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Review Article

Cellular therapies for idiopathic pulmonary fibrosis: current progress and future prospects

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Abstract: Idiopathic pulmonary fibrosis (IPF) is an interstitial, fibrotic lung disease characterized by progressive damage. Lung tissues with IPF are replaced by fibrotic tissues with increased collagen deposition, modified extracellular matrix, all which overall damages the alveoli. These changes eventually impede the gas exchange function of the alveoli, and eventually leads to fatal respiratory failure of the lung. Investigations have been conducted to further understand IPF's pathogenesis, and significant progress in understanding its development has been made. Additionally, two therapeutic treatments, Nintedanib and Pirfenidone, have been approved and are currently used in medical applications. Moreover, cell-based treatments have recently come to the forefront of developing disease therapeutics and are the focus of many current studies. Furthermore, a sizable body of research encompassing basic, pre-clinical, and even clinical trials have all been amassed in recent years and hold a great potential for more widespread applications in patient care. Herein, this article reviews the progress in understanding the pathogenesis and pathophysiology of IPF. Additionally, different cell types used in IPF therapy were reviewed, including alveolar epithelial cells (AECs), circulating endothelial progenitors (EPCs), mixed lung epithelial cells, different types of stem cells, and endogenous lung tissue-specific stem cells. Finally, we discussed the contemporary trials that employ or explore cell-based therapy for IPF.

Keywords: Idiopathic pulmonary fibrosis, cell therapy, stem cells, lung

Introduction

Lung tissue demonstrates a relatively slow cellular turnover rate under normal circumstances. In the case of injury, the tissue is believed to have a limited ability to repair itself, although it is vulnerable to scar tissue formation [1, 2]. Cell-derived therapies offer a promising novel treatment that can aid in regenerating lung tissue without forming scar tissue.

Pulmonary fibrosis has many forms, but the most common is Idiopathic Pulmonary Fibrosis (IPF). IPF is a chronic condition consisting of progressive scarring of the lung parenchyma, which leads to chronic cough, dyspnea, and diminished quality of life [3]. The prognosis for this disease is incredibly poor; survival time after diagnosis is estimated to be around 4 years [4]. It is hypothesized that the etiology of the IPF may arise from interference to the regenerative capabilities of the lung [5]. Epithelial and mesenchymal cell interactions are thought to be the most notable. This interaction plays a vital role in both lung formation and repair after acute or chronic injury [6]. In addition, myofibroblasts are known to congregate in fibroblastic foci at injury sites in fibrotic lung tissues. The extent of both fibroblastic foci and collagen deposition demonstrates a positive correlation with disease prognosis [7, 8].

Recent studies have determined that unlike previously believed, IPF is not a fibroblast-driven disease, but an epithelial-driven one [9]. The current consensus is that the disease is incurred, as well as driven by repetitive damage and subsequent abnormal behavior of type II Alveolar Epithelial cells (AECII). This aberrant behavior is usually caused by the cells' inability to adequately regenerate the alveolar epithelium, leading to the alveolar surface being ob-

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scured with non-native epithelial cells, limiting gas exchange and causing inflammation. There are 2 main pathways that these processes can take: Epithelial to mesenchymal transition (EMT), whereby epithelial cells gain the features of mesenchymal cells and grow abnormally, and epithelial mesenchymal crosstalk (EMC), where damaged AEC II cells send current signals to initiate fibroblast migration to the alveoli and lead to progressive inflammation.

While the exact mechanism for IPF has yet to be identified, the common consensus is that there is a genetic predisposition to the disease. Specifically, mutations in the telomerase enzyme as well as shorter telomere lengths have been implicated in IPF [10, 11]. Additionally, genes regulating surfactant proteins A2 and C (SFTPA2 and SFTPC, respectively) [12, 13], lipid transport ATP-binding cassette member A3 (ABCA3) [14], mucus production mucin 5B (MUC5B) [15] and the enzyme telomerase are important in the formation of the IPF. The MUC5B experiences a single-nucleotide polymorphism which leads to mucus hypersecretion in the fibrotic lungs. The most affected telomerase genes in fibrotic lung tissues include telomerase reverse transcriptase (TERT) [16], human telomerase RNA component (hTR), dyskerin (DKC1), telomerase interacting factor 2 (TINF2), and the regulator of telomerase elongation helicase (RTEL1) [17, 18]. As a result of dysfunctional telomerase, the length of chromosomes become shorter over time, leading to signs of early aging in addition to IPF in the lung.

