

# Pathogenesis and treatments for idiopathic pulmonary fibrosis extracellular vesicles

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## ABSTRACT

Idiopathic Pulmonary Fibrosis (IPF) is a lung condition that worsens over time and is brought on by increased lung tissue fibrosis in response to ongoing epithelial injury. IPF treatment options are still limited because existing treatments only slow the spread of the disease. Exosomes and microvesicles are examples of Extracellular Vesicles (EVs), which have recently been identified as paracrine communicators through the component cargo. The community of cell specific microRNAs and proteins found in EVs can control recipient cells gene expression, which will modulate their biological activities. Cell types and their physiological and pathological states of donor cells are reflected in EV payloads. The roles of EVs in the epithelial phenotype and fibro proliferative response in the

development of IPF have been highlighted in numerous recent studies. Given their inherent biocompatibility and particular target activity, some native EVs may also be employed as drug delivery vehicles in a cell free treatment approach for IPF. A brand new possible substitute for cell based methods has been put forth: EV based remedies. The benefit is that depending on their source, EVs may be less immunogenic than their parental cells. This is probably because the surface of EVs contains less of the transmembrane proteins that make up the Major Histocompatibility Complex (MHC) proteins. Mesenchymal Stem Cell (MSC) derived EVs have been rapidly developed over the past ten years as therapeutic products ready for clinical trials against a variety of diseases.

**Keywords:** Mesenchymal stem cell; Microvesicles; Etiology; Extra cellular matrix; Anti-fibrotic

## INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF), the most well studied member of the Interstitial Lung Diseases (ILD) category of uncommon and chronic lung conditions. IPF is a chronic ILD that progresses as a result of increasing lung tissue fibrosis in response to chronic epithelial cell damage. The destruction of alveolar architecture and replacement of healthy lung tissue by increased Extra Cellular Matrix (ECM) compromise pulmonary compliance, which ultimately results in respiratory failure and mortality. A nonproductive cough and increasing dyspnea are symptoms of IPF. Although the actual cause of IPF development is still unknown, risk factors have been identified, including dust and tobacco use. IPF has a lower five years survival rate than a number of cancers. Anti-fibrotic medications and oxygen supplementation are typically part of the treatment. Despite the breakthroughs, there are still few therapeutic options available because current treatment plans merely slow the spread of the disease. The tactics can also be difficult because the exacerbation events that follow a period of stability in IPF make its path unpredictable. Extracellular Vesicles (EVs), which include exosomes, microvesicles, and apoptotic bodies, have gained recognition in the past ten years as a new paracrine mediator for the transmission of biological elements. MicroRNAs (miRNAs), proteins, and lipids are the primary payloads of EVs that are delivered to destination cells. EVs are emerging as potential biomarkers for various lung diseases and novel cell to cell communication mediators [1].

## LITERATURE REVIEW

### IPF pathogenesis and therapy

IPF is a chronic ILD characterised by abnormal ECM deposition in many lung parenchymal areas. According to current research, IPF develops as a result of repetitive and persistent damage to the alveolar epithelium, which sets off immune system signalling cascades that lead to chronic inflammation and ultimately fibrosis. Transforming Growth Factor- $\beta$  (TGF

pathway is one of the primary signals involved in the development of excessive inflammatory responses in IPF [2]. Genetic mutations, cell death, and cellular senescence are a few examples of the biological processes that contribute to persistent alveolar epithelial damage in IPF. Although it was formerly believed that IPF was an inflammatory condition, mounting evidence and the ineffectiveness of immunosuppressive and anti-inflammatory medications non clinical settings have refuted this idea. Corticosteroids and immunosuppressants have been used in the past, but the panther-IPF trial has led to a current recommendation against their usage for IPF. The only medications suggested for the treatment of IPF in the most recent revision of the ATS/ERS/JRS/ALAT guidelines, released in 2015, are nintedanib and pirfenidone, together with antacids. The two main medications that the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) both approved for the treatment were pirfenidone, a TGF inhibitor, and nintedanib, a tyrosine kinase inhibitor [3]. Both medications have been proven to stop IPF acute exacerbations and delay the disease's progression. Both of these medications have negative effects and neither is able to arrest the growth of IPF entirely [4].

