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REVIEW ARTICLE

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The role of exosomes from BALF in lung disease

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Abstract

Exosomes are released from a variety of immune cells and nonimmune cells, the phospholipid vesicle bilayer membrane structure actively secreted into tissues. Recently, exosomes were demonstrated to be effectively delivered proteins, cholesterol, lipids, and amounts of DNA, mRNA, and noncoding RNAs to a target cell or tissue from a host cell. These can be detected in blood, urine, exhaled breath condensates, bronchoalveolar lavage fluid (BALF), ascites, and cerebrospinal fluid. BALF is a clinical examination method for obtaining alveolar cells and biochemical components, reflecting changes in the lungs, so it is also called liquid biopsy. Exosomes from BALF become a new method for intercellular communication and well-documented in various pulmonary diseases. In chronic obstructive pulmonary disease (COPD), BALF exosomes can predict the degree of COPD damage and serve as an effective monitoring indicator for airflow limitation and airway remodeling. It also mediates antigen presentation in the airways to the adaptive immune system as well as costimulatory effects. Furthermore, BALF exosomes from acute lung injury and infective diseases are closely related to various infections and lack of oxygen status. BALF exosomes play an important role in the diagnosis and prognosis of lung cancer. The effect of immunomodulatory role for BALF exosomes in adaptive and innate immune responses has been studied in sarcoidosis. The intercellular communication in the microenvironment of BALF exosomes in pulmonary fibrosis and lung remodeling have been studied. In this review, we summarize the novel findings of exosomes in BALF, executed function by protein, miRNA, DNA cytokine, and so on in several pulmonary diseases.

KEYWORDS

BALF, COPD, exosomes, lung cancer, pulmonary infection

1 | INTRODUCTION

Exosomes are released from a variety of immune cells and nonimmune cells (Raposo & Stoorvogel, 2013), the phospholipid bilayer membrane structure actively secreted into tissues (Thery et al., 2009), and the exosome's diameter is 30–100 nm. Exosomes originate from the cell endosomes and subsequently form multivesicular bodies (MVBs) (Kordelas et al., 2014; Raposo & Stoorvogel, 2013). Exosomes contain a set of endosomal-associated proteins (including Rab GTPase, SNARES, Annexin, and FrultLIN), some of which are involved in the biosynthesis of MVBs (TSG101 and annexin). In addition, exosomes are also enriched in a large number of transmembranes protein or lipid binds to extracellular

proteins (CD9, CD63, CD81, cell adhesion molecules, and growth factor receptors), cholesterol, sphingomyelin, and hexose ceramide (Lotvall et al., 2014; Raposo & Stoorvogel, 2013). In addition to proteins, cholesterol, and lipids, exosomes contain large amounts of DNA, mRNA, miRNA, and other small noncoding RNAs. Exosomes can carry and protect a variety of molecular information into the circulatory system and protect it from degradation, and facilitate the analysis from stored and frozen biological samples (Thery et al., 2002), thus becoming a research hotspot in recent years. Exosomes can be present in a variety of body fluids, such as blood, urine, bronchoalveolar lavage fluid (BALF), ascites, and cerebrospinal fluid. Many types of cells can release exosomes, suggesting that these vesicle structures carrying a large amount of information may serve as a means of intercellular communication (Peinado et al., 2012), and are important participants in the process of cells exerting their biological functions (Kahlert et al., 2014; Valadi et al., 2007). After release from the cell, the exosomes regulate the receptor cells mainly through two mechanisms, one is to interact with the receptor on the target cell and activate the related signaling pathway, the other is to release the content after endocytosis or fusion with the plasma membrane. It causes the receptor cells to change in the expression of related genes and protein translation (Mathivanan et al., 2010), thus affecting the function of the recipient cells.