Additionally, the exposure to lung irritants (i.e., smoking, inhalation of antimicrobial agents, and aspiration of gastric contents) and aging are positively correlated with IPF [19]. More recently, the analysis of differentially expressed genes (DEGs) between IPF and normal lung tissue has led to the identification of four major hub genes, which include CDH2, SPP1, POSTN, and VCAM1 [20]. Furthermore, miRNAs miR-4262, miR-155-5p, and miR-181b-5p are likely implicated in IPF pathogenesis and subsequently have key interactions with the four hub genes [21]. Signaling pathway analysis in the form of RNA-seq studies have emphasized the importance of pathways such as SCGB3A1, BPIFB1, and MUC5B, in their relation to metaplastic epithelial cells, immune response, and apoptosis. These pathways are specifically involved with secreto-proteins and mucin dysfunction, and offer a potential therapy in the treatment of this disease [22].

The traditional model for IPF pathogenesis starts with a lung injury that leads to an inflammatory cascade, cytokine release from inflammatory cells, remodeling of the parenchyma and increased activity of fibroblasts. Notably, anti-inflammatory medications do not seem to be effective for IPF symptoms, which suggests a limited role, if any, for inflammatory cells in the pathogenesis of IPF [23-26]. Additionally, it is also becoming clear that there are differences between familial and sporadic IPF, at least radiologically [27]. It does appear, however, that the radiologic changes become similar in advanced pulmonary fibrosis. Subsequent investigations are necessary to understand these differences and to investigate mechanisms and formulate different treatment options if needed.

There are no curative therapies for IPF at this time. Non-pharmacological management of the IPF involves delivering supplemental oxygen, avoiding negative environmental factors (i.e., smoking), pulmonary rehabilitation, and lung transplantation. While lung transplant is effective in preventing the recurrence of IPF, it is not a sustainable treatment for all IPF patients since donor organs are difficult to find [28]. Two antifibrotic agents, Pirfenidone and Nintedanib, have FDA approval for use in IPF patients and previous studies have shown them to retard progression of the disease and decrease mortality [29, 30]. Nintedanib, a tyrosine kinase inhibitor, restricts neo-angiogenesis by inhibiting vascular endothelial growth factor receptors (VEGFR), fibroblast growth factor receptors (FGFR), colony-stimulating factor-1-receptors (CSF1R), platelet-derived growth factor receptors (PDGFR), and FMS-like tyrosine kinase-3 (FLT3) [26]. On the other hand, pirfenidone exerts its mechanism of action by inhibiting the exaggerated fibrotic response in response to epithelial injury [31]. These two treatments are pharmaceutical based therapies that exist in the form of medications, usually ingested orally as pills and diffused throughout the bloodstream. The American Thoracic Society's (ATS) guidelines for IPF management has a strong

recommendation against warfarin, imatinib, ambrisentan, and prednisone/azathioprine/N-acetylcysteine combination, as well as sildenafil, macitentan, and bosentan. They also recommend against the use of antacid treatment and anti-reflux surgery as sole therapies for IPF. The ATS does, however, conditionally recommend nintedanib and pirfenidone due to confidence in these treatment modalities. During acute exacerbations, the ATS recommends the use of corticosteroids, and, as the disease progresses, either palliative care or lung transplant for long-term management of IPF [4].

Cellular therapies for IPF generally involve the introduction of targeted cells (either stem cells or otherwise immunologically active cells) to the lungs via injection or aerosolization to allow the tissue to uptake and integrate the cells. This either induces differentiation or activation of the cells for use in combating the chronic inflammation characterized by IPF [32-34]. Overall, the efficacy of these treatments depends heavily on adequate uptake within the lung. Currently, there are no cell therapies that have conclusively proven to improve IPF prognosis. However, recent research suggests that therapies utilizing extracellular vesicles show particular effectiveness in combating autoimmune disorders, fibrosis, and tissue damage. As such, the usage of mesenchymal stem-cell extracellular vesicles (MSC-EVs) could be of particular interest as it pertains to IPF stem cell therapy [35]. Overall, there are promising prospects regarding the discovery of novel therapies for IPF, but the safety and efficacy of such prospects must still be carefully evaluated as there are major concerns for cell-based treatment of IPF in regards to the oncogenicity and immune response to stem cells.

This article discusses the approaches used for treating the IPF, focusing on cell-based therapy, which has shown to be a promising treatment for the IPF [36].

