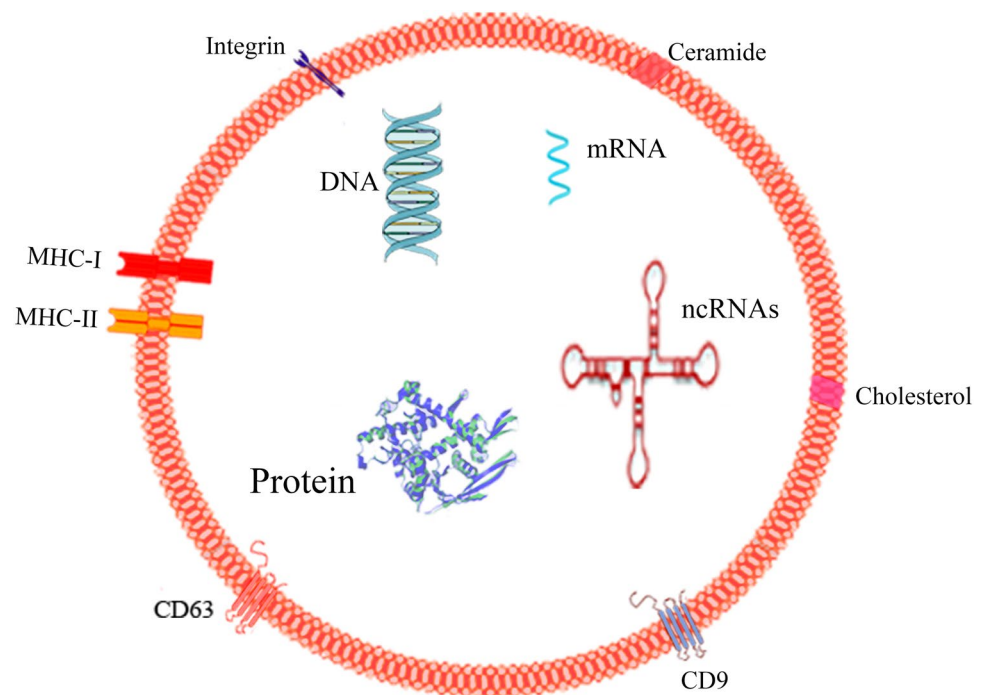
interleukins (IL-2, IL-6, IL-7, IL-10), granulocyte colony-stimulating factor (G-CSF or GCSF), monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage Inflammatory Proteins (MIP)-1A, and interferon gamma-induced protein 10 (IP-10). Patients suffering from severe disease represent a significant drop in the lymphocyte count (Zheng et al. 2020; Diao et al. 2020; Huang et al. 2020a). Results from the Flow cytometric analysis of patients with severe COVID-19 show that natural killer (NK) cells and lymphocytic T Cells (CD4+ and CD8+) are significantly reduced in these patients. In addition, in the early stage of the COVID-19, the expression levels of programmed cell death protein 1 (PD-1), natural killer group 2A (NKG2A), T-cell immunoglobulin mucin-3 (Tim-3) have a significant association with functional exhaustion observed in the T lymphocytes (Zheng et al. 2020; Diao et al. 2020). PD-1, which is expressed on the surface of both NK cells and T lymphocytes is demonstrated to be contributed in the promoting self-tolerance and subsiding immune responses via promoting differentiation of regulatory T cells and inhibiting the activity of T cells (Salmaninejad et al. 2019). The expression of NKG2A is observed on the surface of CD8+ T cells, natural killer T (NKT) cells and NK cells. NKG2A binding to the histocompatibility antigen alpha chain E (HLA-E) is involved in the inhibition of the NK and T cells activation (Creelan and Antonia 2019). Tim-3, as a co-inhibitory receptor expressing on innate immune cells and interferon (IFN)- $\gamma$  producing T

cells, have crucial functions in the suppressing T helper 1 cells (Th1) responses and the expression of cytokines such as IFN- $\gamma$  and TNF- $\alpha$  (Das et al. 2017).