BALF is a clinical examination method for obtaining alveolar cells and biochemical components by injecting physiological saline into the alveoli through bronchoscopy and aspirating under negative pressure. BALF is originally used for the study of pulmonary interstitial and airway immunity and inflammatory mechanisms and has rapidly become a standard diagnostic procedure for abnormalities of pulmonary dispersal, including infectious diseases, noninfectious immune diseases, and even malignant diseases. This technique allows cells and solute to be collected from the lower respiratory tract for micro-microculture, cytological identification, and genetic diagnosis. Information obtained from BALF is considered to be a complement to lung biopsy pathology. Compared with lung biopsy, BALF is safer, less invasive, with few complications, and the resulting sample is larger than the source bronchus and multiple lung lobes, compared to the tissue fragments obtained by bronchial biopsy or open biopsy. More, it can more clearly reflect changes in the lungs, so it is also called liquid biopsy (Costabel & Guzman, 2001; Roth et al., 2008). Identification of cells, proteins, genes, or microbes contained in BALF contribute to the diagnosis and differential diagnosis of the disease. Exosomes are also an important component of BALF. The cells secreting BALF exosomes include epithelial cells, endothelial cells, stem cells, alveolar macrophages, tumor cells, and so forth, wherein epithelial cells and macrophages are the main sources of BALF exosomes (Alipoor et al., 2016). In addition to its cellular communication function, BALF exosomes also exert the function of the lung's innate immune system through the mucociliary clearance defense system (Bourdonnay et al., 2015; Rose & Voynow, 2006).

This article retrospectively analyzed the various components carried by BALF exosomes and systematically explained the potential role of BALF exosomes in the formation and development of respiratory diseases (Figure 1).

2 | EXOSOMES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is a serious health problem and is currently the fourth most common cause of death in the world (Vestbo et al., 2013). The main clinical manifestations of COPD are mainly chronic bronchitis and/or emphysema with airflow limitation. In most cases, COPD is caused by smoking, which causes the development of chronic airway inflammation and emphysema, leading to irreversible airflow limitation and accelerated decline in lung function (Celli & MacNee, 2004). Pulmonary parenchymal endothelial cell injury, epithelial cell damage, and epithelial–mesenchymal transition are the main causes of COPD.

Studies have shown that after endothelial cell injury, a large number of endothelial-derived microparticles (EMPs) can be released into BALF, and EMPs are closely related to lung remodeling and airflow limitation (Takahashi & Kubo, 2014). Damaged epithelial cells can release large amounts of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), GM-CSF, transforming growth factor-β (TGF-β), and C-X-C motif chemokine ligand 8, whereas levels of TGF-β in COPD patients are associated with the severity of airway obstruction. The exosomes released by epithelial cells can affect the process of cell mesenchymal transition and affect the function of recipient cells. Therefore, BALF exosomes can predict the degree of COPD damage and serve as an effective monitoring indicator for airflow limitation and airway remodeling. A study by David A et al. found that the expression of miR-451a and miR-663a in BALF exosomes was significantly altered in COPD patients compared to healthy subjects and that these two microRNAs acted on matrix metalloproteinases and CEBPβ and TGF-β1, respectively. And other cytokines, which play a role in chronic inflammation and fibrosis in the lungs (Armstrong et al., 2017). Also the exosomes from activated neutrophil in BALF had the ability to degrade extracellular matrix by proteolytic damage via the integrin Mac-1 and NE, and sufficient to trigger alveolar unit loss (Genschmer et al., 2019). Thus airway and alveolar could both be affected by the exosomes in the BALF. As a result, the exosomes from endothelial and epithelial cells, macrophages, and neutrophils participated in the airway remodeling and fibrosis.

3 | EXOSOMES IN ASTHMA

Asthma is a common chronic inflammatory respiratory disease characterized by narrowing of the airways under various stimuli, such as allergens, infections, and air pollutants (von Mutius, 2009). The pathogenesis is affected by both genetic factors and environmental factors (Renz et al., 2011). The role of BALF exosomes in the pathogenesis of asthma is unclear.

In 2003, two individuals, such as Admyre, successfully isolated exosomes from BALF in healthy subjects for the first time and demonstrated the presence of membrane surface proteins on the surface of exosomes such as HLA-DR, CD63, CD86, and CD54 (Admyre