Cell types used in IPF cell-based therapies

Stem cell utilization in the treatment of IPF is quite varied. Although this paper covers various therapeutic effects that can be achieved by using stem cells such as those described in "Alveolar epithelial cells - type I and II" section - "Lung spheroid cells (LSCs)" section below, the presence of other kinds of stem cells such as MDSCs, as described in *2.5* may serve as indicators of disease progression. This indicates that cellular therapies do not always entail treatment and relief to those suffering from IPF and other forms of pulmonary fibrosis: it could also serve as an important indicator for disease progression.

Most stem cells described treat pulmonary fibrosis via their regenerative properties, effectively healing and correcting the damaged lung tissue. Stem cells' diverse and multi differentiable properties continue through their mechanisms of action, as all therapeutic stem-cell therapies are extremely varied. This makes it impossible to simply categorize all stem-cells into one or two overarching categories. Such therapeutic effects presented by stem cells can range from cell regeneration, such as those represented by Endometrial Regenerative cells (ERCs), to promotion of cell checkpoints that reduce the rate of apoptosis, as seen in Adipose tissue-derived MSCs (ADSCs). The migration of certain stem cells into diseased areas also does not follow a uniform pattern; as such, this article attempts to explore and review methods of stem cell migration and recruitment into host tissue, such as those involving chemotaxis. Certain stem cell types may recruit better compared to others in certain scenarios, such as those described in "Circulating endothelial progenitor cells (EPCs)" section, which compares adipose derived MSCs and bone marrow derived MSCs. Overall, more research is needed to understand the full potential of stem cells, ranging from their therapeutic to their malignant potential. In the following subsections, this paper will evaluate and explore many different cell types used in cellular therapies, their differences and similarities, and effectively summarize their abilities in pulmonary fibrosis treatment.

Alveolar epithelial cells - type I and II

The alveolar epithelium of the lung has two types of cells, the epithelial cell type 1 and II. The epithelial cell type I (AECI) cells facilitate the process of gas exchange within the lung's capillaries. Alveolar epithelial cell type II (AECII) cells, on the other hand, secrete surfactant proteins, which reduces the alveolar surface pressure [32, 37, 38]. When the quantity of AECI cells is decreased, such as during a lung injury,

AECII cells can differentiate into AECI cells and begin to remodel and maintain the architecture of the alveoli. Moreover, the AECII cell treatment was able to completely reverse lung damage after transplantation into rodent models of lung fibrosis [39].

Multiple methods to isolate AECII cells are described. Two popular methods include isolation from allogeneic lung tissue biopsy and culturing various stem cells [39, 40]. Freshly isolated stem cells demonstrate a slight advantage over cultured cells since they are more effective and safer than cultured cells since they lack tumor forming potential [41]. AECII cells may also be derived from bone marrow stem cells (BMSCs) or human embryonic stem cells, though this derivation does not have much supporting research and is currently being investigated further [33, 42]. Embryonic stem cells (ESCs) can also be induced to produce both AEC cells and airway specific epithelial cells by supplementation with specific growth factors in the culture media [43, 44]. Regardless of the source, AECII cells transplanted in the lung of IPF models have been shown to lead to a reduction of collagen and direct contribution to the healing process in the injured lungs [34]. With their ability to reverse fibrosis, AECII cells offer a promising method for reversing fibrotic changes to lung tissue.

A summary of studies that explore the applications of AECs are shown in **Tables 1**, **2**.

Mixed lung epithelial cells

Acquiring specific types of lung epithelial cells is an intensive process, whether it be isolation of cells directly from lung tissue, or using growth factors to encourage stem cells to differentiate into specific cell types (as in the case of AEC cells described above). Accordingly, using mixed epithelial lung cells (LMDECs) has been proposed as being more feasible than a single cell type alone [45]. The majority of LMDECs, or lung mesenchymal-derived epithelial cells, express SP-C and CD44, CD45, and hematopoietic lineage markers. Additionally, the $LMDEC^{Maj}$ population includes some BASCs (bronchioalveolar stem cells) that express SP-C, CCSP, and Sca1. Overall, these mixed epithelial cells are not characterized by their specific cell types, but by their protein and epigenetic markers since these properties can be the same across multiple different cell lineages [45]. Intratracheal introductions of LMDECs into a BLM-induced models of IPF have also been reported to somewhat resolve conditions of lung fibrosis, due to their ability to respond to stromal derived factor 1 (SDF-1), migrate to fibrotic sites, and differentiate into AEC I cells for use in lung repair. The effects of LMDECs involve more than the response to SDF-1. In fact, the subpopulation that was SP-C(+), CD44(+), CD45(+), hematopoietic cell lineage(+), and $LMDEC^{Maj}$ was found to contribute significantly to the protective effect, and were able to take part in regeneration [45]. Cellular based treatment for various fibrotic conditions can be difficult to prepare, and in many cases, it may not be worth the time and effort required to use this method. However, mixed lung epithelial cells are relatively easy to prepare and have been shown to be effective, which makes them another candidate for the treatment of fibrotic pulmonary conditions.

