

EDITORIAL

Extracellular Vesicles and Their Significance in COVID-19

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ARTICLE INFO

Article history

Received: 25 April 2022

Accepted: 05 May 2022

Published Online: 18 May 2022

Over the last few years, there is huge scientific attention towards the research related to Extracellular Vesicles (EVs), because of their unique property of inter cellular communications and effective biological significance in diagnosis and therapy^[1]. Extracellular Vesicles are lipid bilayer membrane bound biological entity, which contains different bioactive compounds (cargoes) such as microRNAs (miRNAs), mRNAs, proteins, and lipids. Based on their origin and size, EVs have been categorized into three different types (a) Exosomes (40 nm-150 nm) are smallest EVs, which are synthesized by endocytic pathways in the cells and secreted in extracellular space

through exocytosis process, (b) Microvesicles are secreted from direct budding off plasma membranes and their size varying from 50 nm to 1000 nm and, (c) Apoptotic bodies are formed during apoptotic cell death process and respectively larger in size > 1000 nm^[1-3]. EVs have been identified using different markers, that includes tetraspanins proteins (CD9, CD63, CD81, and CD83), endosomal sorting complexes required for transport (TSG101, Alix), heat shock proteins (Hsp60, Hsp70, Hsp90), and Rab proteins (RAB27a/b)^[1].

EVs have been considered as key transporters of cargoes for intercellular communication by passing

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DOI: <https://doi.org/10.30564/ahpr.v4i1.4661>

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signals from one cells to neighbour or remote (target) cells to regulate their physiological process. In pathological conditions, the quantity of EVs and their molecular cargo varies as compared to normal cells. In such condition, EVs may remodel the target cell by affecting the immune cells, consequently could regulate cell proliferation and migration in cancer and other diseases via enhancing inflammation^[4], that depicts their role in pathogenesis of various diseases such as cancer, diabetes, cardiovascular, neurodegenerative and kidney disease^[5]. In latest COVID-19 pandemic disease, EVs has been associated with dual role in both pathogenesis and therapeutics. Researcher reported that EVs derived from virus infected cells modulate the immune system of the host, leading to increase in the rate of viral load^[6,7]. Recent studies have demonstrated that the structures of SARS-CoV2 and EVs are very similar. Therefore, it was hypothesized that SARS-CoV2 might exploit EVs to get exit from the cells; whereas EVs may use virus penetration mechanism for the delivery of their cargoes. Hence, the concept of interaction between virus and EVs could be employed for the development of vaccines and drug against COVID-19 management^[8]. EVs have been also associated in enhancing the lung immunity and it is well known that lung is most affected organs in COVID-19, hence EVs might be very useful in repairing lungs during COVID-19 infections^[9].

Therapeutic Potential of EVs for COVID-19

Mesenchymal Stem Cells (MSCs) were known for their therapeutic utilities in the treatment of various diseases, because of their potential regenerative and immunomodulatory properties. The numerous research studies have demonstrated that MSC-derived EVs perform similar role to their origin of cells i.e., MSCs, suggesting that therapeutic potentials of MSCs in various diseases are mainly performed by their secreted EVs^[1]. Studies have suggested that both EVs and MSCs have anti-inflammatory and immunomodulatory properties, which might suppress developing edema in lungs^[1]. Hence, EVs derived from MSCs have drawn great scientific attention for their therapeutic utilities as a cell-free therapy for various diseases.

EVs were assumed to be involved in the treatment of COVID-19 disease via delivering their immunomodulatory and anti-inflammatory microRNAs (miRNAs) and proteins to infected or activated alveolar cells in lungs^[10-12]. It has been reported that EVs carry various types of miRNAs such as let-7, miR-124-3p, miR-21-5p, miR-146a and miR-145. Of which, miR-124-3p was associated with the suppression of oxidative stress and inflammatory

cytokines through interaction of its receptor P2X ligand-gated ion channel 7 (P2X7)^[10]. Also, it has been demonstrated that there is huge production of inflammatory cytokines, leading to cytokines storm and lung damages during COVID-19 infection. Another miR-21-5p of EVs has been linked with reduced apoptosis of lung cells by inhibiting PTEN and PDCD4, whereas miR-146a were involved in transformation of pro-inflammatory macrophages to anti-inflammatory condition using suppression of NF- κ B signalling pathway^[10]. In last, miR-145 of EVs have been reported to enhance the phagocytic capacity of macrophages for quick and speedy removal of pathogens in respiratory tract and lungs^[13]. Hence, these miRNAs of EVs could be utilized as potential therapeutic molecule against COVID-19. However, our knowledge on these EVs is very limited, and more experimental works are much needed to make sure their therapeutic potential to combat COVID-19 pandemic.

EV-Based Vaccines for COVID-19

EVs have been known for various properties such as highly stable, less toxic, and low-immunogenicity, which make them a potential biological entity in developing vaccines against COVID-19^[14]. Currently, vaccines are very promising in preventing SARS-CoV-2 infection in humans all over the world. As of now, various vaccines are being utilized to enhance immunity against SARS-CoV-2, which saved huge population from death worldwide^[14]. Till date, lipid nanoparticles have been considered as a good carrier for vaccine development against COVID-19. Many vaccines utilized nanoparticles, which encapsulated mRNAs-1273 (BNT162b1, CVnCoV) and saRNAs (LNPN CoVsRNA) and have been given to human population as a preventive measure for COVID-19 infection in different regions including Germany, Belgium, and the United States^[15]. As a naturally biological nanovesicles, EVs may be an alternative novel source of carrier in developing vaccine to combat with this deadly pandemic^[16,17]. Vaccines utilizing EV carry SARS spike proteins and its efficacy was checked and compared with adenoviral vector vaccine. Both types of vaccines (EV-vaccines and adenoviral vectors) have shown promising results in neutralizing antibodies at the same level. Later, maximum level of antibody reutilization was achieved when combination of both adenoviral vector and EV based vaccine was assessed, which was higher than the convalescent serum of SARS patients^[18].

EVs were reported to bind with immune cells and activate immune reactions, which helps in recognition and neutralization of specific types of cells^[19]. Also, EVs have been shown to have a greater efficiency than

that of soluble proteins which are utilized in vaccine development. This property might contribute in producing higher copies of the same viral protein, resulting into enhanced cross-linking of EVs and B-cell receptors^[20]. These pieces of evidences suggest that EVs carrying SARS-CoV-2 components might be very useful in developing COVID-19 vaccine.

Conclusions

In spite of multiple treatment methods such as drugs and vaccines applied for overcoming COVID-19 pandemic, a multidirectional strategy must be established to reduce the pervasiveness of SARS-CoV2. Even after getting multiple dose of vaccines, people have been tested positive for COVID-19, and their symptoms got severe and worsen. Therefore, in order to treat the severe cases and prevent aggravation, Extracellular Vesicle (EVs-Exosomes and Microvesicles) therapy might be a potential alternative therapeutic choice. As EVs has been known to have immunomodulatory, regenerative, and antibacterial properties, which might contribute to COVID-19 therapy. Based on these evidences, EVs might be utilized as a cell-free therapy and as a natural drug delivery vehicle in COVID-19 management.

Acknowledgment

Sanjay Kumar would like to thanks Sharda University for all the resources.

Conflict of Interest

There is no conflict of interest.

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