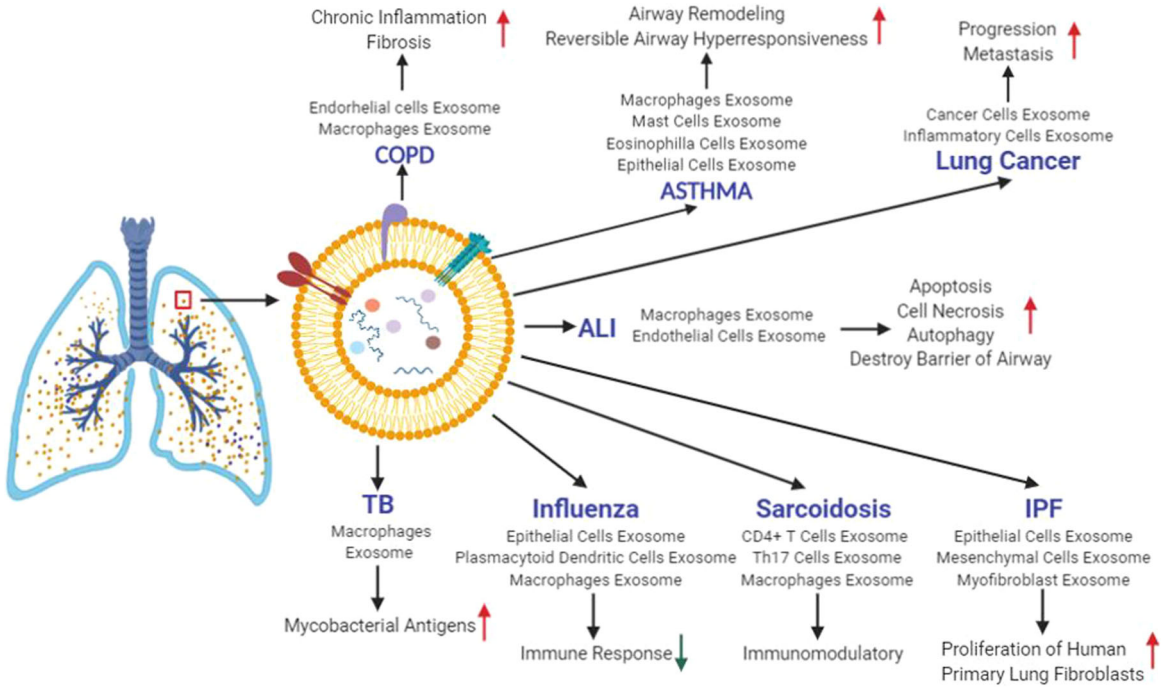

FIGURE 1 Schematic representation of exosome's mode of action in pulmonary diseases. Bronchoalveolar lavage fluid (BALF) exosomes promoted the chronic inflammation and fibrosis in the lung. BALF exosomes mediate antigen presentation to the adaptive immune system and promote the activation of alveolar macrophages, mast cells and eosinophilia to airway remodeled, reversible airway hyperresponsiveness, and airway obstruction in asthma. The polypeptides in BALF exosomes can be used as an important marker to identify tuberculosis being an active disease or latent tuberculosis (TB) infection. Exosomes reduce the immune response against influenza virus infection. In sarcoidosis, exosomes participate in the immune regulation for the disease development. Human BALF exosomes have an important role in the diagnosis, treatment, and prognosis of lung cancer. The components of BALF exosomes will facilitate the proliferation of human primary lung fibroblasts in idiopathic pulmonary fibrosis (IPF). Balf exosomes in acute lung injury (ALI) were found that contained a large number of proteins related to apoptosis, cell necrosis, and autophagy.

et al., 2003). These findings suggest that BALF exosomes may mediate antigen presentation in the airways to the adaptive immune system as well as costimulatory effects. A further study has shown that bronchial asthma BALF exosomes contain a large amount of leukotriene biosynthetic enzymes, which can promote the release of leukotrienes from alveolar macrophages, causing asthma symptoms such as bronchoconstriction, edema formation, and high mucus secretion (Dahlen et al., 1980). Compared with healthy subjects, cytokines and inflammatory mediators formed by BALF exosomes in bronchial asthma result in increased mast cell number or activation, eosinophilia, airway remodeling, reversible airway hyperresponsiveness, and airway obstruction (Fujita et al., 2014). miRNAs are considered to be a useful biomarker for disease and can be transported outside the cell by exosomes and then bound to target cells (Tkach & Thery, 2016). Bettina Levänen et al. studied the changes in miRNA profiles in BALF exosomes of bronchial asthma that are highly correlated with their FEV_1, a subset of these miRNAs are important cytokines in asthma (including IL-13, IL-10, IL-6, and IL-8) and the MAPK and JAK-stat signaling pathways have significant effects. The study found that the miRNA-200 family of BALF exosomes in bronchial asthma is downregulated, which affects the mesenchymal transition of bronchial epithelial cells (Gregory et al., 2008; Hackett, 2012) and participates in airway remodeling. Recently, the lipid in exosomes has been developed the role of inducing apoptosis by Ceramides and promoting macrophage chemotaxis in mouse (Kakazu et al., 2016; Podbielska et al., 2016). Understanding the several composition of exosomes from asthmatic BALF will provide new insights for developing new therapeutic strategies.