Stem cells

Stem cells are at the forefront of regenerative medicine, specifically with applications to the treatment of chronic diseases. The stem cells with a specific application in lung diseases include Mesenchymal stem cells (MSCs), bone marrow-derived stem cells (BMSCs), umbilical-derived stem cells (uMSCs), Adipose-derived Stem cells (ADSCs), Endometrial Regenerative Cells (ERCs), Induced Pluripotent Stem Cells (iPSCs), Endometrial Stem Cells (ESCs), and endogenous lung stem cells. These cells have two main abilities of interest in treating IPF: non-oncogenic self-replication, and differentiability into a wide variety of cell types. Adult stem cells (ADSCs, BMSCs, and uMSCs) are also often used to investigate the treatment options of chronic diseases such as the IPF [46, 47]. However, there are still many valid ethical concerns for the use of stem cells, especially among members of the public and those in the legislature. With the regenerative abilities that stem cells possess, there is great potential for treatments that directly impact and have the capacity to increase the quality of life for millions of people worldwide. The scientific community is excited about the potential for stem cells, and while there are methods that may be ethically dubious, there are certainly options that do not raise moral or ethical dilemmas.

Table 1. Summary of key IPF preclinical study results using AECII cells

Type/source of cells	Delivery route/dose	Efficacy results	Reference
AECII cells	Intratracheal route. A dose of 2.5×10^6 cells per rat	After BLM installation, treated rats demonstrate the ability to restore lung surfactant protein levels to pre-BLM installation levels.	[115]
AECII cells	Intratracheal route. A dose of 2.5×10^6 cells per rat	After BLM instillation, treated rats exhibit significantly reduced severity of lung fibrosis in addition to reduced deposition of collagen.	[37]
AECII, AECI, and Clara cells derived from human ESCs	Intratracheal route. A dose of 1×10^5 human-ESC cells per rat	After BLM installation, treated mice exhibit reduced collagen deposition along with increased levels of AECI and AECII present.	[44]
AECII, AECI, and club cells derived from rat LSCs	IV route. A dose of 5×10^6 LSC cells per rat	LSC administration alongside BLM in rats was shown to slow fibrosis progression and reduce the severity, decrease the amount of apoptosis, and increase lung tissue angiogenesis in response to acute injury.	[68]
ADSCs	IV route. A dose of 5×10^6 cells per mouse	Mice treated with AFSCs 2 hours after BLM instillation demonstrated nominal fibrotic changes, while mice treated with AFSCs 14 days after BLM installation showed marked collagen deposition and alveolar destruction, however, it was less severe than untreated control.	[89]

Table 2. Human clinical study results summary using AECII cells

Type/source of AECII cells	Delivery Route/dose	Efficacy results	Safety results	Reference
Allogenic AECII cells	Intratracheal route. A dose of 1,000 to 1.2×10^9 cells per patient	Advancement of IPF disease progression in treated patients is terminated.	AECII cells are safe and well tolerated in humans.	[116]

The current progress in stem cell research for IPF is discussed herein in "Stem cells" section.

Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are a type of stem cell that can be derived from many sources, including the umbilical cord, bone marrow, or adipose tissue [48]. MSCs are multipotent and can differentiate into a multitude of cell lineages [48]. They can specifically target damaged or injured tissues when administered, and from there, they can disperse throughout the body unlike many other stem cells.

MSCs have specific qualities that make them an attractive candidate for therapeutic treatment for different diseases, including anti-oncogenic properties such as being anti-proliferative and anti-apoptotic [46]. They also have other properties that facilitate the therapeutic implementation such as being immune-modulatory and anti-inflammatory [49]. Overall, due to their versatile properties, MSCs offer a promising future for different chronic disease therapies, and are potentially one of the best cellular treatment options specifically for IPF.

A summary of the studies that explore the applications of MSCs are shown in **Tables 3**, **4**.