### Extracellular vesicles

Almost all cells have the ability to produce EVs into the extracellular environment in addition to different kinds of soluble molecules including cytokines and chemokines. Generally speaking, EVs comprise a variety of substances including proteins, messenger RNAs (mRNAs), miRNAs, and lipids enclosed in a phospholipid bilayer taken from either the plasma membrane or endocytic compartments of donor cells. When EV components are transported to different cells, a variety of cellular signalling pathways and biological reactions are elicited. Based on their size, biogenesis, and secretory pathways, EVs are typically divided into exosomes, microvesicles, and apoptotic bodies. Exosomes are tiny extracellular vesicles (30 nm-150 nm in diameter) that are released into the extracellular space after plasma membrane fusion by late endosomes/Multivesicular Bodies (MVBs). The Tumour Susceptibility Gene 101 protein (TSG101), ALG-2 interacting protein X (ALIX), neutral Sphingomyelinase 2 (nSMase2), tetraspanins, Rab proteins, syntenin, and phospholipase D2 all

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play role in the regulation of MVB fusion with the plasma membrane. Microvesicles are medium/large Extracellular Vesicles (EVs) with a diameter of 100 nm–1000 nm that are produced by direct budding at the plasma membrane and released into the extracellular space. Many of the proteins and lipids in these EVs are comparable to those found in the cell membranes from hence they are derived. Due to their numerous activities and implications, exosomes and microvesicles have received the majority of attention in research that deal with EVs [5].

Through cell to cell contact, EVs can transport a variety of significant molecular messengers that can affect a variety of physiological and pathological processes in recipient cells. EVs can connect with recipient cells to transmit their components through a variety of methods. Direct fusing with the plasma membrane, fusion with the endosome membrane, plasma membrane receptors, and endosomal rupture are among ways that EV might release their contents. EVs can release their components into the cytoplasm of target cells after being taken up by recipient cells, which might modify particular signalling pathways. The recipient cells' gene expression can be changed by the cell specific population of mRNAs and miRNAs present in EVs, which can either activate or inhibit biological processes.

## DISCUSSION

### The roles of extracellular vesicles in IPF pathogenesis

The physiological or pathological state of the generating cells can affect EV components. EVs from certain cell types, such as senescent cells and activated immune cells, can cause pulmonary fibrosis even though stem cell derived EVs have the capacity to repair and regenerate damaged tissues. The developing roles of EV cargoes in the epithelial mesenchymal trophic unit during the onset of pulmonary fibrosis have been demonstrated in numerous investigations. WNT5A positive EVs were discovered in BALF from IPF patients. They demonstrated that EVs can carry secreted WNT proteins to encourage lung fibroblast growth. The WNT signalling pathway has recently been shown to be involved in the pathophysiology of several lung illnesses, including IPF. An essential part of stem cell renewal, cell migration, cell polarity, and inflammatory responses is played by WNT5A, a non-canonical WNT ligand. Numerous cell types in the lungs, including lung fibroblasts and epithelial cells, express the ligand. They discovered that a significant source of EV bound WNT5A is lung fibroblasts. This research emphasises the pathophysiological relevance of EVs in IPF by showing that WNT5A on EVs isolated from IPF BALF causes disease progression.

### Extracellular vesicle based therapy for idiopathic pulmonary fibrosis

EVs have the potential to be effective medicine delivery systems. In terms of drug delivery, EVs are thought to be safer than artificial nanoscale carriers like liposomes and nanoparticles since they are biologically less prone to cause allergic immunological reactions. According to some data so far, endogenous anti-fibrotic components found in native EVs can be produced as natural therapeutic agents for pulmonary fibrosis. Additionally, genetically modified EVs with desired internal cargoes and precise targeting effectiveness have better chances of curing a variety of diseases.

Native EV based therapy strategies for IPF are currently being gradually researched. Previous studies have shown that stem cell therapy, a form of regenerative medicine, is an effective treatment option for a variety of lung conditions, including IPF. According to recent studies, this biological and therapeutic role of the cells is predominantly caused by paracrine actions acquired from stem cells. Therapeutics without cells has a number of advantages over using cells, including the ability to avoid embolization and immunological incompatibility problems. The development of cell free EV based therapies as a potentially effective substitute for cell based therapy in regenerative medicine is a result. In this context, EVs have several advantages over cell based therapies, including the fact that they are less immunogenic than their mother cells, perhaps as a result of a decreased expression of transmembrane proteins such the Major Histocompatibility Complex (MHC). The EV based medicines have significant advantages in clinical therapy because stem cell derived EVs naturally include various

bioactive chemicals. Experimental pulmonary fibrosis models have been used to study a variety of cell derived EVs, including MSCs, adult stem cells, fibroblasts, bronchial epithelial cells, and lung tissue spheroid cells.

