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Extracellular vesicles engagement during respiratory viruses infection

Maria Alfreda Stincarelli [1], Rosaria Arvia [1], Simone Giannecchini [*]

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

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ABSTRACT

Respiratory viruses infection is a worldwide human concern annually. The main viral respiratory diseases are caused by a variety of viruses sharing similar threats and affecting the respiratory system. Among all, influenza viruses, respiratory syncytial virus, parainfluenza viruses, respiratory adenoviruses, rhinoviruses, human bocaviruses, human metapneumovirus and coronaviruses are the main common respiratory viruses affecting human population. The recent coronavirus disease 19 pandemic has revealed critical knowledge gaps required to update in the transmission and pathological induced pathways for respiratory viruses. To date, several evidences suggest that human viruses can hijack extracellular vesicles (EVs) to deliver proteins, mRNAs, microRNAs and whole viral particles during viral life cycle in the host. Thus, several investigations have reported that also respiratory viruses use EVs to deliver viral nucleic acid and proteins, even including the potentiality of carrying whole viral particle. This evidence demonstrates the ability of the EVs produced in infected cells to deliver respiratory viral components to uninfected cells, positively or negatively counteracting new viral infection. Additionally, EVs derived from biological fluids of clinical samples may increase the risk to induce severe respiratory viruses-associated diseases in site far from the respiratory tract and for prolonged time. Here, it has been reviewed the advantages of the respiratory viruses EVs interaction regarding their ability to enhance viral infection, to evade antiviral response, to regulate virus-immune response and to mediate diseases. All these data confirm a potential role of the association between EVs and respiratory viruses infection. This suggests that further studies to define the implication of this interaction in viral life cycle in human population are needed.

1. Introduction

To date, the high circulation of the respiratory virus infections among healthy humans, with potentially lethal consequences in fragile people, poses a major concern in public health. Among the main emerging respiratory virus epidemics, seasonal influenza virus type A and B and their potential pandemic threat, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS)-CoV and the newly emerged SARS-CoV-2 pandemic, are responsible for different grade of severity worldwide (Nichols et al., 2008; Pavia, 2011; Abdelrahman et al., 2020). Moreover, other different respiratory viruses such as human coronaviruses (HCoVs) OC43, HKU1, 229E, and NL63, human respiratory syncytial virus (HRSV), human Adenoviruses (HAdVs), human bocaviruses (HBoVs), parainfluenza viruses (PIVs), human metapneumovirus (HMPV), and enteroviruses/rhinoviruses are causes of respiratory tract (lungs, throat, airways) infection (Nichols et al., 2008; Pavia, 2011).

Seasonality of the circulation of most of the respiratory viruses (including enveloped and naked viruses with DNA and RNA genome; Table 1) is well known. Outbreaks of influenza virus, human coronaviruses, and HRSV occur clearly in winter (Abdelrahman et al., 2020; Tamerius et al., 2011; Midgley et al., 2017), some enteroviruses, exhibiting frequency in summer (Abedi et al., 2018), HAdvs, HBoVs, HMPV, and rhinoviruses (with a peak in spring and fall) detected throughout the year (Morikawa et al., 2015; Bastien et al., 2006; Haynes et al., 2016) and PIVs showing a type-specific pattern of seasonal circulation (Abedi et al., 2016).

The virus infection of the respiratory tract is mediated by direct/indirect contact with respiratory secretions expelled by coughs, sneezes, talks or laughs. In general, the viral spread can be mediated by small droplets that remain suspended in the air and travel long distances, and/or by larger droplets that don't remain suspended in the air and run across short distances (Wang et al., 2021). In this context, the lower respiratory tract is targeted by aerosol-mediated infections, whereas the upper respiratory tract may be targeted by larger droplets (Wang et al., 2021). In most cases, respiratory viruses enter and replicate in nasopharyngeal epithelial cells or in the epithelium of the lower respiratory tract.

* Corresponding author. Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze, Viale Morgagni 48, I-50134, Firenze, Italy.
E-mail address: simone.giannecchini@unifi.it (S. Giannecchini).
[1] Both authors contributed equally.

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Abbreviations

SARS-CoV	severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
HCoVs	human coronaviruses
HRSV	human respiratory syncytial virus
HAdVs	human Adenoviruses
HBoVs	human bocaviruses
PIVs	parainfluenza viruses
HMPV	human metapneumovirus
NDV	New castle disease virus
ARDS	acute respiratory distress syndrome
EVs	Extracellular vesicles
ESCRT	endosomal sorting complexes required for transport
MVBs	multivesicular bodies
ERGIC	endoplasmic reticulum and Golgi intermediate compartment
ICAM	integrins cell adhesion molecules
HAV	Hepatitis virus A
HEV	Hepatitis virus E
HIV	human immunodeficiency virus
JCPyV	Polyomavirus JC
BKPyV	Polyomavirus BK
BALF	bronchoalveolar lavage fluid
miRNA	microRNA
CCL	Chemokine Ligand
TNC	tenascin-C
TNF-alfa	tumor necrosis factor-α
IL	interleukin
ACE2	Angiotensin-converting enzyme 2
PD	Parkinson disease
CNS	central nervous system
FGB	fibrinogen-β

Table 1
Main common respiratory viruses, structure, size, genome, seasonality and principal syndromes.

