Cell & Developmental Biology

Lee et al., Cell Dev Biol 2016, 5:2
DOI: 10.4172/2168-9296.1000175

Mini Review Open Access

# Extracellular Vesicles Facilitate the Intercellular Communications in the Pathogenesis of Lung Injury

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## Abstract

Extracellular vesicles (EVs) are a group of heterogeneous, nano-sized structures surrounded by lipid bilayer membranes that are released by cells. Depending on their size and mechanisms of formation, EVs are often referred to as exosomes, microvesicles (MVs) and apoptotic bodies (AB). EVs are evolutionally conserved vesicles that mediate intercellular communications and cross-talk, via transferring proteins, lipids and nucleic acids. Accumulating evidence suggests that EVs exert essential physiological and pathological functions on both their mother and recipient cells. Therefore, growing interests focus on the potentials of EVs to serve as novel targets for the development of therapeutic and diagnostic strategies. Currently, extensive reports are yielded from cancer research. However, besides malignancy, EVs may also serve as crucial regulators in other devastating conditions, such as the acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). The generation, regulation and function of EVs in ARDS/ALI are largely unexplored. In this mini review, we will briefly review the current understanding of EVs and their known physiological/pathological functions in the pathogenesis of ARDS/ALI. Previously, only scattered reports have been published in this field. We believe that further investigations focusing on EVs and their compositions will shed light on novel insights in the research of ARDS/ALI.

**Keywords:** Apoptotic body; Inflammation; Oxidative stress; Hyperoxia; Extracellular vesicle (EV); Exosome; Infections; Lung injury

## Background

Accumulating evidence suggest that extracellular vesicles (EVs) mediate cell-cell cross talk [1], particularly in the fields of tumor genesis [2-6]. In recent years, extracellular vesicles have been isolated from most non-malignant cells and biological fluids including saliva [7], bronchial lavage fluid (BALF) [8,9], breast milk [10], amniotic fluid [11], blood [12,13], and urine [14]. Findings have also suggested that EV-shuttling molecules, including proteins, RNAs, microRNAs (miRNAs) and lipids, potentially exert essential roles in the pathogenesis of human diseases [15].

Acute respiratory distress syndrome (ARDS) is a devastating entity encountered in critical ill patients. Despite the recent advances on medical knowledge and strategies, the mortality and mobility of ARDS remain unacceptably high [16]. There is dire need of identification of novel targets to develop diagnostic and therapeutic strategies Human lungs have a large surface area only second to skin and are in contact with air constantly. The lung epithelium plays an essential role in innate immunity and host defense due to constant exposure to environmental stimuli including microorganisms and disease pathogens [17]. Lung injury frequently occurs in response to diverse noxious stimuli and pathogens numerous types of cells reside in the lungs and intercellular communication during lung injury is poorly understood. The discovery of EVs shines a light on our understanding of the development of human lung injury.

## Classification of EVs

EVs refer to a group of heterogeneous vesicles in which the contents, size and mechanisms of formation are different [15]. The International Society of Extracellular Vesicles recently defined three main subgroups of EVs [15]. Exosomes are the smallest subgroup measuring approximately 30-100 nm in diameter [18-20]. Microvesicles (MVs) are the second largest subgroup in size, ranging from 100 nm to 500 nm [18-20]. Apoptotic bodies (ABs) have the largest size and are the most variable vesicles amongst the three subgroups. They range from 500-2000 nm in diameter and are comparable to platelets [18-20]. Mechanistically, exosomes are released from cells after multivesicular bodies (MVBs) fuse with the plasma membrane [5,20]. MV formation involves direct protruding from plasma membranes [19,20]. Similarly, ABs is formed by plasma membrane blebbing during the process of apoptosis [21]. However, our interests focus more on the exosomes and MVs rather than ABs, given that vesicles and their compositions derived from live cells potentially play more crucial functions in the development of lung injury. That being said, currently there is no single marker can uniquely identify each subgroup of EVs. The groups of proteins which have often been used as markers of EVs are not specific to either exosomes or MVs. These proteins include, but are not limited to: tetraspanins such as CD9, CD63, CD81 and CD82; 14-3-3 proteins, major histocompatibility complex (MHC) molecules and heat shock proteins; HSPs, Tsg101 and the Endosomal Sorting Complex Required for Transport (ESCRT-3) binding protein Alix [22-26].

## EV Composition

Thus far, proteins, nucleic acids and lipids have all been identified in EVs [27]. These compositions are derived based on the parent cells [27]. For example, lung surfactant proteins

(SPs) have been detected in the EVs derived from lung epithelial cells [28]. These cell-specific proteins can serve as markers to reflect the origins of the EVs. Abundant cytoskeletal-, cytosolic-, heat shock-, plasma membrane proteins, and proteins involved in vesicle trafficking have been found in both exosomes and MVs [29].

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**Received** June 13, 2016; **Accepted** June 30, 2016; **Published** July 07, 2016

**Citation:** Lee H, Zhang D, Minhas J, Jin Y (2016) Extracellular Vesicles Facilitate the Intercellular Communications in the Pathogenesis of Lung Injury. Cell Dev Biol 5: 175. doi:10.4172/2168-9296.1000175

EV-shuttling cytokines identified so far include, but are not limited to, interleukin 1β (IL-1β), IL1α, IL-18, macrophage migration inhibitory factor (MIF), IL-32, tumor necrosis factor (TNF), IL-6, vascular endothelial growth factor (VEGF), IL-8 (CXCL8), fractalkine (CX3CL1), CCL2-5 and CCL20 [30]. Whether the EV-containing cytokines and chemokines are functional in their recipient cells remains unclear and requires further investigation.