Bone marrow-derived MSCs (BM-MSCs)

Bone-marrow-derived MSCs (BM-MSCs) are the largest source of MSCs and therefore, have been widely tested for the treatment of the IPF. In addition to their ability to differentiate into restoratively useful cells and migrate within the host, BM-MSCs have been reported to induce production of paracrine factors that specifically target and help reverse conditions of pulmonary fibrosis. These factors include growth factors such as KGF, HGF, and EGF that protect epithelial function, signaling molecules such as NO, S1P, Ang-1, and VEGF that enhance endothelial barrier, and anti-inflammatory cytokines (IL-1ra, IL-10, and TSG-6) secreted by MSCs. MSCs also exert immunomodulating effects through chemokines and receptors (ICAM-1, VCAM-1, and CXCR3) [50]. These components collectively contribute to the paracrine effects of MSCs in promoting tissue repair. A particular type of BM-MSC, the granulocyte-colony-stimulating factor (G-CSF)-augmented BM-MSCs show a potential to cause an increased lung

Table 3. Summary of important trials using MSCs

Type/Source of MSCs	Delivery route/dose	Efficacy results	Reference
Human placental MSCs	IV route. A dose of 1×10^5 cells per mouse	Slowed effects of fibrotic development, including decreased collagen deposition and the production of pro-fibrotic cytokines. MyD88 and TGF-β signaling increased.	[117]
Murine placenta-MSCs, human placenta-MSCs	IV route dose of 1×10^6 cells/mouse, or IP route dose of 4×10^6 cells/mouse	Marked decrease in neutrophil infiltration and reduced fibrotic progression, regardless of delivery route.	[55]
Human umbilical MSCs	IV route. A dose of 1×10^6 cells per mouse	Treated mice experienced reduced exudative infiltration after 7 days and reduced inflammatory cytokine expression after 14 days. Additional reduction of TNF-α associated with better outcomes.	[54]
Lung resident MSCs	IV route. A dose of 0.15×10^6 or 0.25×10^6 cells per mouse	Treated animals show reduced infiltration of lymphocyte and granulocyte and display reduced fibrotic damage.	[118]
BM-MSCs. Amnion-MSCs, or human amniotic epithelial cells (hAECs)	IV. A dose of 1×10^6 cells per mouse. 2 repeated doses at 0 and 7 days of treatments	Amnion-MSC treatments were more effective and decreased both fibrosis and TGF-β levels, but increased MMP-9 activity, GM-CSF secretion and IL-1RA induction.	[119]
Human BM-MSCs (overexpressing microRNAs let-7d or miR-154)	IV route. A dose of 5×10^4 cells per mouse	B-MSCs (overexpressing let7d) administration led to a decrease in both collagen deposition and CD45-positive cells.	[120]
BM-MSCs (transfected with HGF)	Intratracheal. A dose of 3×10^6 cells per rat	Treated rats exhibited reduced collagen deposition and decreased fibrosis.	[121]
BM-MSCs	IV route. A dose of 5×10^6 cells per mouse	Treated mice exhibited decreased collagen deposition and inflammation.	[96]
BM-MSCs	IV route. A dose of 5×10^5 cells per mouse	Treated mice exhibited inhibition of pro-inflammatory cytokines IL-1 and TNF-α and increased lung protection.	[122]
BM-MSCs	IV route. A dose of 2.5×10^6 cells per rat	Treated rats exhibited decreased collagen deposition and oxidative stress.	[123]
BM-MSCs	IV route. A dose of 5×10^6 cells per mouse	Treated mice exhibited suppressed inflammation but reduced reparative growth factor production.	[90]
BM-MSCs	IV route. A dose of 10^6 cells per rat	Treated rats exhibited a decrease of pulmonary inflammation and some fibrotic factors (TGF-α, VEGF, TNF-β, IL-6, IL-1β, and NOS).	[124]
BM-MSCs (human)	IV route. A dose of 5×10^5 cells per mouse	Treated mice exhibited reduced endoplasmic reticulum and oxidative stress, and reduced TGF-β1 production within alveolar cells.	[93]
BM-MSCs (human)	IV route. A dose of 5×10^6 cells per mouse	Slight pattern of BM-MSCs engraftment in BLM-induced fibrosis in immunodeficient NOD/SCID and NOD/SCID/β2 microglobulin (β2M) null mice.	[125]
Hypoxia preconditioned BMMSCs	Intratracheal route. A dose of 5×10^5 cells per mouse	Treated mice exhibited decreased fibrosis and inflammation and improvement of lung function.	[94]
Knockdown BMMSCs	IV route. A dose of 5×10^4 cells/g body weight	Treated mice exhibited low levels of interleukin-1b and apoptosis, decreased fibrosis, and increased HGF levels.	[126]
Gingival-derived MSCs	Intratracheal route. A dose of 1×10^6 cells per mouse	Treated mice exhibited reduced pulmonary fibrosis, inflammation, oedema, and apoptosis. Downregulated. MDA and MPO levels, and upregulated GSH and SOD levels.	[127]