Virus	Structure and size	genome	Seasonality prevalence	Principal syndromes
human respiratory syncytial virus	Enveloped (150 nm)	Negative-sense, single-stranded RNA	Winter (November–March)	Upper respiratory syndrome, bronchiolitis, croup, bronchitis, pneumonia
human parainfluenza virus	Enveloped (150–200 nm)	Negative-sense, single-stranded RNA	March–June and August–November	Upper respiratory syndrome, croup, bronchiolitis, bronchitis, pneumonia
human rhinovirus	Naked (15–30 nm)	Positive-sense, single-stranded, RNA	Spring/Fall	Upper respiratory syndrome, asthma and COPD exacerbation
Adenovirus	Naked (60–90 nm)	Double-strand DNA	All year	Upper respiratory syndrome, pharyngoconjunctival fever, bronchitis, pneumonia
human Coronavirus	Enveloped (60–160 nm)	Positive-sense, single-stranded RNA	Winter (December–April)	bronchitis, pneumonia
SARS-CoV 1,2	Enveloped (60–160 nm)	Positive-sense, single-stranded RNA	All year	severe acute respiratory syndrome, Coronavirus disease 2019
Influenza virus	Enveloped (80–120 nm)	Negative-sense, segmented RNA	Winter (November–April)	
human metapneumovirus	Enveloped (150–600 nm)	Negative-sense single-stranded RNA	Spring	Upper respiratory syndrome, bronchitis, pneumonia
human bocavirus	Naked (18–26 nm)	Single-stranded DNA	All year	Upper respiratory syndrome, bronchiolitis, asthma exacerbation, bronchitis, pneumonia

However, in severe cases, a subsequent systemic spreading of the virus may also occur (Wang et al., 2021). Respiratory virus acute infections are usually self-limited confined to the upper airways and eliciting relatively mild symptoms such as sneezing and rhinorrhea (Zaas et al., 2009). However, in susceptible patients (newborns and the elderly) severe forms may occur affecting the lower airways. These severe forms produce shortness of breath, bronchiolitis, pneumonia or acute respiratory distress syndrome (ARDS) (Olenec et al., 2010). Respiratory viruses infection may produce low cytotoxic effects but can also cause extensive inflammation, epithelial shedding and an increased vascular permeability (Nelson et al., 2022). During infection the innate immunity, mainly regulated by the interferon pathway and several cytokines and chemokines, is implicated in virus-induced inflammation (Devasthanam, 2014). In particular, the interferon system involves the following steps: 1- the viral recognition receptors (group of receptors located in the cytoplasm and on the surface of endosomes) including RIG-1, MDA-5, and TLRs 3, 7, 8, and 9; 2- the signaling pathways leading to interferon production (mediated by IRF-3, NFκB, and AP-1); 3- interferon-induced antiviral proteins (JAK-STAT signaling pathway composed of the JAK and TYK2 kinases, IRF-9, and STAT proteins) (Devasthanam, 2014; Luo and Zhang, 2017). The pro-inflammatory response is mediated by the NF-kB pathway, with the activation of pro-inflammatory cytokines (TNF-α, IL-1, IL-6), chemokine (IL-8), inflammatory enzyme (COX-2), angiogenic factor VEGF, protease MMP-9 and anti-apoptotic factors (GADD45β, BFL1 and BCL-X1) (Luo and Zhang, 2017). As reported for other viruses, mechanisms that circumvent the interferon signaling pathways are produced by the respiratory viruses to evade host defenses (Devasthanam, 2014). These include viral proteins that inhibit the IRF-3, NFκB, and AP-1 signaling pathways and the JAK-STAT signaling pathway. In this context, the well documented evolved strategies implicated in the inhibition of upstream mediators (like TLRs 7 and 8, RIG-1, MDA-5) of interferon induction are the influenza virus NS1 protein, Parainfluenza virus V protein, HRSV and many SARS-CoV-2 proteins (Schlende et al., 2005; Gack et al., 2009; Andrejeva et al., 2004; Znaidia et al., 2022). Respiratory viruses not only induce a local inflammatory reaction in infected epithelial cells, but may also act remotely through neuronal pathways. Additionally, humoral immunity is also activated in response to viral infections with the production of serotype-specific antibodies. However, the nature of the outcome and host response is dependent on age, previous infections and vaccination status of the host.

The aim of this review is to understand on how extracellular vesicles (EVs), exploiting factors of respiratory viruses, can influence transmission and host airway response mostly by their ability to enhance viral infection, to evade antiviral response, to regulate virus-immune response and to mediate diseases.

2. EVs and viruses shared biogenesis pathway

Examination of the virus life cycle reveals cellular molecular factors that regulate the endocytosis and the exocytosis pathways implicated in early and late stages of viral cell infection (Fig. 1 (Yamauchi and Helenius, 2013; Robinson et al., 2018);). Notably, these cellular pathways, in which the endosomal sorting complexes required for transport (ESCRT) and the Rab host factor play a pivotal role, enrolled in the viruses processing and maturation, are implicated in EVs generation (Robinson et al., 2018). EVs are a heterogeneous group of membrane vesicles secreted by almost all cell types (Raposo and Stoorvogel, 2013). The main role of EVs is implicated in discarding unwanted material (proteins, nucleic acid), signaling vehicles in normal cellular homeostatic processes, as T-cell stimulation and immune tolerance (Colombo et al., 2014; van Niel. et al., 2018). Additionally, EVs may be produced as a consequence of pathological developments (van Niel. et al., 2018; Mathivanan et al., 2010; György et al., 2011; Kubo, 2018). EVs include multiple classes based on the main mechanism of their generation (György et al., 2011): 1- Exosomes (vesicles 30–150 nm in size), which are produced by the endocytic pathway, accumulate into large multivesicular bodies (MVBs) and are mainly delivered by fusion with the cell membrane; 2- ectosomes or microvesicles (vesicles 100–1000 nm in size), which are formed by direct budding from the plasma membrane or released by the fusion of double-membraned autophagosomes with the plasma membrane; 3- apoptotic bodies (vesicles 100–5000 nm in size), which are released upon cell fragmentation during apoptotic cell death (van Niel. et al., 2018; Mathivanan et al., 2010). All these EVs share some molecular marker (mainly Tetraspanins: CD9, CD81 CD63) and other host cell specific molecules (van Niel. et al., 2018).

Exosomes, accumulated intraluminal vesicles into MVBs produced by early endosomes, can fuse with lysosomes, to be used in the degradation pathway, or with the cellular membrane and released into the extracellular space. These processes are mediated by several molecular factors. These include high enrichment tetraspanin molecules, endosome membrane reorganization and the recruitment of ESCRT (Pols and Klumperman, 2009; Colombo et al., 2013) which mediates membrane invagination and exosome formation (Wollert and Hurley, 2010; Davies et al., 2009). Additional ESCRT-independent mechanisms as the syndecan-syntenin-ALIX pathway or the mechanism through the inward budding of the limiting membrane of the MVBs required sphingolipid ceramide (a lipid-mediated mechanism) (Stuffers et al., 2009), have also been reported. Finally, once MVBs are formed, their fusion with the plasma membrane is mediated by the cytoskeleton; fusion machinery, such as the SNARE proteins; and molecular switches (such as small molecular weight GTPases). Alternatively, MVBs may be released through budding from the plasma membrane regardless of Rab GTPases (Goni and Alonso, 2009).