RNAs were first identified in EVs in 2006 [31]. The EV-containing RNAs appear much smaller (less than 700 nucleotides (nt)) in comparison to cellular RNAs. However, fragments of long RNAs such as the mRNAs, long non-coding RNAs (lncRNAs), ribosomal RNA (rRNA) have all been identified in EVs [18,32,33]. More interestingly, miRNAs, the 20-22 nt small non-coding RNA molecules, have also been found in a variety of EVs [34], suggesting that EVs serve as a cargo for circulating miRNAs. Oncogenic DNAs, mitochondrial DNA (mtDNA), single-stranded DNA, double-stranded DNA (dsDNA) have all been identified in EVs [35-39].

Lipids were first described in prostate-derived EVs (named prostasomes) in 1989 [40]. Emerging new lipid families have been described in EVs, including prostaglandin E2, F2, J2 and D2 [41]. Lysobisphosphatidic acid may participate in exosome biogenesis and contribute to vesicle budding from cell membranes [42]. The lipids from cellular plasma membranes are expectedly found in the lipid bilayers of exosomes. These includesphingomyelin, phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylserine, ganglioside GM3 and phosphatidylinositol [43-45].

## EV Uptakes by Target Cells

Multiple theories have been proposed on how EVs reach their recipient cells and transmit carried information Postulated mechanisms include, initial internalization of the EVs into the recipient cells, with subsequent transport of EV-shuttling molecules, such as proteins, cytokines, RNA/DNA molecules or fragments, non-coding RNAs, miRNAs, etc. [46,47] into the recipient cells. Currently, EV-mediated small non-coding RNA or small interfering RNAs (siRNAs) delivery has been confirmed in a number of cell types [48-50]. The proposed mechanisms for EV uptake by the recipient cells primarily include clathrin-mediated endocytosis (CME), phagocytosis, macro-pinocytosis and plasma membrane fusion [46]. A second mechanism may include interactions between EV proteins and plasma membrane receptors on recipient cells [3,51-53]. Additionally, fusion with the plasma membrane of the recipient cells provides another route to deliver EV compositions into the recipient cells [54].

## EV Functions in the Development of Lung Injury

The most commonly proposed roles of EVs include the emission and transportation of signaling/regulatory molecules for intercellular communications, subsequently resulting in the modulation of the immune system and antigen presentation. There is increasing attention on the application of EVs in diagnostics and therapeutics for human diseases, particularly in the field of cancer diagnosis and cancer metastasis diagnosis. Despite the growing applications of EVs in the field of oncology, the functions of EVs in lung diseases remain unclear.

### Role of EVs in acute lung injury (ALI)

Numerous observations have linked EVs with the development of lung injury/ARDS. For example, during the pathogenesis of a variety of type of lung injury, the generation of "microparticles" (MPs) has been observed in the platelets, neutrophils, monocytes, lymphocytes, red blood cells, and endothelial and epithelial cells [55]. Endothelial cell-derived "EVs" have been reported to contain S1PR3 and represent the inflammatory states of acute lung injury (ALI) [56]. Endothelial cell (EC)-derived EVs are also believed to be important markers of lung vascular injury in the development of ventilator induced lung injury (VILI) [57]. Endothelial EVs significantly increase after exposure of endothelial cells to physiological or pathological mechanical stress, such as cyclic stretch. Similar observations have been made in the infection-associated ALI. Robustly higher amounts of endothelial EVs are noted after exposure to LPS [57].

Stored, packed RBCs release RBC-originated MPs which contribute to neutrophil priming, activation and transfusion associated ALI (TRALI) [58]. In addition to RBCs, the platelet-derived MPs increase during the storage period, prime the fMLP-activated PMN respiration burst, which may induce TRALI [59]. Moreover, monocyte-derived MPs up regulate the level of pro-inflammatory factors in lung epithelial cells, primarily through activating NF-κB and PPAR-γ dependent pathways [60].

Mitochondria-mediated ROS play a crucial function in the pathogenesis of ALI [61]. Mitochondria in bone-marrow-derived stromal cells are released in a microvesicle-containing manner, and subsequently play a protective role in ALI [62]. On the other hand, alveolar epithelial cell-derived "EVs" are reported to serve as the main source of tissue factor (TF) pro-coagulant activity in ARDS [63].

Recently, using the hyperoxia induced ALI mouse mode (HALI), Moon et al. have demonstrated that lung epithelial cells release a robust amount of EVs [28]. These EVs are derived from live cells rather than apoptotic or dying cells. Their sizes fall mainly the range of exosomes or MVs (100-500 nm). Interestingly, stromal cells remove harmful mitochondria via EVs in a similar mechanism. Lung epithelial cells also release robust amount of EV-enwrapped caspase 3. This observation suggests that in additional to being a messenger, EVs also serve as a cargo for "trash" disposal. Moreover, Moon et al further observed that epithelial EVs trigger alveolar macrophage activation and pro-inflammatory cytokine releases, confirming their roles in mediating cell-cell cross-talk [28].

In summary, the potential roles of EVs in the pathogenesis of ARDS/lung injury have been reported in a variety of settings, including but not limited to - infection, oxidative stress, transfusion and mechanical stretch-associated ALI. Almost all cell types release EVs, and these EVs may be protective or detrimental, depending on the type of stimuli, the type of mother cells and the type and compositions of the EVs. Despite the above mentioned observations, detailed characterization and mechanistic exploration on EVs involving in ALI/ARDS remain largely unclear. Further directions include extensive investigations on the EV-functions under diverse stimuli, EV-compositions and classifications, as well as the mechanisms of EV formation.

### Acknowledgement

This work is support by NIH R01HL102076 (Y.J.), NIH R21 AI121644 (Y.J.) and NIH R01 GM111313 (Y.J.)

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