4 | EXOSOMES IN ACUTE LUNG INJURY (ALI)

ALI and its more severe form are acute respiratory distress syndrome (ARDS), which is caused by major injuries such as sepsis, trauma, pneumonia, and inhalation of gastric contents (Hackett, 2012), The main pathological changes is manifested by increasing release of inflammatory mediators and disruption of the integrity of the alveolar and vascular endothelium barriers, thereby affecting the ventilation function of the lungs.

Tae Hoon Kim et al. isolated exosomes from bronchoalveolar lavage fluid (balf) in patients with ARDS and found that BALF exosomes in ARDS contain a large number of proteins related to apoptosis, cell necrosis, and autophagy. Further, in vitro studies have shown that BALF exosomes in ARDS inhibit the production of angiogenic endoglin VEGF. This indicates that the content of BALF

exosomes is closely related to disease infection and lack of oxygen status (Kim et al., 2019). Yuan et al. used LPS to induce acute lung injury in mice, and found that the mouse alveolar lavage fluid exosomes contain a large number of miRNAs and cytokines that regulate immune responses, and exosomes derived from macrophages were found by in vitro coculture model. It can destroy the expression of tight junction protein in bronchial epithelial cells, indicating that exosomes can act as messengers between immune cells and intrinsic structural cells, and can destroy the barrier of the airway (Yuan et al., 2018). Previous studies have shown that Syndecan-1 in endothelial cells has the potential to protect the endothelial barrier function and inhibit the inflammatory response. By obtaining exosomes with high expression of Syndecan-1 in vitro, LPS can protect from pulmonary edema and inflammation after lung injury in mice, reducing cell numbers and protein levels and reducing proinflammatory cytokines expression (such as IL-1β, TNF-α, and IL-6) after LPS challenge in bronchoalveolar lavage (Zhang et al., 2019). The exosomes in BALF provide a new direction for the diagnosis and treatment of exosomes in acute lung injury.

5 | EXOSOMES IN INFECTIVE DISEASES

Pulmonary tuberculosis (TB) is a serious public health problem with high morbidity and mortality worldwide. The key to antituberculosis treatment is timely diagnosis and effective use of antituberculosis drugs (Getahun et al., 2015). Macrophages are the main host cells carrying *M. tuberculosis* (M.tb) (Rajaram et al., 2014).

Bronchoalveolar lavage fluid (BALF) is rich in macrophages and is the first barrier against tuberculosis infection. Giri and Schorey (2008) found that exosomes secreted from BCG-infected macrophages isolated from *M. Bovis*, when infected by intranasal administration, stimulated mice to produce antigen-specific CD4+ and CD8+ T cells suggest that exosomes of macrophages contain many mycobacterial antigens. During *M. tuberculosis* infection, the components of TB are transported from the multivesicular bodies of macrophages to exosomes, but the specific mechanism of this process needs further study (Beatty & Russell, 2000). Pramod K. Giri et al. used *J. tuberculosis* culture filtrate protein (CFP) to treat J774 cells and isolated exosomes. Twenty-nine proteomics proteins were detected by proteomics and found to be in vivo. Furthermore, the exosomes promote the activation of macrophages, dendritic cells, and naive T cells (Giri et al., 2010). Next, Kruh-Garcia et al. (2014) and Sinha et al. (2018) found the polypeptides in BALF exosomes can be used as an important marker to identify tuberculosis being an active disease or latent infection, which is easy to the identification and diagnosis of tuberculosis infection and greatly improve the diagnosis and treatment rate of tuberculosis (Kruh-Garcia et al., 2014; Sinha et al., 2018). Thus, lipoarabinomannan (LAM), the component of Mtb cell wall, is considered as a predictive exosome biomarkers of TB diagnosis, treatment and outcome through BALF in the M bovis BCG–infected mice (e (Bhatnagar et al., 2007). Also, the antigen 85 complex (Ag85) containing Ag85A, Ag85B, Ag85C, which are involved in the mycobacterial pathogenesis and cell wall synthesis (Wiker & Harboe, 1992) are found in exosome-derived *M. tuberculosis*-infected macrophages, BALF of female BALB/c mice and circulation of TB patients (Han et al., 2012; Shende et al., 2007). Furthermore, miR-155, miR-26a, mir-21 miR-29a miR-424, considered as promising circulating miRNA of TB infection and therapy are also existing in BAL (Bibaki et al., 2018; Dyskova et al., 2015; Gohir et al., 2020; Kim et al., 2018; Kishore et al., 2018; Sinigaglia et al., 2020). These mycobacterial antigens and miRNA would further be identified as the biomarkers in the diagnosis of TB through BALF.