Microvesicles biogenesis requires several molecular rearrangements

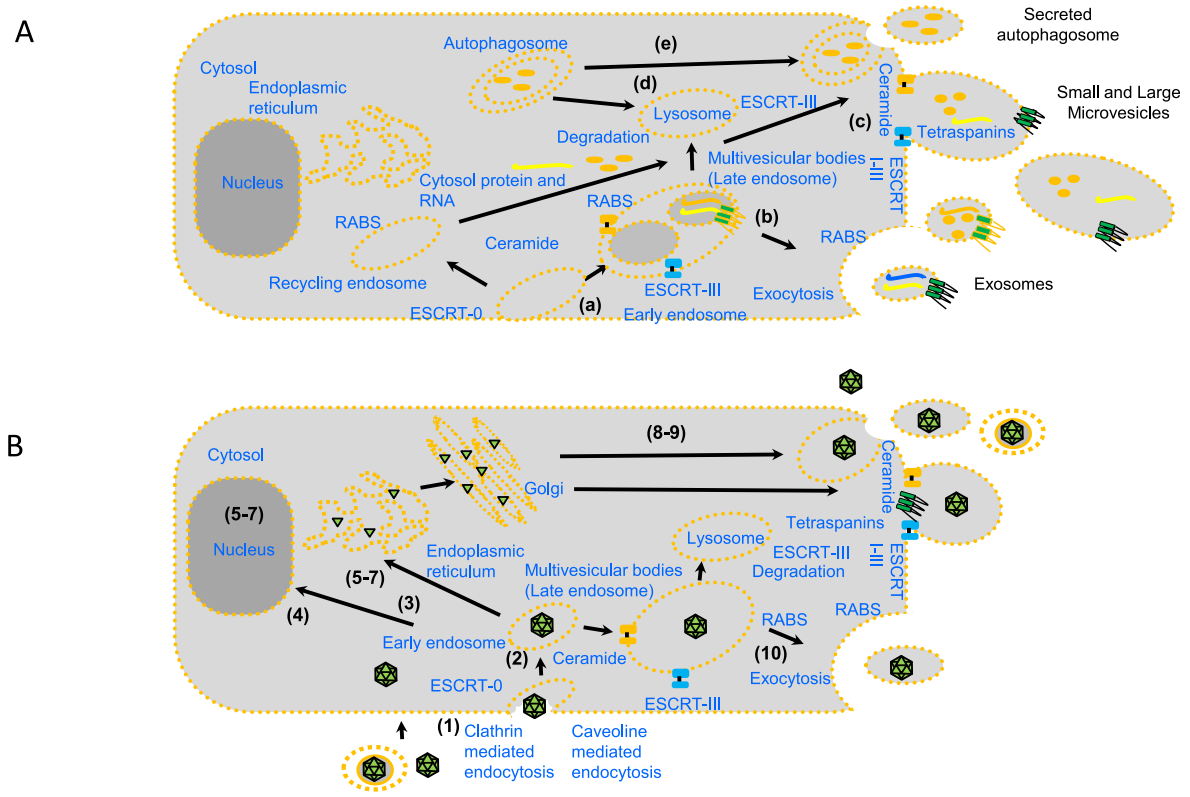

Fig. 1. Shared features between Extracellular vesicle formation and virus life cycles. EVs are formed either (a–b) as early endosomes that accumulate intraluminal vesicles within the lumen of multivesicular bodies (MVBs) that fuse with the plasma membrane to release exosomes or (c) by budding of the plasma membrane (microvesicles). Early endosomes can fuse with lysosome to fulfill the degradation pathway (d). In some cases, autophagy mechanism can leed to the formation of EVs (e). Virus infection starts with receptor-mediated interactions with specific receptors (1). Then, receptor-mediated membrane fusion (HRSV, PIV, CoV, HMPV) or endocytosis (Rhinovirus, HAdVs, HBoVs, and fusion with endosomal membrane: CoV, Influenza virus), occurs mainly by internalization through caveosomes that traffic through the cytoplasm using a microtubule network to the late endosome before being delivered to the ER (2–3). Virus internalized through clathrin-coated vesicles can also happen. In the endoplasmic reticulum, virions benefit from chaperones, disulfide isomerases and reductases, which facilitate partial capsid uncoating (3). The viral genome is delivered in cytoplasmic (HRSV, PIV, Rhinovirus, CoV, HMPV) or transported into the nucleus (HAdVs, HBoVs and Influenza virus) via the nuclear pore complex (4). Expression of early genes occurs, and initiate viral genome replication (5–6). Late genes are then expressed (7). Late proteins self-assemble to form capsids into which newly synthetized viral genome is packaged (8). Progeny virions are released from infected cells after cell lysis (Rhinovirus, HAdVs, HBoVs), by exocytosis (CoV) or budded from cell membrane (HRSV, PIV, Influenza virus, HMPV) (9). However, a small fraction of progeny virions may also be released into the extracellular environment through nonlytic egress, which depends on the cellular secretion pathway generating extracellular vesicles (10).

mediated by lipid components (mainly cholesterol) and proteins of the plasma membrane. The main proteins are Ca2+-dependent enzymes, including aminophospholipid translocases, scramblases and calpain, which mediate the exposure of phosphatidylserine from the inner leaflet to the cell surface (Savina et al., 2003). Moreover, the activities of the RHO family of small GTPases and RHO-associated protein kinase, which are important regulators of actin dynamics, are also involved (Al-Nedawi et al., 2008). Additionally, the use of ceramide-dependent mechanisms as well as ESCRT I-III molecules has been reported in microvesicle formation, showing the common role of microvesicles formation and exosomes generation in EVs biogenesis.

