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Multimodal Role of Exosomes in COVID-19 Transmission, Diagnosis, and Therapy

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Abstract

Exosomes are membrane vesicles of endocytic origin released by all cell types under physiological and pathological conditions. Exosomes are important mediators of cell to cell communications and transport biomolecules, including lipids, proteins, DNAs, messenger RNAs, and microRNAs, and perform intercellular transfer of components, locally and systemically. Moreover, exosomes generated by virus-infected cells can partake into key viral proteins and fragments of viral RNA, thus effectively carrying the viral load to other healthy cells, facilitating viral transmission. In this review we focus on the role of exosomes in transfer of SARS-CoV-2 infection and how these virus-loaded exosomes can be used to develop effective therapeutic options.

Keywords: Exosomes; COVID-19; COVID-19 therapy; COVID-19 diagnosis; Exosome biogenesis

Introduction

Since December 2019, SARS-CoV-2 (COVID-19) infection has become a worldwide urgent public health concern [1, 2]. Currently various vaccines are under clinical trials for the treatment of COVID-19 viral infection. It is thus imperative to find a safe and effective therapeutic tool to patients with severe COVID-19 virus infection [3, 4]. But in the hurry to develop, it critical safety concerns and the effectiveness of the therapeutic tool should not be compromised. Though the race is on to find a vaccine against the virus the virus is running faster infecting more people worldwide daily. The month of June witnessed the highest ever number of new COVID-19 cases recorded in a single day 194,191 (June 26, 2020) [5]. The fact which is most alarming, although rare is the re-appearance of the viral RNA in the recovered COVID-19 patients following discharge .One study showed that as much as 9.1% of the discharged COVID-19 patients were shown to be positive for SARS-CoV2 reactivation [6]. Viruses use various sophisticated mechanism for transmission from one cell to another [7]. Exosomes are lipid-bilayer vesicles which are 30–120 nm in size and participate in several pathological conditions [8]. Virus-infected cells release exosomes that contain viral components such as viral-derived miRNAs and proteins and also receptors for viruses that make recipient cells susceptible to virus entry [9]. Exosomal receptors such as CD9 and ACE2, makes the recipient cells susceptible to virus docking [9, 10]. Understanding molecular crosstalks behind exosome-mediated COVID-19 virus infection and reinfection may provide us with an avenue to identify its systemic spread and develop novel therapeutics tool to boost our fight against the virus. In this review, we discuss exosome biogenesis and its role in different COVID-19 virus transmission and its potential as a novel therapeutic agent.

Materials and Methods

Exosome biogenesis

According to guidelines of the international society of extracellular vesicles (ISEV), extracellular vesicles (EVs) encompasses three types of vesicles namely exosomes, microvesicles (MVs), and apoptotic bodies (ABs) [11]. They are categorized based on their origin and size. Each subclass of EVs has specific physicochemical properties along with specific roles in normal and pathological conditions. Exosomes are the smallest subclass of EVs ranging from 30–120 nm in diameter and originating from the endosomal pathway where they are formed by inward budding of multivesicular bodies (MVBs) membrane, thereby creating intraluminal vesicles (ILVs) inside MVBs [12]. Upon fusion of MVBs with the plasma membrane, ILVs are secreted into the extracellular space. Endosomal Sorting Complex Required for Transport (ESCRT) machinery located on MVB's membrane is responsible for generation of ILVs. ESCRT machinery mediates loading of exosomal content, membrane remodeling and invagination to form ILVs. ESCRT consists of four complexes such as ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III and appendix molecules that segregate and sorts proteins inside ILVs. Exosome biogenesis is a multistep sequential event, initiated by ESCRT-0 which identifies cargo, and sort them into nascent ILVs, following which in following the collaboration of ESCRT-0, I and -II, leads to membrane invagination and then vesicle maturation. Finally the vacuolar ATPase Vps4 facilitates membrane scission and ILVs formation within the lumen of MVBs. Recently, ESCRT-independent mechanisms of exosome generation have been reported [13]. Ceramide, a cone-shape lipid, mediates exosome biogenesis in an ESCRT-independent manner. Ceramides mediate a spontaneous inward curvature on MVB's membrane, leading to the production of ILVs. ESCRT-dependent and ESCRT-independent mechanisms may act alternatively or synergically to generate MVBs inside the cells. Following this the mature MVBs are either destined for degradation by fusing with lysosomes or fuse with the plasma

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membrane to release ILVs into the extracellular milieu as exosomes [14].