Table 4. Summary of important trials using MSCs

Type/source of MSCs	Delivery route/dose	Efficacy results	Safety results	Reference
Placental MSCs (allogeneic)	IV route. A dose of 1 & 2×10^6 cells/kg. One dose	Treated patients exhibited no advancement of IPF and stable maintenance of lung function.	Minor acute adverse events.	[128]
BM-MSCs (allogenic)	IV route. A dose of 20×10^6 (n=3), 100×10^6 (n=3) & 200×10^6 cells (n=3). One dose	Exploratory results: 5.4% mean decline in % predicted DLCO and 3.0% mean decline in % predicted FVC in treated patients.	No serious events, but IPF progression resulted in 2 non-treatment related deaths.	[129]
BM-MSCs (allogenic)	IV route. Four infusions of 2.0×10^8 cells, repeated after 12 weeks	Overall, no major difference in outcomes for patients, however, highlighted the effects of high dosage treatments in humans.	Minor adverse effects such as fever and chills, one case of developed ischemic stroke, four non-treatment related deaths.	[36]

healing capacity in the animal models of lung injury [51]. Consequently, significant attention has been given for the use of G-CSF in the treatment of the IPF, as well as other fibrotic lung injuries. Many studies have replaced BM-MSCs with G-SF for both autologous and allogeneic cell transplantation, but more research is still needed to determine the effects of using BM-MSCs in the treatment of the IPF and lung injury [52].

A summary of key preclinical and clinical studies using BM-MSCs is listed in **Tables 3**, **4**.

The umbilical cord- or placental-derived MSCs

MSCs derived from the umbilical cord, placenta, or aborted fetus tend to have high plasticity, so they tend to differentiate into other cell lineages of all germ layers more easily. Furthermore, MSCs derived from the umbilical cord and placenta display low levels of immunogenicity in culture and in vivo [53]. Due to the potential to source these cells from fetuses, this cell type presents some ethical dilemmas.

There are several clear differences between the characteristics of umbilical cord-derived MSCs (uMSCs) and placenta-derived MSCs such as: 1. uMSCs tend to be less available compared to pMSCs, 2. Placenta-derived MSCs have the ability to integrate into the lung and other organs when they are introduced via xenotransplantation.

A study by Moodley et al. found that the use of uMSCs in BLM-induced lung injury can reduce both lung inflammation and fibrosis by enhancing the expression of anti-inflammatory modulators, but reducing the expression of cytokines [54]. In addition, in murine studies, transplanted placenta-derived MSCs can reduce BLM-induced lung fibrosis by suppressing the infiltration of neutrophils, suggesting a potential treatment for lung fibrosis [55]. Moreover, placenta-derived MSCs have high plasticity and immunogenicity, reinforcing its importance for lung repair and regeneration [56].

Examples of studies conducted using placenta-derived MSCs and uMSCs are shown in **Tables 3**, **4**.

Adipose tissue-derived MSCs (ADSCs)

ADSCs can give rise into multiple cell lineages, and can be used as an alternative to BM-MSCs that make them a remarkable topic of interest. ADSCs can be obtained via liposuction from patients, and they demonstrate excellent results in cell therapy, producing a wide range of bioactive factors, such as hepatocyte growth factor (HGF), IL-1, IL-6, and IL-8 receptor antagonists [57, 58].

ADSC-based therapy resulted in both decreased AEC and Clara cell hyperplasia. Additionally, it also resulted in the prevention of septum thickening, and increased alveolar size and inflammatory cell infiltrations [59]. Apoptosis and TGF-β levels were dampened after ADSC-based therapy. This is important, especially in diseases such as IPF, where the main goal is to prevent lung degradation. The ADSC-based therapy can be also used in renal function in cases like the acute pyelonephritis [58]. Timing of ADSC-based therapy is critical for its efficiency in lung fibrosis. For example, a study by Uji and colleagues found that ADSC administration 14 days after introducing bleomycin can reduce both efficacy and efficiency of AD-