3. Viruses advantages in using EVs during infection

Increased evidences have recently pointed out that, other than enveloped or naked viruses features for virus hosts transmission, additional viruses strategies to improve virus propagation exploit EVs. In particular, the discovery of hepatitis A (HAV) and E (HEV) virus membrane-associated virion (Feng et al., 2013; Nagashima et al., 2014), and the demonstration of viruses transmitting as populations clustered within EVs (Chen et al., 2015), have paved the way to new assumption. Thus, the viruses EVs engagement mechanism has been implicated in the virus strategies to produce highly virulent process for viral spread among animal and human population. Despite the investigation of this virological feature is in its infancy, the list of viruses exploiting EVs during infection is steadily growing (Chen et al., 2015; Kerviel et al., 2021). This includes EVs used to deliver viral mRNA, microRNA and proteins, naked genomes and also whole virus particles (Martins and Alves, 2020). Several advantages of this viral EVs interaction (Fig. 2), documented and confirmed for different viruses, including also respiratory viruses, are: 1- EVs enhancing viral infection/transmission; 2- EVs evading antiviral response; 3- EVs regulating virus-immune response; 4- EVs mediating respiratory tract distant diseases.

4. On the EVs enhancing respiratory virus infection

The main important action of viruses is their ability to transmit and replicate into the host. To carry out this, viruses have evolved several strategies that hijack cellular molecular machineries. The respiratory viruses have a way of transmission extremely efficient, but subjected to external conditions such as temperature, humidity and UV light (Moriyama et al., 2020). Moreover, their high infectious doses are important in their transmission. Thus, all strategies act to improve external virus resistance and to increase the infective unit dose, playing a fundamental role for respiratory viruses efficacy. The presence or not of the envelope structure can impact on the virion susceptibility to environmental condition. The lipidic composition of enveloped viruses differs according to the structure of the host membrane lipids acquired. This includes plasma membrane, nuclear membrane, intermediate vesicles, endoplasmic reticulum and Golgi intermediate compartment (ERGIC) that may be made up to 50–60% of phospholipid and cholesterol. This feature may play a role in the different resistance of enveloped viruses, compared to naked

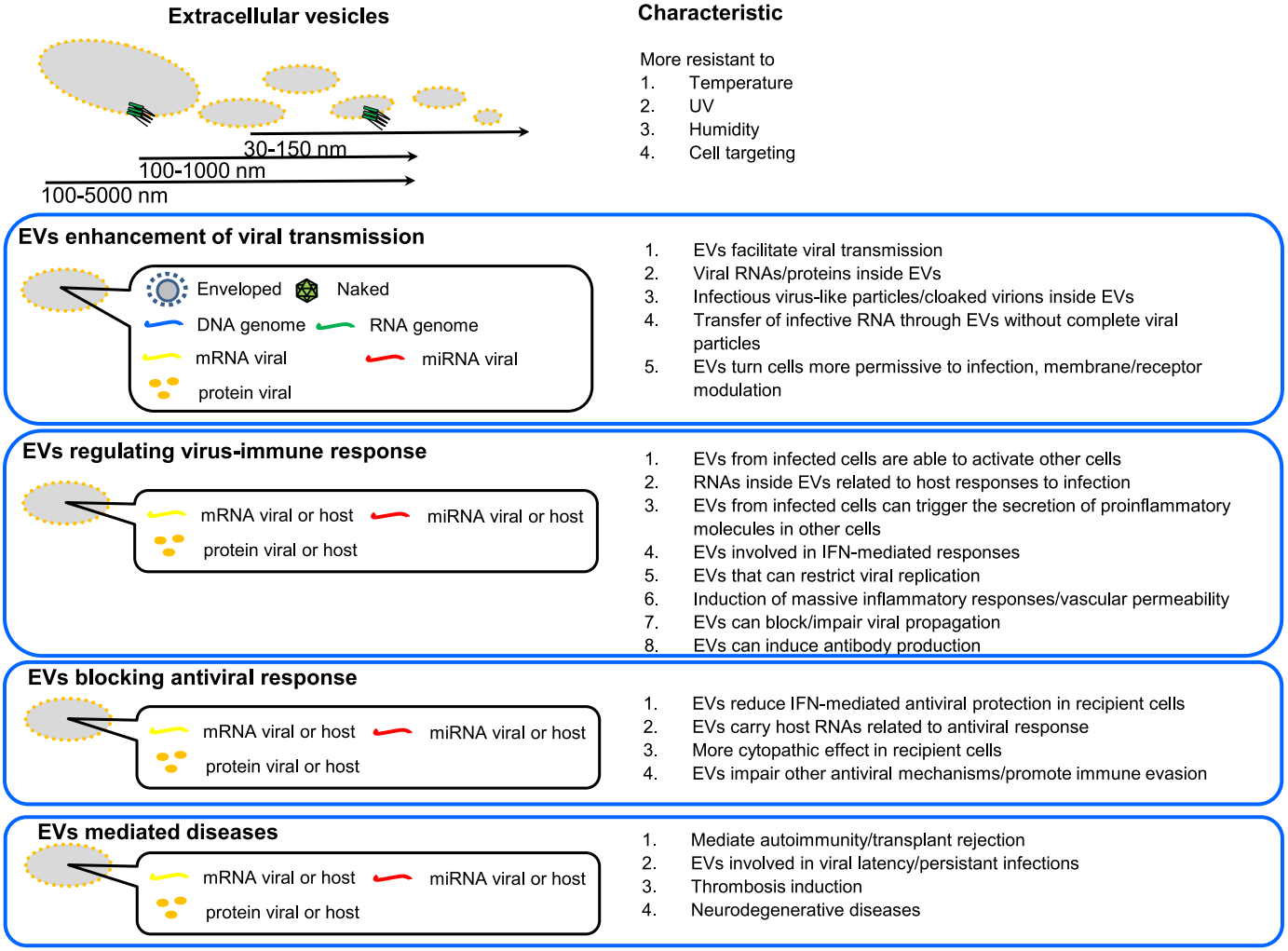

Fig. 2. Potential role of EVs in virus transmission, immune regulation, antiviral response and disease outcome.