The influenza virus is the main cause of human respiratory diseases. To establish an effective infection and cause disease, the influenza virus must overcome the host's inherent immune response. The interferon (IFN) family plays an important role in limiting the early stages of viral infection, and highly pathogenic viruses are often associated with excessive cytokine responses (Baskin et al., 2009; Kash et al., 2006). Airway epithelial cells, plasmacytoid dendritic cells (pDC) and macrophages are the major producers of IFN during influenza virus infection (Cheung et al., 2002; Hogner et al., 2013; Ioannidis et al., 2013; Jewell et al., 2007; Kallfass et al., 2013; Kaminski et al., 2012). Studies have shown that miRNA expression is altered in infected cells (including cells infected with influenza virus) (Buggele et al., 2012; Li et al., 2010, 2011). Exocrine, as an intercellular communication medium, contains functional messenger RNA (mRNA) and microRNA (miRNA) (Li et al., 2010; Valadi et al., 2007), so it is very meaningful to use BALF exosomes for influenza virus research. Tadashi Maemura et al. studied exosomes in BALF of mice infected with influenza virus and found that miR-483-3p identified in BALF exosomes can target CD81, thereby upregulating IFN-β expression. It plays an important role in the immune response against mouse influenza virus infection (Maemura et al., 2018). Thus, the marker in exosomes could be the marker for TB and influenza virus diagnosis and targets for therapy.

6 | EXOSOMES IN LUNG CANCERS

Lung cancer is a serious public health problem and the leading cause of cancer-related deaths worldwide. The cause is not yet clear. Due to the lack of effective diagnostic methods and the asymptomatic nature of the disease, most patients have reached the advanced stage of the disease at the time of diagnosis, resulting in a poor prognosis (Huang et al., 2017; Reck & Rabe, 2017). With a large number of discoveries derived from various tumor exosomes and exosomes, the use of exosomes as cancer biomarkers and personalized medical platforms has become an emerging technology (Balaj et al., 2011; Li et al., 2017; Thakur et al., 2014). For example, Thakur et al., 2014). Jae Young Hur et al. successfully isolated exosomal DNA from plasma and bronchoalveolar lavage fluid (BALF) in patients with non-small cell lung cancer for EGFR genotyping, using this biopsy sample The positive rate of Fudan was the same (Hur et al., 2018). The biomarker of lung cancer is detected by the exudate of alveolar lavage fluid. Because it can directly contact the tumor site, the DNA in the

obtained exosomes has higher quality and larger quantity and has broader clinical application prospects.

There is increasing evidence that the tumor microenvironment is closely related to tumor progression (Rowley, 2014). Exosomes serve as important mediators for mediating cell-to-cell communication (Becker et al., 2016; Tkach & Thery, 2016) and may play an important role in tumor progression and metastasis (Hoshino et al., 2015; Lazar et al., 2016; Melo et al., 2014). Previous studies have used the mouse lung cancer model to obtain BALF exosomes and conduct research on respiratory-related cell lines in vitro. Yang et al. showed that the levels of pro-inflammatory cytokines TNF-α and IL-6 in BALF of lung cancer mice were significantly increased, which could significantly promote the growth, proliferation, migration, and infiltration of lung cancer cell line A549, suggesting BALF-derived exosomes can alter the microenvironment by enhancing the inflammatory response in lung cancer (Bhatnagar et al., 2007; Qazi et al., 2010; Torregrosa Paredes et al., 2012) and play a key role in the development and metastasis of tumors (Grivennikov et al., 2010; Zhang et al., 2019). Jin et al. found that levels of miR-126 and Let-7a in BALF exosomes were significantly higher in patients with lung adenocarcinoma than in healthy controls (Kim et al., 2018). Recently, Yang et al. found that bacterial pathogens colonized in COPD enhanced the growth, migration, and invasion of Mouse Lewis lung carcinoma cells by BALF exosomes in KRAS-dependent mouse models and Gprc5a-knockout mouse models. Therefore, the study of human BALF exosomes has a more important role in the diagnosis, treatment, and prognosis of lung cancer.