Exosome in Virus Transmission

Exosomes can transfer viral proteins, RNA, DNA and receptors from infected cells to healthy cells that make healthy cell more susceptible to infection. Exosomes and viruses share many common properties like, size, structure, generation and even in uptake by the recipient cell. ESCRT machinery is involved in both exosome and virus generation. Exosomes are known to transfer HIV proteins to target cells and contribute towards infection spread by making target cells susceptible to HIV infection. Exosomes carries HIV protein Nef which is capable of inducing senescence or death in CD4+ T lymphocytes [15, 16]. It also suppresses cytotoxic immune responses of T cells. In addition to T cells, Nef+ EVs could suppress the adaptive immune response by inhibiting the production of IgA and IgG in B cells. Another virus Hepatitis C virus (HCV) is also encapsulated into MVBs and escapes diseased cell via the exosomal secretory pathway [9]. Longatti et. Al [17] showed that exosomes are the key tool for HCV transmission. Exosomes mask the HCV virus with host structure thus, escaping host immune response and increases infection by utilizing host receptors [18]. Cytomegalovirus (CMV)-infected cells shed exosomes that suppress antiviral responses of the host and increases viral infectivity [9, 19]. Exosomes from CMV-infected cells contains lectin and DC-specific intercellular adhesion molecule-3 grabbing non-integrin proteins (DC-SIGN), which are required for virus uptake. Exosomes from EBV-infected cells secrete proteins, which may affect viral infectivity. Exosomes from EBV-infected nasopharyngeal carcinoma cells contain galectin-9 [20] that interacts with the T-cell immunoglobulin and mucin domain 1 (TIM-1) on T cell membrane and causes apoptosis in T cells. Exosomes-derived from EBV-infected cell increased the expression of adhesion molecules like ICAM-1 in target cells thus making it more potent for the uptake of virus particles [21].

Exosomes in COVID-19 virus Transmission

Coronaviruses are enveloped, spherical or pleomorphic viruses, that have single-stranded positive-sense RNA genome. They refer to a wide virus family causing common cold and severe infection like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [22]. In December 2019, a new novel coronavirus infectious disease characterized by acute respiratory impairment broke out in Wuhan city of Hubei province in China. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) commonly known as COVID-19 virus [23]. COVID-19 virus may use the host cell protein dipeptidyl peptidase 4 (DPP4, CD26) for entry, viral spike glycoprotein interacts with DPP4, and gains entry into the host cell. Several tetraspanins which are enriched in exosomal membrane may aid in coronavirus fusion event [24, 25]. Earnest et al. observed that the exosomal tetraspanin protein CD9 and TMPRSS2 facilitate MERS-coronavirus entry and robust infection of mouse lungs in vivo [26]. It would not be surprising if CD9 also promotes entry of COVID-19 virus. Coronavirus infections also increased circulating exosomes which contained lung-associated self-antigens as well as viral antigens and 20S proteasome. The presence of COVID-19 virus within the vacuoles or double membrane vesicles (DMVs) was observed by careful post-mortem histopathological analysis of the renal samples of patients infected by COVID-19 virus [27, 28]. Furthermore, DMVs with possible viral assemblies were found near the rough endoplasmic reticulum (RER), suggesting a similar mechanism of the COVID-19 viral assembly is analogous to that of SARS-CoV [29]. These findings raised the possibility for the use of the exosomal pathway for transport of COVID-19 virus. There is evidence indicating that exosomes transfer angiotensin-converting enzyme 2 (ACE2) a receptor of COVID-19 virus to recipient cells [30], supporting 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 RNAs, miRNAs and proteins may be packaged into exosomes the same as other viruses and transferred to healthy cells making them more susceptible towards infection.