viruses, to the temperature and detergent stability. It is experimentally proven that several respiratory viruses can exhibit differences in their vitality in response to variations of temperature and humidity. This can be determined by the properties of the viral surface proteins and lipidic membrane (Noti et al., 2013). Thus, viral transmission of viruses circulating in winter is strictly correlated with their stability at low relative humidity, compared to viruses circulating in summer or all-year, enhanced at higher humidity (Noti et al., 2013). In this context, among the enveloped respiratory viruses, it is assumed that cholesterol, sphingomyelin and phosphatidylserine lipidic, components of the viral membrane, can be determinant in its fluidity and integrity, like reported for cellular membrane counterparts (Harder et al., 1998; Ketter and Randall, 2019). Lipidic molecular species analysis of biological fluid-derived EVs have shown more than three-fold enrichment in cholesterol, sphingomyelin, and phosphatidylserine lipids over cell membranes (Skotland et al., 2019, 2020). In this context, exosomes exhibit a higher enrichment compared to apoptotic bodies and microvesicles (Osteikoetxea et al., 2015). Thus, the evidence that EVs showed a high detergent resistance point out that viruses delivered through EVs may enhance their stability in environmental condition, modulating their transmissibility. In recent years several studies highlighted EVs as a new strategy used in viral transmission. Thus, EVs produced in cellular environment for host functions can be used by the virus for its own purpose (Lee et al., 2018; Kulshreshtha et al., 2013; Bastarache et al., 2009). Of note, the main evidence reported that genome of respiratory viruses has been found associated to EVs. However, the features of particle size of many respiratory viruses (mainly ranged from 30 to 350 nm, Table 1) are compatible also for their whole particle inclusion inside the EVs. This, as demonstrated for other viruses, is possible not only for naked virus but also for the enveloped ones (Feng et al., 2013; Nagashima et al., 2014). In the effort to investigate the presence or not of EVs associated to respiratory viruses infection, several purification techniques (including ultracentrifugation, size exclusion chromatography and resin-based separation) have been used to obtain EVs highly purified from the biological fluid. Moreover, EVs characterization in size and in molecular marker has been required before their use in the studies reported. Using such procedures, it has been reported that EVs isolated from lung epithelial cells overexpressed SARS-CoV-2 RNAs, indicating that SARS-CoV-2 virus hijacking the endocytic/exosomal pathway may be delivered in a virus-loaded exosomes cargo (Kwon et al., 2020; Nunez Lopez et al., 2021; Barberis et al., 2021). Moreover, electron microscopy investigation showed that not only viral RNA alone but also virions of SARS-CoV and SARS-CoV-2 can be included within double membrane-enveloped vesicles in infected cells (Ghosh et al., 2020; Mason, 2020; Purvinsh et al., 2021). These results suggest the possibility that EVs-associated SARS-CoV-2 may be implicated, at least in part, in the observed high resistance to external environment during spreading in the human population. A point of interest in the ability of SARS-CoV-2 to be associated to EVs is also the possibility that this may be implicated in the SARS-CoV-2 re-infection. Among the possible explanations, it has been proposed that presence of genomic SARS-CoV-2 hidden inside EVs (mainly exosomes) permit to be not recognized for a certain period of time, determining the negative test result of infected subjects. Then, these subjects turn out to exhibit a positive viral re-infection/reactivation (Elrashdy et al., 2021). Moreover, like reported for rhinoviruses, high infectious virus unit mechanism, in which the presence of multiple copies of viral genome are included within EVs, permits a higher efficient multiplicity of infection (Chen et al., 2015; Mutsafi and Altan-Bonnet, 2018). Thus, it is possible that also SARS-CoV-2, present in multiple copies carried within EVs, enter in the same cells determining a high spread transmission (Majra et al., 2021). This possibility could also overcome the marginal genomic defective molecules present in viral population by a potential complementation mechanism, when delivered at the same time in a target cell through EVs. Even if to be demonstrated, this phenomenon can be an additional explanation (other than large crowds, without appropriate personal protective equipment, low ventilation, hygiene condition and mass movement of people) of the super-spreader transmission described for SARS-CoV-2 (Mutsafi and Altan-Bonnet, 2018; Majra et al., 2021).

EVs association to respiratory viruses is reported also for other viruses. For influenza virus, it has been shown that monocytes apoptotic bodies, generated from influenza virus infection of monocytes, contained viral mRNA, protein and also virions enhancing its propagation (Atkin-Smith et al., 2020). Of note, it has been also reported that the presence of high pathogenic influenza virus H7N9 in exosomes, produced *in vitro* during infection, can be potentially the pathway that leads to infection in extrapulmonary tissues (Wu et al., 2020). Additionally, for caprine parainfluenza virus type 3, it has been shown an increased secretion of cellular exosome delivering viral proteins and RNA capable of transferring viral genetic materials to recipient cells, establishing a productive infection (Mao et al., 2020).

Evidences reported that viruses (such as rhinovirus) seem to potentially egress also via autophagosome-derived vesicles (Mutsafi and Altan-Bonnet, 2018). In particular, conversely to the enveloped viruses, a naked virus is prone to use EVs not to increase its resistance to the external conditions, but to improve a wide spread to cellular substrate as reported for HAV and HEV (Feng et al., 2013; Nagashima et al., 2014). Thus, the use of EVs by the virus to infect cells add the possibility of a viral receptor–independent infection. Specifically, it has been demonstrated that internalization of exosomes is a receptor-mediated endocytic mechanism. In this mechanism, many receptors (C-type lectin receptor, cadherins, immunoglobulins, selectins, mucins and integrins five classes cell adhesion molecules (ICAM), heparan sulfate proteoglycans) found in several cellular types, play a key role (Gonda et al., 2019). All these data show an increased viral transmission, given by the ability of the virus to be delivered in EVs to enter into uninfected cells, even in the absence of its specific receptor, reaching a wide distribution of cellular substrate in the host.