## Exosomes contents

Exosomes belong to multivesicular bodies (MVB) family of EVs with approximately 30–100 nm in diameter (Fig. 2) (Azmi et al. 2013). Analysis by proteomic techniques and electron microscopy have revealed that exosome contents are determined by to major factors, the contents of donor cell and modulated sorting mechanisms (Valadi et al. 2007). The major contents of exosomes include nucleic acids (DNA, mRNA, and miRNA), lipids, and numerous proteins such as extracellular matrix proteins, enzymes, receptors, and transcription factors, which are present in either the surface or inside the exosomes (Mathivanan et al. 2010; D'Asti et al. 2012). Studies analyzing the exosome compositions have demonstrated that protein contents of exosomes consist of two categories; first, proteins that are common in all exosomes, some important of them include heat shock proteins (Hsp)-70 and -90, transferring and fusion proteins such as flotillin, Rab2, Rab7, and annexin, cytoskeleton proteins like actin, myosin, tubulin; second, proteins that specifically originate from cell and tissue of origin such as tetraspanins, integrins, transferrin receptors (TfR), CAMs, and MHC class I, II (Van Niel et al. 2006; Poliakov et al. 2009).

**Fig. 2** An overview of the structure of exosomes



Similar to protein compositions of exosomes, the lipid contents of these EVs are also cell-specific or conserved. Two important biological functions are suggested for the presence of lipids in the exosomes structure, protecting their shapes and participating exosome biogenesis and controlling homeostasis (Vidal et al. 1989; Ganapathi et al. 2018; Chu et al. 2005). Lyso-bisphosphatidic acid (LBPA) playing critical roles in the exosomes formation, sphingomyelin and phosphatidylcholine are among the significant lipid structures in exosomes (Huotari and Helenius 2011; Taylor et al. 2006). Fusion of exosomes to target cells has been demonstrated to change the lipid composition of target cells.

## Biogenesis of exosomes

Exosome biogenesis is initiated by the stimulation of cell-specific receptors and activation of downstream signal transactions. All steps in the biogenesis of exosomes are highly regulated (Keller et al. 2006). The first step is the formation of early endosome, which is achieved by the fusion of primary endocytic vesicles (Huotari and Helenius 2011). The membrane composition and contents of incoming endocytic cargoes can be shared to early endosome by combining to them, which is facilitated by caveolin- or clathrin-dependent or independent pathways (Mayor and Pagano 2007). Then, early endosomes return their cargoes to the plasma membrane, which is referred to as recycling endosomes, or change into late endosomes. After recycling, the membrane of early vesicles buds inward and their cargo was sequestered and distributed into vesicles (Huotari and Helenius 2011).

After primary steps, exosomes arrive at their final intracellular destination. At the last step, exosomes may fuse with lysosomes and get degraded, or by fusing with plasma membrane, secrete their contents into extracellular milieu (Baietti et al. 2012; Ostrowski et al. 2010). Rab27A and Rab27B from Rab family facilitate the transferring of exosomes to the plasma membrane and their fusion with membrane, hence play pivotal functions in the exosome release (Baietti et al. 2012; Ostrowski et al. 2010). Interaction of synaptotagmin protein on the exosomes surface with syntaxin on the plasma membrane initiates the fusion process. Then, exosomes dock the membrane through interaction of V-SNARE on the exosomes with T-SNARE on the plasma membrane. This process leads to releasing of exosomes to the extracellular environment (Kennedy and Ehlers 2011).

## Exosomes in viral infection

An accumulating number of previous studies have demonstrated the crucial function of exosomes in the tissue homeostasis, interactions between host and pathogen and more importantly, pathogenesis of numerous disorders