Exosomes as a COVID-19 Diagnostic Tool

The difference in composition of exosomes in health and infected patients has been extensively reported. These differences, together with easy isolation, stability of exosomes and easy storage, make exosomes an excellent biomarker for diagnosis [31]. Several studies have indicated the potential role of exosomes to detect infection from minimally or non-invasive biological samples. It appears that viruses are not only able to export their own products in exosomes, but also to influence which cellular products are packaged within the exosomes. Analysis of specific exosomal content serves as a biomarker to diagnose various diseases including liver injury, cancer etc. Secretion of miRNAs in exosomes of patients with chronic hepatitis B virus (HBV) infection (CHB) [whose levels of alanine aminotransferase (ALT) were normal, while they did have liver tissue inflammation] changed depending on the severity of liver tissue inflammation [32]. The analysis of the exosomal-miRNA status represents a novel method to monitor CHB that does not rely on detection of ALT. Hepatitis C virus (HCV) has also been shown to alter the miRNA cargo of exosomes. The cargo of exosomes from patient samples showed that exosomes contain a complex of HCV RNA with Ago2, HSP90, and miR-122 [33]. A productive HCV infection occur independent of free virus after uptake of HCV-infected exosomes [34]. Therefore, miR-122 may represent a novel therapeutic target for blocking HCV infection. Similarly, we can observe the difference in exosomal cargo from COVID-19 infected and non-infected cells. Analysis of the exosoamal cargo might give us crucial information regarding differential secretion of cargo in COVID-19 -infected cells as compared to healthy cells. Specific proteins identified within exosomes isolated from COVID-19 -infected cell may serve as an important biomarker for the disease. It might help in easier and more cost-effective detection of the disease [9]. The available PCR-based methods cannot distinguish between the infectious virus and the non-infectious nucleic acid of the same virus. Analysis of exosomal cargo can give us crucial information regarding the pathogenicity of its content, thereby allowing us to distinguish between infectious and non-infectious exosomal

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content [35]. Another study found positive PCR of COVID-19 RNA only in the lungs, but not in other tissues. Concomitant, electron microscopic analysis revealed the presence of the coronavirus particles in the lung biopsy [36]. Based on these observations it was recommended that the PCR detection of the COVID-19 nucleic acid should be conducted on broncho-alveolar lavage fluid. Isolation of exosomes from patient's blood to detect the presence of viral proteins or RNA can bypass these invasive protocols with a simple blood test. Exosomes can also play an important role in masking the pathogenic viral components thus escaping standard therapeutic tools which might later lead to reinfection or reactivation.