In view of EVs high external resistance in environmental condition (Harder et al., 1998), certain influenza A virus isolates and parainfluenza virus, may inhibit autophagosome maturation and fusion with lysosomes. Thus, they redirect their budding to filamentous membrane protrusions, conferring robustness against temperature mediated inactivation of produced virions (Ding et al., 2014; Beale et al., 2014; Münz, 2017). Finally, there is also a report in which extracellular amoebal-vesicles could enable virus dissemination, with the transmission of respiratory viruses, protecting them from inactivation via sunlight, and antiviral host factors (Dey et al., 2021).

5. On the EVs evading antiviral response again respiratory virus infection

One of the main advantages of a virus using EVs, as demonstrated for different persistent viruses (HCV, HAV, HEV, JCPyV, BKPyV), is that infection with EVs is not subjected to neutralization activity by antisera directed against the viral structural capsids or envelope glycoproteins (Bukong et al., 2014; González-López et al., 2018; Mao et al., 2016; Santiana and Altan-Bonnet, 2019; Scribano et al., 2020; Takahashi et al., 2010; Handala et al., 2020). Thus, even if it needs to be confirmed, also for respiratory viruses, EVs antibody escape could be a mechanism implicated in re-infection or in high viral transmission. Additionally, the carriage of virus into EVs could be a strategy that the virus uses to reduce the level of danger signals produced by cellular lysis during the viral egress from infected cells. This activity, which may reduce the inflammatory response, has been reported to be adopted by a naked virus such HEV by using EV cargo (Takahashi et al., 2010). This evidence could be more relevant in the case of respiratory virus infections that are well known to be a powerful inducer of inflammatory response, especially for naked virus that egress with cellular lysis. Additionally, in the virus uses of EVs, generated from autophagosome membranes (enriched in phosphatidylserine lipids (PS)), it may also induce a potent anti-inflammatory response (Chen et al., 2015). This likely is mediated by the vesicles

interactions with PS-receptors on the receiving host cell surface (Chen et al., 2015).

6. On the EVs regulating respiratory virus-immune response

Several functional studies demonstrate that EVs released from many types of cells of airway respiratory tract, with epithelial cells and macrophages as main contributors, can be mediators of a starting and increasing cytokine storm activity (Lee et al., 2018; Kulshreshtha et al., 2013; Bastarache et al., 2009). Thus, it has been emerged that viruses modulating EVs biogenesis, composition, and trafficking, may impact infection pathogenesis and disease progression. In this context, during virus infection exosome-mediated export of host/viral components may serve as a viral strategy to evade pathogen sensing pathway in infected cells, but also as host strategy to induce innate responses in neighboring uninfected cells for antiviral control. As reported EVs, mainly exosomes, contain a wide variety of molecules, including proteins, lipids, DNAs, mRNAs, and microRNAs (miRNA). Among these molecules, microRNAs delivered in EVs have the most attention because of their function as regulators of gene expression (Bartel, 2009).

Several studies have shown that RSV during infection can modify the composition of EVs delivered in biological fluid to modulate the host innate immune response (Chahar et al., 2018; Anderson et al., 2016). In this activity, it has been reported that the dysregulation of host microRNAs related to the antiviral response affects also the memory immune response to RSV (Chahar et al., 2018). Comparative analysis of the airway secretory EVs-associated microRNA in children have reported similar effect for rhinovirus (Gutierrez et al., 2016). This study reported an association of rhinovirus infection and airway secretion of EVs containing miR-155. MiR-155 is a well-known interferon and inflammatory response pathway mediator, predicted to regulate antiviral immunity (Gutierrez et al., 2016). Moreover, it was also shown that influenza A/H1N1pdm09 infection could induce A549 cells to secrete exosomes in which several microRNAs exhibited significantly altered expression levels during infection (Ge et al., 2022). Of note, among the microRNAs chosen for validation, some of differentially expressed microRNA during influenza virus infection showed their potential target direct to interferon pathway-related genes (Ge et al., 2022). Additionally, EVs delivering miR-483-3p, miR-374-5p and miR-446i-5p, from bronchoalveolar lavage fluid (BALF) of influenza virus infected mice, were reported to be able to regulate innate immunity (Maemura et al., 2018). This activity was ascribed to significantly upregulating not only of IFN-β expression but also expression of proinflammatory cytokines (Maemura et al., 2018). A study with Newcastle disease virus (NDV), a bird and poultry virus belonging to *Paramixoviridae* family, reported that the virus employed exosomes to entry into neighboring cells, carrying microRNAs inhibiting the IFN pathway to promote viral infection (Zhou et al., 2019). Of additional interest is that recent data indicating that exosomal miR-145 and miR-885 during SARS-CoV-2 infection are essential in modulating thromboembolic events in COVID-19 (Gambardella et al., 2023).

Evidence confirms that also several proteins can be delivered into EVs after viral infection. In this context, the ability of modulating biogenesis, composition, and trafficking of EVs has been also reported for adenovirus. In particular, it has been demonstrated that EVs from adenovirus-infected cell delivered heat shock protein and the inflammatory marker interleukin (IL)-1β (Ipinmoroti et al., 2021). Additionally, it was reported that during RSV cell infection the enhanced release of the chemokines MCP-1, IP-10, and RANTES in exosomes, plays a role in antiviral effects of the innate immune response (Chahar et al., 2018; Boonarkart et al., 2021; Corsello et al., 2022). Thus, EVs-derived from cells infected with RSV may induce the expression of IFN-dependent antiviral genes, exerting their antiviral activity via an interferon-dependent mechanism (Chahar et al., 2018; Boonarkart et al., 2021). Bioinformatic analysis showed that many proteins involved in translation, like components of spliceosome machinery and the ribosome, are secreted in EVs in response to influenza virus infection. Such EVs delivered several proteins, including antiviral cytokines and autophagy related proteins (Cypryk et al., 2017). For NDV, it has been reported that during virus infection increased excretion of NLRX1 mRNA through exosomes, determining the antiviral response and promoting virus proliferation (Xu et al., 2019). Additionally, in EVs from NDV infection the existence exosome-delivered viral NP protein might contribute to exosome-mediated enhancement of viral replication (Xu et al., 2021). In this context, recently, plasma derived exosome from SARS-CoV-2 infected patient differed from healthy subject and revealed the presence of several proteins involvement in pathways associated with immune response, coagulation, and inflammation (Lam et al., 2021).