including virus infection (Kita et al. 2019; Sahoo and Losordo 2014; Schorey et al. 2015). In addition, viral infection takes advantages from exosomes to entrance, spreading, virus packaging, escaping the immune system and pathogenies (Alenquer and Amorim, 2015; Anderson et al. 2016; Urbanelli et al. 2019; Wurdinger et al. 2012). In addition, there are huge similarities between exosome and viruses from the biogenesis, their fate and releasing point of views. Therefore, it is suggested that viruses and exosomes may be related (Cremer et al. 2016). Various reviews have examined the modulation of host immune systems by virus infections, and the critical roles of exosomes in these events (Schorey et al. 2015). During viral infection, host cells are stimulated by viruses and secrete exosomes. These extracellular vesicles act as pathogen-related molecular pattern, contain inflammatory markers and lead to robust inflammatory response (Schorey et al. 2015). For instance, cells infected by EBV release exosomes, which contain high amounts of dUTPase. These exosomes result in the activation of nuclear factor – kappa B (NF- $\kappa$ B) signal transduction and induction of macrophage cytokine secretion (Ariza et al. 2013). Moreover, exosomes from HCV- and Zika virus-infected cells are enriched in mRNA molecules which mediate the releasing of INF- $\alpha$  from macrophages and monocytes, respectively (Martínez-Rojas et al. 2020). Kaposi sarcoma-associated herpes virus–infected cells also secrete exosomes that ultimately led to increase in the expression levels IL-6 and hence induction of major damages in endothelial cells (Chugh et al. 2013). A growing body of evidence shows that exosomes act as susceptible recipient cells to viral infections by transmitting viral proteins. For example, studies on the spread of HIV infection showed that HIV proteins are transported to recipient cells through exosomes, making them more susceptible to widespread infections. Another mechanism by which exosomes sensitize receptor cells to viral infections is the transfer of viral co-receptors to cells that are null to the viral co-receptor (Urbanelli et al. 2019; Crenshaw et al. 2018). For example, exosomes released from HIV-1–infected cells contain co-receptors that facilitate the entry of the virus into the cells receiving the exosomes and make these cells susceptible to infection. Nevertheless, the transmission of virus co-receptors in animal models is still unclear and further studies are needed to prove it in vivo (Urbanelli et al. 2019; Crenshaw et al. 2018).

The viral nucleic acids in exosomes released from virus-infected cells are another factor in facilitating viral infections caused by exosomes. Studies have shown that exosomes secreted from HIV-infected cells contain transactivation response element (TAR) RNA, which inhibits Bcl-2 interacting protein by producing miRNAs, increasing resistance to apoptosis. Resistance to apoptosis promotes the production of virus in infected cells (Rezaie et al. 2021).

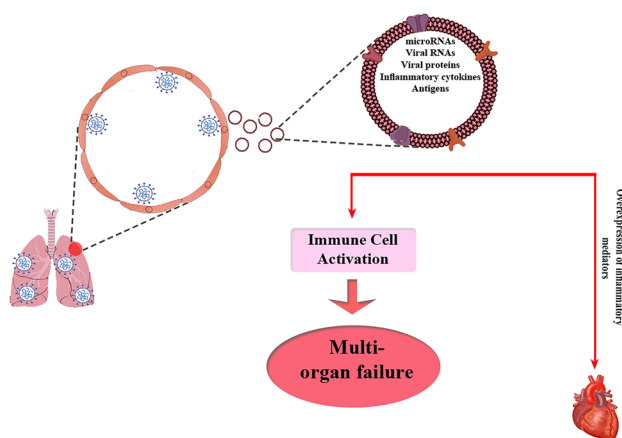
Apoptosis is another endpoint of effects of exosomes secreted from virus-infected cells. Viral Nef protein-enriched exosomes from HIV-infected cells cause apoptosis of CD4 T-helper cells and endothelial cells (Lenassi et al. 2010). Similarly, EBV infection leads to secretion of exosomes containing galactin-9, which mediates induction of apoptosis in cytotoxic T cells (Dukers et al. 2000).

Taking together, activating inflammatory response, apoptosis and cytotoxicity are main mechanisms, by which exosomes released from virus-infected cells result in the tissue damage.

## Potential of exosomes in COVID-19 transmission

Hyperactivation in host immune system, induction in sepsis-like disorder, which is marked by lymphopenia and cytokine storm, are two main characteristics of SARS-CoV-2 infection that pose the issue of the contribution of exosomes in SARS-CoV-2 infection (Fig. 3). This notion is further reinforced by the involvement of trans-Golgi network (TGN) pathway in the replication phase of SARS-CoV-2. Moreover, recent studies by Zhang et al. demonstrated that the metabolic pathways of lipids such as cholesterol play critical roles in the pathogenesis of COVID-19, which strengthens the contribution of exosomes in SARS-CoV-2 infection (Zhang et al. 2020a, 2020b). Interactome analysis for SARS-CoV-2 elucidated the interaction with Rab proteins, which have fundamental function in the biogenetic pathways of exosomes, which is similar to other viruses (Bello-Morales et al. 2012; Fraile-Ramos et al. 2010; Gerber et al. 2015). Additionally, Song et al. showed the presence of lipid profiles with high levels of gangliosides and sphingomyelins and without