Multipotent cells with the ability to differentiate into different cell types include MSCs. Several tissue sources, namely bone marrow, adipose tissue, and umbilical cord tissue, can yield MSCs. The utilisation of MSCs has become a potential cell based therapeutic approach in the field of regenerative medicine over the past ten years. EVs produced from MSCs also have the potential to have a variety of impacts, including immunomodulation and regeneration. The therapeutic benefits of MSC derived EVs for respiratory conditions such IPF, Chronic Obstructive Pulmonary Disease (COPD), and Acute Respiratory Distress Syndrome have been demonstrated in a number of preclinical investigations (ARDS). Mansouri proved that human Bone Marrow (BM) MSC derived EVs can in fact cause monocytes to exhibit an anti-inflammatory behaviour. The results showed that human BM-MSC derived EVs can treat IPF by reducing pulmonary fibrosis and lung inflammation by modulating lung monocytes. Wan et al. have looked into the possibility of treating IPF with EVs produced from human BM-MSCs. By suppressing frizzled 6, they demonstrated that human BM-MSC derived EVs with overexpressed miR-29b-3p might decrease fibroblast growth (FZD6). Zhou showed that miR-186 packaged in human BM-MSC derived EVs inhibits the expression of the Dickkopf-1 (DKK1) and SRY related HMG box transcription factor 4 (SOX4) genes, preventing the activation of fibroblasts and treating pulmonary fibrosis. Mansouri demonstrated that monocytes can in fact exhibit an anti-inflammatory behaviour when exposed to EVs produced from human Bone Marrow (BM)-MSCs. According to the findings, pulmonary fibrosis and lung inflammation can be reduced by human BM-MSC derived EVs, which can also modulate lung monocytes to cure IPF. Wan et al. investigated the potential of using EVs made from human BM-MSCs to treat IPF. They showed that human BM-MSC derived EVs with overexpressed miR-29b-3p might inhibit fibroblast development by decreasing Frizzled 6 (FZD6). Zhou demonstrated that the expression of the Dickkopf-1 (DKK1) and SRY related HMG box transcription factor 4 (SOX4) genes is inhibited by miR-186 packed in human BM-MSC derived EVs, limiting the activation of fibroblasts and curing pulmonary fibrosis.

## CONCLUSION

EV mediated cellular crosstalk is a unique regulator of pulmonary fibrosis, according to recent investigations. Notably, EVs produced from lung fibroblasts may be important in the etiology of IPF. Many pre-clinical investigations have demonstrated that MSC derived EVs have potential therapeutic roles in respiratory disorders, including IPF, for EV based therapies. Importantly, EV activities depend on changes in the microenvironment, including exposure to cigarette smoke, cytokines, and culture conditions, in addition to the cell type. For instance, our team showed that normal EVs produced from HBEC exhibit anti-fibrotic capabilities by inhibiting the development of myofibroblasts and cellular senescence. On the other hand, myofibroblast differentiation linked to airway remodelling can be induced by EVs generated from HBECs exposed to cigarette smoke. Understanding how culture conditions impact EV phenotypes is crucial when developing a cell culture process for EV production. In fact, it has been established that hypoxia has an impact on EV components including proteins and RNAs and that the MSC seeding density affects EV yield. Additionally, new research indicates that cellular senescence might be involved in the dysregulation of EV components, which would reduce their therapeutic effectiveness. The impact of cell quality control on EV functions must be thoroughly understood during the early stages of product development because managing donor selection and the cell culturing procedure will probably be necessary in clinical settings.

MSC derived EVs have recently demonstrated rapid development as therapeutic agents prepared for clinical trials. Twenty clinical trials using EVs generated from MSCs as therapeutic therapies have so far been filed. Concentration by Tangential Flow Filtration (TFF) followed by Size Exclusion Chromatography (SEC) is emerging as the preferred method for clinical grade EV synthesis because it better preserves the functional activity of EVs. TFF is an effective way to create EV populations from sizable amounts of conditioned media that have a rarefied EV content in a

repeatable way. Large starting volumes could be bulk processed, and highly purified bioactive EVs could be created in a clinical setting by combining TFF and SEC.

#### REFERENCES

1. Fujita Y. Extracellular vesicles in idiopathic pulmonary fibrosis: pathogenesis and therapeutics. *Inflamm Regen.* 2022;42(1):1-8.
2. Fujita Y, Kosaka N, Araya J, et al. Extracellular vesicles in lung microenvironment and pathogenesis. *Trends Mol Med.* 2015;21(9): 533-42.
3. Kubo H. Extracellular vesicles in lung disease. *Chest.* 2018;153(1): 210-6.
4. Worthington EN, Hagood JS. Therapeutic use of extracellular vesicles for acute and chronic lung disease. *Int J Mol Sci.* 2020;21(7):2318.
5. Chen L, Qu J, Kalyani FS, et al. Mesenchymal stem cell based treatments for COVID-19: Status and future perspectives for clinical applications. *Cell Mol Life Sci.* 2022;79(3):142.