Exosomes in COVID-19 Treatment Tool

The difference in composition of exosomes in health and infected patients has been extensively reported. These differences, together with easy isolation, stability of exosomes and easy storage, make exosomes an excellent biomarker for diagnosis [31]. Several studies have indicated the potential role of exosomes to detect infection from minimally or non-invasive biological samples. It appears that viruses are not only able to export their own products in exosomes, but also to influence which cellular products are packaged within the exosomes. Analysis of specific exosomal content serves as a biomarker to diagnose various diseases including liver injury, cancer etc. Secretion of miRNAs in exosomes of patients with chronic hepatitis B virus (HBV) infection (CHB) [whose levels of alanine aminotransferase (ALT) were normal, while they did have liver tissue inflammation] changed depending on the severity of liver tissue inflammation [32]. The analysis of the exosomal-miRNA status represents a novel method to monitor CHB that does not rely on detection of ALT. Hepatitis C virus (HCV) has also been shown to alter the miRNA cargo of exosomes. The cargo of exosomes from patient samples showed that exosomes contain a complex of HCV RNA with Ago2, HSP90, and miR-122 [33]. A productive HCV infection occur independent of free virus after uptake of HCV-infected exosomes [34]. Therefore, miR-122 may represent a novel therapeutic target for blocking HCV infection. Similarly, we can observe the difference in exosomal cargo from COVID-19 infected and non-infected cells. Analysis of the exosoamal cargo might give us crucial information regarding differential secretion of cargo in COVID-19 -infected cells as compared to healthy cells. Specific proteins identified within exosomes isolated from COVID-19 -infected cell may serve as an important biomarker for the disease. It might help in easier and more cost-effective detection of the disease [9]. The available PCR-based methods cannot distinguish between the infectious virus and the non-infectious nucleic acid of the same virus. Analysis of exosomal cargo can give us crucial information regarding the pathogenicity of its content, thereby allowing us to distinguish between infectious and non-infectious exosomal content [35]. Another study found positive PCR of COVID-19 RNA only in the lungs, but not in other tissues. Concomitant, electron microscopic analysis revealed the presence of the coronavirus particles in the lung biopsy [36]. Based on these observations it was recommended that the PCR detection of the COVID-19 nucleic acid should be conducted on broncho-alveolar lavage fluid. Isolation of exosomes from patient's blood to detect the presence of viral proteins or RNA can bypass these invasive protocols with a simple blood test. Exosomes can also play an important role in masking the pathogenic viral components thus escaping standard therapeutic tools which might later lead to reinfection or reactivation.

Exosomes in COVID-19 Treatment Tool

Exosomes can be remodelled as immunogenic factors for the treatment of SARS coronavirus infection. Kuate et al. reported that exosomes containing the SARS coronavirus spike S protein induced high titers of neutralizing antibody that were promoted by priming with the SARS coronavirus spike vaccine and then increasing with the useful adenoviral vector vaccine [37]. Besides, exosomes from coronavirus may be useful for delivering therapeutic agents directly to the infected cells as they contain specific targeting molecules, ACE2. They may be loaded with specific drugs or biological modulators that inhibit virus spreading and replication and targeted to specific virus infected cells. Exosomes can influence both adaptive and innate immune response. Exosomes carries peptide/MHC class II complexes and can prime specific immune responses [38]. In this regard Anticoli et al. [39] built an exosome-based platform for the generation of vaccines. It aimed at stimulating an effective antigen-specific cytotoxic T lymphocyte (CTL) immune reaction. A highly detectable and specific CD8+ T cell reaction was observed for all viral proteins tested, which included Ebola virus virion proteins VP24, VP40, and nucleoprotein (NP), the Crimean-Congo hemorrhagic fever virus NP, the influenza virus NP, the West Nile virus non-structural protein 3 (NS3), and the hepatitis C virus NS3. Another potential use of exosomes in vaccines is as adjuvants. Qazi et al. show that ovalbumin (OVA) loaded exosomes can act as an adjuvant. They exposed dendritic cells to OVA, following which they isolated exosomes loaded with OVA [40]. Co-administration OVA-loaded exosomes with antigen enhanced the humoral response, augmented specific T-cell responses, and promoted a Th1-type shift in the immune response. Interestingly, a phase I/II clinical trial (NCT04389385) has been registered to test the efficacy of T cell derived exosomes as a potential treatment for COVID-19. In this treatment regime donor originated COVID-19 specific T-cells (CSTC) are in vitro activated and expanded by exposing them to specific viral peptide fragments in the presence of natural immune stimulatory proteins (cytokines). These activated T cells stimulate the secretion of IFN gamma within exosomes. The study proposes to treat COVID-19 patients who are at early stages of pulmonary disease with CSTC-exosomes to control disease progression [41]. Furthermore, mesenchymal stem cell-exosomes had anti-inflammatory responses in 24 severe COVID-19 patients. These patients were given a dose of ExoFloTM (a BM derived MSC-exosome product) at a single hospital center [42]. Of the 24 patients, 17 fully recovered. These results suggest a promising role exosome might play as a therapeutic tool to fight this novel COVID-19 virus (**Figure 1**).