diacylglycerol (DAG), which is an exosome-specific lipid pattern in the sera from patients infected with SARS-CoV-2. Surprisingly, there was a strong association between the severity of the disease gangliosides (GM3)-enriched exosome (Song et al. 2020a, 2020b). The important issue that should be noted is that researches about the pathogenesis of SARS-CoV-2 infection are still in its infancy and further studies are needed for better understanding of exosome involvement in SARS-CoV-2 infection. In addition, an increasing number of researches have indicated that exosomes are mainly involved in the transmission of non-coding RNAs such as microRNAs between various cells and have been contributed to the development of cardiovascular disorders. In this regard, in a study by Kwon et al., it was reported that lung epithelial A549 cells transfection with non-structural and structural genes of SARS-CoV-2 led to releasing of viral RNA-enriched exosomes. Human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) took up these exosomes, which led to overexpression of inflammatory mediators in these cells (Kwon et al. 2020). This study, in particular reinforces the accuracy of the critical functions of exosomes in the pathogenesis of SARS-CoV-2. In addition, the results of Kwon's study also may be an explanation for the myocardial inflammation observed in the patients with COVID-19. On the other hand, Bouhaddou et al. reported that cellular protein kinases were modulated by the SARS-CoV-2 infection, which suggests that infected cell-driven exosomes contain special proteins that are involved in the activation of inflammation and hence results in the tissue damages in other organs (Bouhaddou et al. 2020). Taking together, exosomes may play more roles in the pathogenies of COVID-19 and targeting exosomes as therapeutic option for this novel lethal disease will be absolutely interesting and merit to research.



**Fig. 3** The role of exosomes in the pathogenesis of COVID-19: Exosomes may transmit viral components as well as proteins, genomes, and mRNA related to COVID-19 from infected lung epithelial cells to other organs, causing multiple organ failure

## Potential of exosomes in COVID-19 treatment

As mentioned before, there is not any specific therapeutic option for combating the COVID-19. Previous studies have showed the potential of exosomes for treating SARS coronavirus infection. In a study by Kuate et al. it was demonstrated that exosomes carrying SARS coronavirus spike S protein was successful in inducing neutralizing antibody titers. This response is also triggered by priming with the SARS coronavirus spike vaccine and then enhancing with the useful adenoviral vector vaccine (Kuate et al. 2007). These results indicated that exosomes can be applied for treating SARS coronavirus infection. In another study, Kuate et al. used exosomes as a carrier for S protein of the SARS coronavirus. They substituted transmembrane domains of SARS-S by those of the G protein of vesicular stomatitis virus,

which led to production of a chimeric protein (SGTM). This chimeric protein was used as a vaccine against SARS coronavirus (Kuate et al. 2007). Therefore, exosomes released from SARS-CoV-2–infected cells may also activate immune response. However, due to uncertainty about the exact roles of exosomes in the pathogenesis of SARS-CoV-2 infection, therapeutic potential of these extracellular vesicles in COVID-19 needs more detailed researches.

On the other hand, a hot point in the COVID-19 researches is using mesenchymal stem cells (MSCs) in treating this disease. Particularly, exosomes derived from these cells have attracted more attention. Therefore, various studies have investigated the efficiency and safety of using exosomes derived from MSCs in treating patients with COVID-19. For example, Vikram et al. tested the therapeutic potential of bone marrow MSC-derived exosomes in the 24 patients infected with SARS-CoV-2 and moderate to severe ARDS (Sengupta et al. 2020). Introduction of exosomes to patients was shown to be safe and led to significant improvement in the clinical status and oxygenation. A recent clinical trial has investigated the efficacy of inhalation MSC-derived exosomes in alleviating the symptoms of COVID-19 (NCT04276987) (Fig. 4).