Table 5. Summary of important IPF preclinical studies using the ADSCs

ADSC Type	Delivery Method	Efficacy	Reference
ADSCs	IV, 2.5*10^4, or 2.5*10^5 cells per mouse	Decreased lung fibrosis and inflammation, exhibiting dose-dependency.	[130]
Human derived ADSCs	IP, 3×10^5 cells per mouse	Decreased, lung fibrosis, inflammatory cell infiltration, and epithelial cell hyperplasia, linked with inhibited TGF-beta expression and epithelial cell apoptosis.	[59]
ADSCs (young vs. old donor)	IV, 5*10^5 cells/mouse	Old mice (>22 weeks old) were treated with young ADSCs, exhibited great reduction in fibrosis, oxidative stress, MMP-2 activity, and apoptosis markers compared to mice that were treated using old ADSCs.	[86]

Table 6. Summary of major human IPF clinical studies using the ADSCs

ADSC Type	Delivery Method	Efficacy	Safety	Reference
ADSCs-SVF	Endobronchial route. A dose of 5×10^5 cells/kg of body weight in 10 cc. Three doses for 3 months	All patients alive (for at least two years after treatment), with the median overall survival being 32 months, and median overall progression-free survival of 26 months.	No ectopic tissue formation was exhibited, no difference in adverse events compared to placebo.	[131]
ADSCs-SVF	Endobronchial route. A dose of 5×10^5 cells/kg of body weight in 10 cc. Three does for 3 months	No decrease amongst the functional parameters, as well as life quality indicators.	No ectopic tissue formation was exhibited, no difference in adverse events compared to placebo.	[80]

SC based therapy [60]. Additionally, Uji and colleagues also claimed that factors such as experimental animal age/gender, IPF disease stage, and failure of ADSCs to migrate to heavily fibrotic areas of lung tissue can also reduce the impact of ADSC-based therapy [60].

Examples of clinical and preclinical studies on treating the IPF using ADSCs are shown in **Tables 5**, **6**.

Endometrial regenerative cells (ERCs)

The endometrial regenerative cells (ERCs) were used recently for lung repair and regeneration. ERCs can be directly and noninvasively harvested from human menstrual blood [61]. These cells are particularly promising since they are easy to supply and come from waste tissues so that they can be used without ethical concerns. ERCs can potentially differentiate into ectodermal, endodermal, and mesodermal cell lineages; therefore, their application can be utilized beyond pulmonary regeneration [62]. Preclinical studies showed remarkable results in treating IPF in a murine model. ERCs' effect on bleomycin-induced IPF in mice indicated that the immunosuppressive and antifibrotic properties of these cells are effective in reducing the extent of fibrosis, decreasing hydroxyproline and tissue growth factor beta (TGFβ), and upregulating both hepatocyte growth factor (HGF) and matrix metalloproteinase 1 (MMP-1) [63]. These cells are unique in that they are only derived from natural waste tissues, so harvesting them is completely non-invasive. Since they are easily harvested, lack ethical concerns, and have shown good results in the murine model, it is suggested that there should be more research into these cells, especially in humans.

A summary of an important preclinical study on ERCs utilized in IPF therapy is shown in **Table 7**.

The induced pluripotent stem cells (iPSCs)

The induced pluripotent stem cells (iPSCs) are derived from mature somatic cells by reprogramming somatic cells to an embryonic-like state, which essentially "resets" the cells. Once in their naïve state, the iPSCs can differentiate into various cell types [46]. While effective, iPSCs face challenges when used on a large scale. Notably, it is quite difficult to convert iPSCs into pulmonary progenitors and then

Table 7. Summary of an important preclinical study using ERCs

Type/source of ERCs	Delivery route/dose	Efficacy results	Reference
Human menstrual-blood derived ERCs	IV Route. A dose of 1×10^6 cells per mouse	Treated mice showed less pulmonary edema, significantly reduced structural changes, reduced inflammatory cell infiltration, and less interstitial fibrosis as compared to untreated control.	[63]