Autophagy and exosomes production coordinately enhance the M1 polarization and recruitment of macrophages in influenza virus infection (Xia et al., 2022). These findings provide data supporting the role of MPs as an innate defense against influenza virus and as an approach to enhance the defense (Xia et al., 2022; Zheng et al., 2020; Schneider et al., 2020; Bedford et al., 2020). Additional study reported that in the exosomes derived from H5N1-infected chickens, viral proteins, NP and NS1 induce an increased level of pro-inflammatory cytokines, such as IFN-γ, IL-1β, and IL-8, (Jantaratrirat et al., 2018). Thus, EVs released into the airways during influenza virus infection trigger pulmonary inflammation changes in protein composition, induce expression of host proteins with anti-influenza activity. EVs deliver viral proteins may also rise host immune responses (Zheng et al., 2020; Schneider et al., 2020; Bedford et al., 2020; Jantaratrirat et al., 2018). Moreover, it has been reported that influenza receptors, like factors α2,3 and α2,6-linked sialic acids, present on the surface of airway exosomes may neutralize influenza virus, preventing cell infection (Hong et al., 2022). Similar effect was reported also for RSV, showing that EVs from human bronchoalveolar lavage can inhibit RSV in a receptor-dependent manner (Boonarkart et al., 2021). Additionally, exosomes delivering Angiotensin-converting enzyme 2 (ACE2), isolated from human plasma or cells, have been proved to neutralize SARS-CoV-2 infection by competing with cellular ACE2 (Wang et al., 2020). Of note, circulating ACE2-associated EVs inhibit the infection of SARS-CoV-2 variants (α, β, and δ) with high cross-neutralizing activity (El-Shennawy et al., 2022).

EVs, expressing ACE2 or carrying several host proteins, circulating in plasma of COVID-19 patients, have been associated with severe pathogenesis. Thus, EVs delivering TNF superfamily and their receptors, IL-6-family proteins, IFN-γ-inducible chemokines and IL-1-family proteins, can clearly differentiate COVID-19 patients with severe disease from patients with moderate or mild disease (Costela-Ruiz et al., 2020; Date et al., 2017). Moreover, EVs have been shown to release or present tissue factors and pro-coagulant phospholipids on their surface, promoting clot formation and accelerating fibrin polymerization (Date et al., 2017; Krishnamachary et al., 2021). Circulating EVs in plasma of COVID-19 patients may carry also highly abundant tenascin-C (TNC) and fibrinogen-β (FGB) compared with that of healthy normal controls, potentially triggering pro-inflammatory cytokine signaling in cells of distant organs (Hassanpour et al., 2020; Mills et al., 2019; Sur et al., 2021). Thus, TNC and FGB transported through plasma exosomes potentially start acting on pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and C–C motif chemokine ligand 5 (CCL5)) via the Nuclear factor-κB (NF-κB) pathway (Sur et al., 2021).

7. On the EVs mediating diseases

The role of EVs in intercellular communication permit the delivering of the cellular cargo from producing cell to cell in the close proximity as well as distant sites in the body. Both may be involved in regulating pathophysiological processes. Thus, EVs may play a key role in the pathogenesis of various diseases, including ARDS, chronic obstructive pulmonary disease, pulmonary hypertension and sepsis (Bern, 2017; Rondina et al., 2011). In this context, virus infection modulating EVs cargo can up-regulate the delivering of specific immune mediators leading to inflammation, cell death and tissue damage, not only in the

virus replication site, but also in distant cellular compartment of the host. Thus, several respiratory virus infections can induce EVs with regulatory activity at long distance from respiratory tract. Thus, EVs cause potential diseases, not determined by direct virus replication, but to their regulatory effect in the host (Zani-Ruttenstock et al., 2021). In this activity, EVs can be implicated in changes of healthy physiological conditions determining pathological consequences. For examples, after infection with influenza A virus and coronaviruses (SARS-CoV-2, SARS-CoV, and MERS-CoV), EVs delivering tissue factors into the circulation can be involved in activation of coagulation and thrombosis (Zani-Ruttenstock et al., 2021; Mackman et al., 2021; Gralinski et al., 2013). EVs delivering altered tissue factors expression was observed in peripheral blood mononuclear cells infected with SARS-CoV-2 and in monocytes, in platelet-monocyte aggregates and neutrophils isolated from COVID-19 patients (Rondina et al., 2011; Mackman et al., 2021; Gralinski et al., 2013). In another study, significant changes in the microRNA composition of EVs in the BALF from patients with influenza virus infection was associated to the ARDS (Scheller et al., 2019). Of note, among deregulated microRNAs examined present in EVs, miR-17-5p was upregulated in patients' BALF (Scheller et al., 2019). EVs-associated tissue factors were also shown to increases alveolar hemorrhage and death in mice after influenza A virus infection (Antoniak et al., 2016). Moreover, several studies have shown that tissue factor CD142, one of the initiators of the coagulation process in the setting of severe infections, is often associated with cell-released EVs (Balbi et al., 2021).

EVs expression during respiratory viral infections can increase the risk of chronic lung allograft dysfunction after lung transplantation (Gunasekaran et al., 2020). In this context, it has been reported that circulating exosomes, isolated from lung transplant recipients diagnosed with rhinovirus, coronavirus and respiratory syncytial virus infection, contains lung self-antigens, viral antigens, and 20S proteasome. These EVs elicited immune responses to lung self-antigens that resulted in development of chronic lung allograft dysfunction in immunized mice (Gunasekaran et al., 2020). Of note, EVs during SARS-CoV-2 infection causes also an acute respiratory syndrome with multi-organ damage that implicates a prothrombotic state leading to widespread microvascular clots (Date et al., 2017).

