

# Roles and Clinical Applications of Extracellular Vesicles in Covid-19 Virus Infection

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## Short Communication

Received: 11/07/2020

Accepted: 23/07/2020

Published: 31/07/2020

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**Keywords:** Covid-19; Virus Infection; Prostatosomes; Biogenesis

Exosomes are a subgroup of extracellular vesicles (EVs) that are lipid-bilayer enclosed entities [1,2]. They are released by most cell types and present in a wide variety of body fluids. They were first described in prostatic fluid and seminal plasma, and traditionally termed "prostatosomes" due to their origin in prostate epithelial cells. Biogenesis of exosomes starts with formation of endocytic (invaginating) vesicles at the plasma membrane of any cell through clathrin- or nonclathrin-mediated endocytosis giving rise to intracellular formation of early endosomes. These endosomes undergo a maturation process that includes an interaction with the Golgi apparatus to become late endosomes [3-9]. The bilayer membrane surrounding late endosomes can in turn be subjected to invaginations, forming intraluminal vesicles completing what is called multivesicular bodies (MVB) intracellularly. The MVB will fuse with the plasma membrane in order to release their content (intraluminal vesicles) by exocytosis. The secreted extracellular vesicles are termed "exosomes". It should be noted that the exosomal membrane is right-side-out in relation to the plasma membrane due to the aforementioned double invaginations.

Membrane cofactor protein, also known as CD46 is associated with the prostatosome membrane. CD46 is a measles virus receptor. Historically Kitamura et al reported that prostatosomes were able to neutralize measles virus infectivity through membrane-bound CD46. These authors also pointed out that soluble forms of CD46 devoid of a membrane architecture were insufficient for blocking viral infection. A reasonable interpretation for this finding was presented meaning that prostatosomes function like a "mock cell" by binding the virus and therewith rendering it unable to infect other cells [10,11]. Hence, a role in antimicrobial defense was early observed being attributed to prostatosomes/exosomes.

Exosomes released into the airways during influenza virus infection have been characterized. The exosomes changed dynamically in protein composition over the course of infection with increasing expression of host proteins with known anti-influenza activity, and viral proteins with potential to trigger host immune responses. It was shown that attachment factors for influenza virus, alpha 2,3 and alpha 2,6-linked sialic acids were present on the surface of airway exosomes. These exosomes had the ability to neutralize influenza virus, thereby preventing the virus from binding and entering target cells [12].

The target for Covid-19 virus is the angiotensin-converting enzyme 2 (ACE2) receptor, predominantly localized in pulmonary alveoli cells and in the brush border of intestinal enterocytes. It could be anticipated that in analogy with release of exosomes into airways during influenza virus infection, exosomes likewise would be found in airways of affected patients during Covid-19 virus infection. Such exosomes in the airways would most probably carry the ACE2 receptor on their membrane surfaces (being right-side-out as mentioned above) similarly to what is the case for their host alveoli cells, thus restraining the viral attack already in the airways [13,14].

Severe Covid-19 virus infection can induce a cytokine storm leading to acute respiratory distress syndrome and multiple organ failure. Mesenchymal stem cell therapies and, more recently, their released exosomes are highly regarded for their regenerative capacities. In addition, they possess immunoregulatory functions affecting all types of innate and adaptive immune cells [15-17]. Therefore, these exosomes could be beneficial, alone or in combination with other therapeutic agents, in patients infected with Covid-19 virus. Since stem cells and therewith their released exosomes do occur in circulating blood, it is suggested that simply, blood plasma transfusions would be beneficial for patients with Covid-19 virus infection due to presence of stem cell exosomes in blood plasma.

There is evidence that viruses can use exosome endocytic routes to enter uninfected cells and hijack the exosomal secretory pathway for infection. What is more, exosomes play a role in immune response against virus pathogens, and virus infected cells produce exosomes that are important mediators of antiviral responses [18].

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