7 | EXOSOMES IN SARCOIDOSIS

Sarcoidosis is a systemic disease of unknown etiology characterized by a non-cased granuloma reaction that may involve multiple organs. This disease is common in young and middle-aged adults and usually manifests as pulmonary infiltration, bilateral lungs. Portal and mediastinal lymphadenopathy, uveitis. Common symptoms include difficulty breathing, coughing, and fatigue. The overall prognosis of pulmonary sarcoidosis is good, with spontaneous regression of radiographic abnormalities observed in up to 80% of patients with no nodule and less than 5% of patients progressed to chronic respiratory dysfunction in 10 years (Hillerdal et al., 1984; Nagai et al., 1999). However, for those patients with advanced diagnosis, the prognosis is poor. Some studies have shown that the main pathological changes of this disease are the interaction of alveolar macrophages, T-assisted (CD4+) cells, and cytokine networks, leading to the formation of granuloma. However, increasing data suggest that Th17 cells play a key role in granuloma formation and maintenance (Miedema et al., 2018). With the application of fibero bronchoscopy biopsy and alveolar lavage cytology, the diagnosis rate of pulmonary tuberculosis is increased to 90%, which is helpful for the in-depth study of the cause of pulmonary sarcoidosis (Govender & Berman, 2015).

The role of BALF exosomes in pulmonary sarcoidosis is unclear. Qazi et al. studied BALF exosomes in patients with pulmonary sarcoidosis and showed that the surface of BALF exosomes showed high expression of MHC class I and class II proteins in patients with pulmonary sarcoidosis compared with healthy people. Four transmembrane proteins CD9, CD63 and CD81, and neuregulin-1, the expression of these proteins is associated with cancer progression; BALF exosomes in patients with sarcoidosis induce peripheral blood mononuclear cells to produce more IL-13 and IFN-γ and Epithelial cells produce more IL-8. And these findings suggest an immunomodulatory role for BALF exosomes in adaptive and innate immune responses (Qazi et al., 2010).

8 | EXOSOMES IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

Idiopathic pulmonary fibrosis IPF is a fatal interstitial lung disease with unknown etiology and limited treatment. Current evidence suggests that IPF is the result of persistent lung epithelial cell damage and abnormal wound healing and that the injured epithelial cells crosstalk with mesenchymal cells, which in turn leads to increased myofibroblast activation and extracellular matrix component deposition (Goldstein et al., 1990; Raghu et al., 2011).

BALF exosomes serve as messengers for intercellular communication in the local microenvironment, and their expression and function in pulmonary fibrosis and lung remodeling are yet to be further studied (Rollet-Cohen et al., 2018). B. Liu et al. showed that miR 125b, miR 128, miR 21, miR 100, miR 140 3p, and miR 374b are upregulated in BALF exosomes of IPF patients, whereas expression of let 7d, miR 103, miR 26 and miR 30a 5p downregulated, further studies confirmed that miR-30a-5p can target TGF-β-activated kinase 1/MAP3K7 binding protein 3 (TAB3). Studies in vitro have found that overexpression of miR-30a-5p reduces TAB3, α-smooth muscle actin and fibronectin expression in A549 cells. This suggests that the decreased expression of miR 30a in BALF exosomes of IPF patients, and the consequent increase in TAB3 expression, may be a key factor in the progression of IPF (Liu et al., 2018). Studies by Martin-Medina et al. have shown that the content of BALF exosomes in patients with IPF is increased, and WNT-5A on the surface of exosomes can promote the proliferation of human primary lung fibroblasts through the TGF-β signaling pathway. The further study of the components of BALF exosomes will facilitate the diagnosis of pulmonary fibrosis and the development of new treatments.

Exosomes in BALF are secreted by intrinsic trachea and epithelial cells as well as a variety of immune cells, and play a role in information communication in the microenvironment. Through this review we could focus on the role of exosomes as key elements in the course of pulmonary disease development and as potential new therapeutic targets.

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