Additional interest is shown by the fact that EVs delivered during virus infection may be a cause of extensive extrapulmonary damages, mainly including myocardial and the central nervous system (CNS) injury as reported in patients of the COVID-19 (Kwon et al., 2020; Patil et al., 2021; Sun et al., 2021; Estrada, 2021; Mysiris et al., 2022; Lam et al., 2022; Song et al., 2020; Ahmed et al., 2021; Han et al., 2019). SARS-CoV-2, through blood circulation, can infect cardiomyocytes and determine acute myocardial injury and myocarditis (Kwon et al., 2020; Patil et al., 2021). However, deregulated EVs ACE2 expression, during SARS-CoV-2 infection in airway system, and delivered in blood may also be a cause of cardiovascular injury (Kwon et al., 2020; Patil et al., 2021). Moreover, it is well demonstrated that long-term neurological symptoms such as headache, fatigue, memory loss, confusion, and difficulty focusing, can be associated with post-COVID-19 infection. In this context, it has been reported several markers implicated in neuronal dysfunction. Among all, amyloid beta, neurofilament light, neurogranin, total tau, and p-T181-tau protein, were showed significantly increased in the EVs obtained from COVID-19 patients compared to controls (Sun et al., 2021). Another research group, using bioinformatic investigation, have asserted that delivering modified host proteins from lungs, via exosomes, may be involved in the disruption of protein-protein interaction in the CNS, thus playing a role in Parkinson disease (PD) (Sun et al., 2021; Estrada, 2021). In this context, the mechanistic hypothesis reported several routes implicated in PD with the disruption of autophagy/ubiquitination processes and generation of high levels of exosomes containing perturbators (mainly Rab7A and NUP62 (p62)). Thus, in COVID-19 patients, these EVs associated molecules may interact with several PD-vulnerable proteins thus potentially inducing Parkinsonism (Estrada, 2021). Another mechanism that may contribute to PD pathogenesis involves the renin–angiotensin system and ACE2 implicated in the potential role of neuroinflammation-mediated neurodegeneration in PD (Patil et al., 2021). Importantly, virus-driven neurological aberrations mediated by HDLs and exosomes moved to CNS. This has been associated to their lipid rafts implicated in the production and transmigration of these lipid particles across the blood brain barrier (Mysiris et al., 2022).

Additional evidence reported that the transcription factors localized in the exosome may regulate genes in lateral substantia nigra, medial substantia nigra, and superior frontal gyrus regions of PD and frontal cortex, hippocampus, and temporal cortex in Alzheimer's disease. Thus, during SARS-CoV-2 infection, BCL3, JUND, MXD1, IRF2, IRF9, and STAT1 transcription factors in the exosomes influence the neuronal gene regulatory network and accelerate neurodegeneration (Song et al., 2020; Ahmed et al., 2021). Also, it was reported that serum exosomes from PD patients exhibited high levels of IL-1 and TNF inflammatory mediators in comparison with the control group (Ahmed et al., 2021). Of note, intravenous inoculation of PD exosomes in mice produced neurons neurodegeneration leading to worsening of motor symptoms (Han et al., 2019).

8. Conclusion

Respiratory virus infection, causes of many diseases, from mild to severe illnesses, contributing significantly to morbidity and mortality worldwide every year, pose a great concern in human population. Vaccination and antiviral strategies are time consuming and subjected to development of viral resistance due to well-known virus variability. Additionally, increasing evidence reported that most RNA viruses, as well as many DNA viruses, associated to acute infection and including SARS-CoV-2, HRSV, rhinovirus, can persist after clinical recovery and elimination of detectable infectious virus (Yilmaz et al., 2021; Ram-Mohan et al., 2022; Kling et al., 2005; Seemungal et al., 2001; Griffin, 2022). Their asymptomatic or associated late progressive disease persistence, as post-acute COVID-19 for SARS-CoV-2, asthma for rhinovirus, chronic pulmonary disease for HRSV, point out the attention on the potential role of RNA persistence in causing specific late complications and in preventing complete recovery from acute infection (Yilmaz et al., 2021; Ram-Mohan et al., 2022; Kling et al., 2005; Seemungal et al., 2001; Griffin, 2022). However, the nature of the viral RNA form (RNA genomic, mRNA and others), the site where it persists in the absence of infectious virus, how evade the immune system to persist, and the type of strategies used to avoid immuno-mediated clearance and killing of infected cells, remain not yet understood (Griffin, 2022). In such scenario, the possible role exerted by the virus in using EVs for its transmission and for modulating antiviral inflammatory response, in infected cells and in trans by deliver EVs cargo to uninfected cells, is a new debated topic. Of note, this acquired a foremost relevance when considered the potential effect after acute infection of the long-term consequence described for some respiratory viruses. Moreover, the possibility to deliver EVs with viral and host molecular cargo to a site distant from respiratory tract, pose a new scenario on the potential of respiratory viruses to induce diseases. To date, with the growing interest in investigating EVs and viruses, the use of minimal and appropriate technique required for EVs purification and characterization is a central importance concern (Crescitelli et al., 2021; Colombo et al., 2021; Shao et al., 2018; Coumans et al., 2017). Several strategies have been used to isolate and analyze EVs from complex biological fluids (Crescitelli et al., 2021). However, EVs isolation and subsequent characterization remain difficult. In this regard, numerous protocols and commercially available reagents have been used to purify EVs from heterogeneous biological samples. These includes differential ultracentrifugation and several commercially available systems (Crescitelli et al., 2021; Colombo et al., 2021). At the same time, characterization of EVs-obtained particles has been performed with several methods, including nanoparticle tracking analysis, western blotting and immunoelectron microscopy (Lötvall et al., 2014; Witwer et al., 2021). Here the potential association of respiratory virus proteins, mRNA, microRNA,

genome and also whole particle in EVs, delivered in biological fluid, confirms what is described for several persistent viruses. In all the investigation reported, several techniques have been used, to purify EVs delivering viral contents from biological fluid and for their characterization. However, for their relative closed features (similar size and presence of shared molecules), it is important to note that the extremely complicate procedure used to separate EVs preparation from viral particle could be a limit for such studies. Thus, the usage of innovative strategies to separate and characterize the EVs is required to investigate their role in respiratory virus transmission and to understand the implication on the immune response and diseases development.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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