### Potential of exosomes in drug delivery against COVID-19

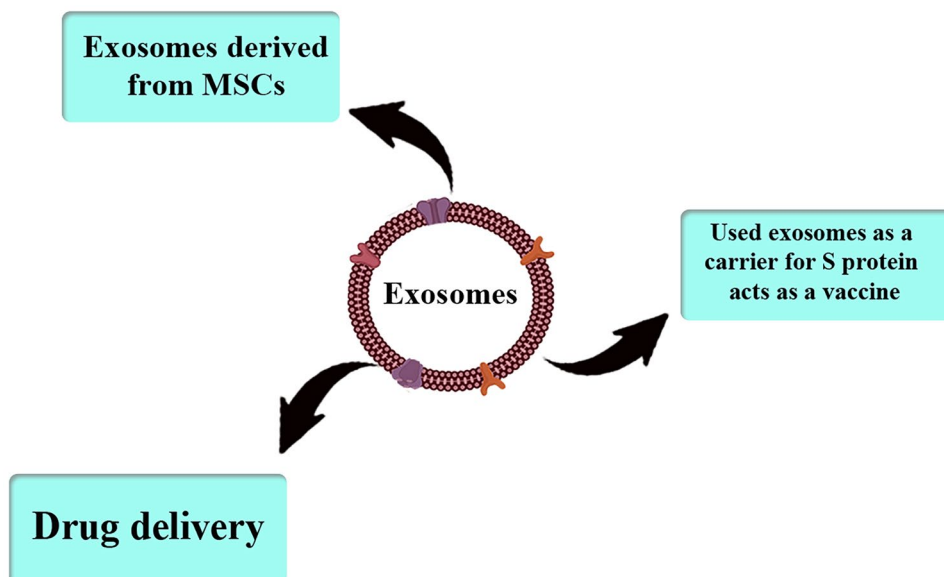
It is well understood that exosomes are appropriate candidate for carrying various materials such as nanoparticles. In addition, coronavirus-derived exosomes may be successfully applied for carrying and transferring therapeutic molecules, since they carry targeting proteins, ACE-2 (Kadriyan et al.

2020). It may be possible drugs or biological modulators that can suppress virus replication and spreading in host cells can be loaded on exosomes. Exosomes exhibit promising features that make them superior to other routine nano-delivery tools. Immature dendritic cell-derived exosomes were demonstrated to rescue sepsis through increasing phagocytosis of apoptotic cells (Miksa et al. 2009). In an animal model of sepsis, Gao et al. reported that exosomes derived for these animals can inhibit the occurrence of sepsis in other animals. These findings show that injected exosomes have the potential of reducing immune response and corresponding tissue damage by downregulation of inflammatory mediators (Jiang et al. 2019). Wu et al. reported that exosomes can be an appropriate alternative therapeutic candidate for treating sepsis cases (Wu et al. 2017). More interestingly, Chu et al. examined the effectiveness of nebulization therapy for COVID-19 patients using MSCs exosomes (Chu et al. 2020). Seven patients with COVID-19 were treated with nebulization of MSC-derived exosomes and it was found that this therapy could promote the absorption of pulmonary lesions, and decrease the time of hospitalization for minor cases of COVID-19 pneumonia (Fig. 4) (Chu et al. 2020).

### Conclusion

COVID-19 is one of the main challenges of human society and it is necessary to study and clarify the pathogenesis of this disease. An accumulating number of studies have demonstrated the critical function of exosomes in the pathogenesis of various diseases including viral sepsis. Virus-infected cells have been reported to be involved in transmitting the virus to other infected cells as well as modulating the

**Fig. 4** An overview of the therapeutic potential of exosomes in the treatment of COVID-19



immune system by secreting exosomes containing protein particles, viral genomes, and inflammatory factors. Similarly, exosomes may also play vital role in the spreading and infection of SARS-CoV-2. Moreover, exosomes may be also a candidate for treating COVID-19, as well as acting as a carrier for delivering therapeutic agents to human body. However, there are still numerous unanswered questions about the role of exosomes in the pathogenesis of COVID-19 and also the use of these structures in the treatment of patients with COVID-19.