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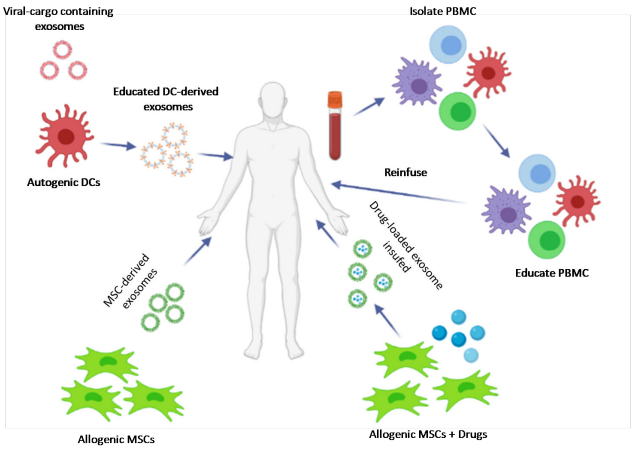
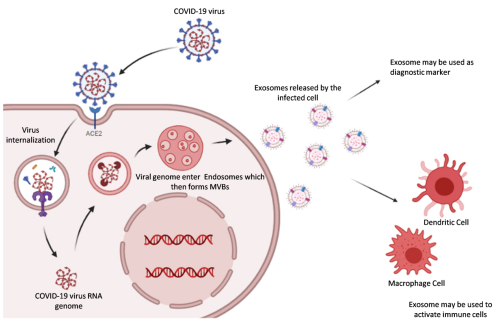


(**Figure 1**): Schematic representation showing the potential role of immune cells and exosomes derived from MSCs and dendritic cells in combating COVID-19 infection. Reinfusion of autologous-activated immune may be fight against COVID-19 virus. Synergistic effect of MSC-derived drug-loaded exosomes or allogenic MSC-derived exosomes may be utilized as an effective approach against the virus. The therapeutic cargo present in exosomes aids in the reduction of inflammation, cellular repair, alveolar fluid clearance, and other damage caused to the lung during viral infection.



(Figure 2): Graphical Abstract

Conclusion

In the recent years many in vitro studies and a limited number of pre-clinical in vivo studies demonstrated that exosomes play pivotal roles in infectious diseases. Exosomes-based therapeutic tools have attracted scientists' attention and revolutionized modern medicine. However, as with numerous experiments on exosomes, there exist challenges in analyzing the results and conclusions from the results remain elusive. The main obstacle is the different approaches for exosome isolation and characterization which were used in different studies. Furthermore, industrial scale-up of the therapeutic exosomal product remains a challenge along with maintaining homogeneity between different batches of the product. Though clinical exosome-based studies are on the rise (https://clinicaltrials.gov), there are currently no USA Food and Drug Administration (FDA)-approved exosome products, thus more scrutiny and validation is necessary. In the case of COVID-19 virus, exosomes may contribute to the spread of the infection. Exosomes harbours receptors for COVID-19 virus entry like CD9 and ACE2, which are involved in promoting COVID-19 virus infection (30). These viral-cargo containing exosomes might be used to train and educate the host immune cells and might further be used as a vaccine to stimulate anti-viral immune response. More preclinical and clinical application of exosomes for treatment COVID-19 infection could be proposed, which might include mesenchymal stem cell-derived exosome therapy, T cell-derived exosome therapy, exosome-based drug delivery, inhibition of exosome biogenesis and uptake, and exosome-based vaccine. There is currently no vaccine or specific antiviral treatment existing for COVID-19 viral infection, thus understanding the exact role of exosomes in COVID-19 sepsis not only increases our knowledge about kinetics of this virus but will also open new avenues promoting more effective prevention and treatment. Overall, the interwoven relationships between viruses and exosomes have indicated novel areas of research with therapeutic potential.

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Ethics approval

Not applicable.

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Conflict of Interest

There is no conflict of interest

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