**Author contribution** All authors contributed equally to the work.

## Declarations

**Conflict of interest** The authors declare no competing of interests.

## References

- Alenquer M, Amorim MJ (2015) Exosome biogenesis, regulation, and function in viral infection. *Viruses* 7:5066–5083
- Anderson MR, Kashanchi F, Jacobson S (2016) Exosomes in viral disease. *Neurotherapeutics* 13:535–546
- Ariza ME, Rivailler P, Glaser R, Chen M, Williams MV (2013) Epstein-Barr virus encoded dUTPase containing exosomes modulate innate and adaptive immune responses in human dendritic cells and peripheral blood mononuclear cells. *PLoS One* 8:e69827
- Azmi AS, Bao B, Sarkar FH (2013) Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. *Cancer Metastasis Rev* 32:623–642
- Baietti MF, Zhang Z, Mortier E, Melchior A, Degeest G, Geeraerts A, Ivarsson Y, Depoortere F, Coomans C, Vermeiren E (2012) Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat Cell Biol* 14:677–685
- Bello-Morales R, Crespillo AJ, Fraile-Ramos A, Tabarés E, Alcina A, López-Guerrero JA (2012) Role of the small GTPase Rab27a during herpes simplex virus infection of oligodendrocytic cells. *BMC Microbiol* 12:265
- Bouhaddou M, Memon D, Meyer B, White KM, Rezelj VV, Marrero MC, Polacco BJ, Melnyk JE, Ulferts S, Kaake RM (2020) The global phosphorylation landscape of SARS-CoV-2 infection. *Cell* 182:685–712. e19
- Cao X (2020) COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol* 20:269–270
- Chu M, Wang H, Bian L, Huang J, Wu D, Fei F, Zhang R, Chen Y, Xia J (2020) Nebulization therapy for COVID-19 pneumonia with embryonic mesenchymal stem cells-derived exosomes
- Chu Z, Witte DP, Qi X (2005) Saposin C-LBPA interaction in late-endosomes/lysosomes. *Exp Cell Res* 303:300–307
- Chugh PE, Sin SH, Ozgur S, Henry DH, Menezes P, Griffith J, Eron JJ, Damania B, Dittmer DP (2013) Systemically circulating viral and tumor-derived microRNAs in KSHV-associated malignancies. *PLoS Pathog* 9:e1003484
- Creelan BC, Antonia SJ (2019) The NKG2A immune checkpoint—a new direction in cancer immunotherapy. *Nat Rev Clin Oncol* 16:277–278
- Cremer T, Gallo RC, Margolis LB (2016) Extracellular vesicles and viruses: are they close relatives? *Proc Natl Acad Sci USA* 113:9155–9161
- Crenshaw BJ, Gu L, Sims B, Matthews QL (2018) Exosome biogenesis and biological function in response to viral infections. *The Open Virology Journal* 12:134–148
- D’asti E, Garnier D, Lee TH, Montermini L, Meehan B, Rak J (2012) Oncogenic extracellular vesicles in brain tumor progression. *Front Physiol* 3:294
- Das M, Zhu C, Kuchroo VK (2017) Tim-3 and its role in regulating anti-tumor immunity. *Immunol Rev* 276:97–111
- Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, Chen L, Li M, Liu Y, Wang G (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol* 11:827
- Dukers DF, Meij P, Vervoort MB, Vos W, Scheper RJ, Meijer CJ, Bloemena E, Middeldorp JM (2000) Direct immunosuppressive effects of EBV-encoded latent membrane protein 1. *J Immunol* 165:663–670
- Fauci AS, Lane HC, Redfield RR (2020) Covid-19—navigating the uncharted. *Mass Medical Soc*
- Fraile-Ramos A, Cepeda V, Elstak E, van der Sluijs P (2010) Rab27a is required for human cytomegalovirus assembly. *PLoS One* 5:e15318
- Ganapathi M, Boles NC, Charniga C, Lotz S, Campbell M, Temple S, Morse RH (2018) Effect of Bmi1 over-expression on gene expression in adult and embryonic murine neural stem cells. *Sci Rep* 8:1–10
- Gerber PP, Cabrini M, Jancic C, Paoletti L, Banchio C, von Bilderling C, Sigaut L, Pietrasanta LI, Duette G, Freed EO (2015) Rab27a controls HIV-1 assembly by regulating plasma membrane levels of phosphatidylinositol 4, 5-bisphosphate. *J Cell Biol* 209:435–452
- Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, Raizada MK, Grant MB, Oudit GY (2020) Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res* 126:1456–1474
- Hassanpour M, Rezaie J, Nouri M, Panahi Y (2020) The role of extracellular vesicles in COVID-19 virus infection. *Infect Genet Evol* 104422
- Hoffmann M, Kleine-Weber H, Pöhlmann S (2020) A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Molecular Cell*
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X (2020a) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 395:497–506
- Huang Y, Yang C, Xu X-F, Xu W, Liu S-W (2020b) Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacol Sin* 41:1141–1149
- Huotari J, Helenius A (2011) Endosome maturation. *EMBO J* 30:3481–3500
- Jiang Y, Gao K, Huang C, Li J, Luo H, Li L, Huang Y, Jin J (2019) Exosomes derived from septic mouse serum modulate immune responses via exosome-associated cytokines. *Front Immunol* 10:1560
- Kadriyan H, Prasedya ES, Pieter NAL, Gaffar M, Punagi AQ, Bukhari A (2020) The potential role of exosome on cytokine storm and treatment of severe COVID-19 infection
- Keller S, Sanderson MP, Stoeck A, Altevogt P (2006) Exosomes: from biogenesis and secretion to biological function. *Immunol Lett* 107:102–108
- Kennedy MJ, Ehlers MD (2011) Mechanisms and function of dendritic exocytosis. *Neuron* 69:856–875
- Kita S, Maeda N, Shimomura I (2019) Interorgan communication by exosomes, adipose tissue, and adiponectin in metabolic syndrome. *J Clin Invest* 129

- Kordzadeh-Kermani E, Khalili H, Karimzadeh I (2020) Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). *Future Microbiol* 15:1287–1305
- Kuate S, Cinatl J, Doerr HW, Überla K (2007) Exosomal vaccines containing the S protein of the SARS coronavirus induce high levels of neutralizing antibodies. *Virology* 362:26–37
- Kwon Y, Nukala SB, Srivastava S, Miyamoto H, Ismail NI, Ong S-B, Lee WH, Ong S-G (2020) Exosomes facilitate transmission of SARS-CoV-2 genome into human induced pluripotent stem cell-derived cardiomyocytes. *bioRxiv*
- Le TT, Andreadakis Z, Kumar A, Roman RG, Tollefsen S, Saville M, Mayhew S (2020) The COVID-19 vaccine development landscape. *Nat Rev Drug Discov* 19:305–306
- Lenassi M, Cagney G, Liao M, Vaupotič T, Bartholomeeusen K, Cheng Y, Krogan NJ, Plemenitaš A, Peterlin BM (2010) HIV Nef is secreted in exosomes and triggers apoptosis in bystander CD4+ T cells. *Traffic* 11:110–122
- Martínez-Rojas PP, Quiroz-García E, Monroy-Martínez V, Agredano-Moreno LT, Jiménez-García LF, Ruiz-Ordaz BH (2020) Participation of extracellular vesicles from zika-virus-infected mosquito cells in the modification of naïve cells' behavior by mediating cell-to-cell transmission of viral elements. *Cells* 9:123
- Mathivanan S, Ji H, Simpson RJ (2010) Exosomes: extracellular organelles important in intercellular communication. *J Proteomics* 73:1907–1920
- Mayor S, Pagano RE (2007) Pathways of clathrin-independent endocytosis. *Nat Rev Mol Cell Biol* 8:603–612
- Miksa M, Wu R, Dong W, Komura H, Amin D, Ji Y, Wang Z, Wang H, Ravikumar TS, Tracey KJ (2009) Immature dendritic cell-derived exosomes rescue septic animals via milk fat globule epidermal growth factor VIII. *J Immunol* 183:5983–5990
- Mousavizadeh L, Ghasemi S (2021) Genotype and phenotype of COVID-19: their roles in pathogenesis. *J Microbiol Immunol Infect* 54:159–163
- Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita CF, Schauer K, Hume AN, Freitas RP (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. *Nat Cell Biol* 12:19–30
- Pal R, Bhansali A (2020) COVID-19, diabetes mellitus and ACE2: the conundrum. *Diabetes Res Clin Pract* 162
- Pegtel DM, Gould SJ (2019) Exosomes. *Annu Rev Biochem* 88:487–514
- Poliakov A, Spilman M, Dokland T, Amling CL, Mobley JA (2009) Structural heterogeneity and protein composition of exosome-like vesicles (prostasomes) in human semen. *Prostate* 69:159–167
- Rezaie J, Aslan C, Ahmadi M, Zolbanin NM, Kashanchi F, Jafari R (2021) The versatile role of exosomes in human retroviral infections: from immunopathogenesis to clinical application. *Cell Biosci* 11:19
- Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes-e-Silva AC (2017) The anti-inflammatory potential of ACE2/angiotensin-(1–7)/Mas receptor axis: evidence from basic and clinical research. *Curr Drug Targets* 18:1301–1313
- Sahoo S, Losordo DW (2014) Exosomes and cardiac repair after myocardial infarction. *Circ Res* 114:333–344
- Salmaninejad A, Valilou SF, Shabgah AG, Aslani S, Alimardani M, Pasdar A, Sahebkar A (2019) PD-1/PD-L1 pathway: basic biology and role in cancer immunotherapy. *J Cell Physiol* 234:16824–16837
- Schorey JS, Cheng Y, Singh PP, Smith VL (2015) Exosomes and other extracellular vesicles in host–pathogen interactions. *EMBO Rep* 16:24–43
- Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N (2020) Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. *Stem Cells Dev*
- Song J-W, Lam SM, Fan X, Cao W-J, Wang S-Y, Tian H, Chua GH, Zhang C, Meng F-P, Xu Z (2020a) Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. *Cell Metab* 32:188–202. e5
- Song Y, Liu P, Shi X, Chu Y, Zhang J, Xia J, Gao X, Qu T, Wang M (2020b) SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. *Gut* 69:1143–1144
- Taylor DD, Akyol S, Gercel-Taylor C (2006) Pregnancy-associated exosomes and their modulation of T cell signaling. *J Immunol* 176:1534–1542
- Théry C, Zitvogel L, Amigorena S (2002) Exosomes: composition, biogenesis and function. *Nat Rev Immunol* 2:569–579
- Urbanelli L, Buratta S, Tancini B, Sagini K, Delo F, Porcellati S, Emiliani C (2019) The role of extracellular vesicles in viral infection and transmission. *Vaccines* 7:102
- Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO (2007) Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 9:654–659
- Van Niel G, Porto-Carreiro I, Simoes S, Raposo G (2006) Exosomes: a common pathway for a specialized function. *J Biochem* 140:13–21
- Velavan TP, Meyer CG (2020) The COVID-19 epidemic. *Tropical Med Int Health* 25:278
- Vidal M, Sainte-Marie J, Philippot JR, Bienvenue A (1989) Asymmetric distribution of phospholipids in the membrane of vesicles released during in vitro maturation of guinea pig reticulocytes: evidence precluding a role for "aminophospholipid translocase." *J Cell Physiol* 140:455–462
- Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367:1260–1263
- Wu J, Wang Y, Li L (2017) Functional significance of exosomes applied in sepsis: a novel approach to therapy. *Biochim Biophys Acta (BBA) - Mol Basis Dis* 1863:292–297
- Wurdinger T, Gatsion NN, Balaj L, Kaur B, Brakefield XO, Pegtel DM (2012) Extracellular vesicles and their convergence with viral pathways. *Adv Virol* 2012
- Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y (2020) COVID-19: immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther* 5:1–8
- Zhang C, Shi L, Wang F-S (2020a) Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 5:428–430
- Zhang X-J, Qin J-J, Cheng X, Shen L, Zhao Y-C, Yuan Y, Lei F, Chen M-M, Yang H, Bai L (2020b) In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab* 32:176–187. e4
- Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, Xu Y, Tian Z (2020) Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 17:533–535
- Zou X, Chen K, Zou J, Han P, Hao J, Han Z (2020) Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 1–8

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.