Table 8. Summary of important preclinical studies using iPSCs

Type/source of IPSCs	Delivery route/dose	Efficacy results	Reference
iPSCs	IV Route. A dose of 2×10^5 cells per mouse	Treated mice demonstrate blockage of TGF-b1/Smad2/3 signaling pathway, EMT, and inflammatory responses to BLM induced injury. Mice show reversal of BLM induced injury.	[42]
iPSC conditioned medium	IV Route. A dose of 2×10^6 cells per mouse	Treated mice show decreased collagen deposits, inflammatory infiltration, and hydroxyproline. Additionally, despite BLM induced injury, there is marked antifibrosis and preserved pulmonary function.	[42]
iPSCs derived to AECII cells	Intratracheal route. A dose of 5×10^5 cells per mouse	Treated mice show reduction in the severity of BLM-induced disease progression. Also, there are a reduced number of inflammatory cytokines, fibrotic cytokines, collagen deposition, and overall lung inflammation.	[78]
iPSCs	IV Route. 2×10^6 cells per kg	Treated mice showed decreased lung fibrosis, decreased hydroxyproline and collagen levels, and IRS-1 gene expression levels return to normal after treatment.	[65]

into specific types of lung epithelium. However, researchers have successfully created lung progenitor cells by recreating the conditions that naturally lead to lung progenitor cells. These reset cells successfully differentiated into the lung epithelium when injected subcutaneously in mice [64]. Another potential use for iPSCs lies in harvesting them from healthy human lungs to create an effective model for human lung disease. A model of such composition would be an excellent precursor to a clinical trial, assuming it shows iPSCs to be safe and effective as they were in the murine model.

One study showed that iPSCs in a BLM-induced IPF murine model have upregulated insulin receptor substrate-1 (IRS-1), which controls insulin like growth factor 1/2 (IGF-1/IGF-2). This suggests that this gene contributes to the pathogenesis of IPF, but the iPSCs were effective in reducing the expression of this gene to normal levels, which could be a part of its antifibrotic mechanism [65].

A summary of preclinical and clinical studies that explore the applications of iPSCs are shown in **Table 8**.

Circulating endothelial progenitor cells (EPCs)

Free circulating endothelial progenitor cells (EPCS) are known to possess several properties which allow them to engage in both lung tissue repair and vascular remodeling [66]. Although there are multiple mechanisms contributing to the IPF pathogenesis, it is well established that abnormal vascular remodeling due to low numbers of EPCs is closely associated with IPF [66, 67].

EPCs contribute to new tissue formation and in injury repair by secreting growth factors [63, 65]. These factors include endothelial-derived angiogenic factors which are responsible for inducing alveoli formation through activation of specialized lung epithelial cells. EPCs can also differentiate into endothelial cells and integrate themselves into the vasculature. Administration of EPCs in animal models of various lung diseases has shown they are a vital part of normal lung repair, so defects of lung EPCs can lead to an inability to repair damage to the pulmonary endothelium [69]. The inability to repair pulmonary endothelium promotes fibrosis and leads to various pulmonary pathologies including IPF. Increasing the number of EPCs through cellular therapy thus increases the lungs ability to repair itself after damage.

Of note, conditions that alter lung structure such that gas-exchange is decreased or otherwise negatively affected, tend to combat low

levels of EPCs by increasing the expression of vascular endothelial growth factor (VEGF) to maintain the lung [66]. The reasoning for this is not well-understood especially in the context of IPF, and more research should be completed to investigate if VEGF on its own can aid in lung regeneration, or if it hinders it.

Lung spheroid cells (LSCs)

Lung spheroidal cells are lung-resident, potent progenitor cells. There has been much promise shown by cultivating them from a three-dimensional suspension culture that produces multicellular spheroidal clumps of cells. The lung spheroids are clusters that contain lung progenitor cells at the core, surrounded by supporting cells. In bleomycin-induced pulmonary fibrosis, engraftment of LSCs via tail vein injection reduced the number of apoptotic cells and increased angiogenesis. LSCs also decreased infiltrates and fibrotic thickening by the Ashcroft score [70]. LSC secretome inhalation in bleomycin induced fibrosis and in silica induced fibrosis led to reduction in apoptosis and reversed the alveolar epithelial damage back to healthy level. It also increased the multiplication of AT2 and AT1 cells and increased the expression of von Willebrand factor(+) vasculature [71]. The safety and efficacy of LSCs has also been established [68].

Myeloid-derived suppressor cells (MDSCs)

Myeloid-Derived Suppressor Cells (MDSCs) are most notable for their anti-inflammatory properties. They can be largely divided into two major types, according to morphology and cell surface phenotypes: 1. polymorphonuclear MDSCs (PMN-MDSC), and 2. monocytic MDSCs (M-MDSC) [72]. The mechanism of action is noted by the creation of anti-inflammatory cytokines such as interleukin-10 (IL-10). External IL-10 production/activity derived from external sources such as surrounding cells may exacerbate the anti-inflammatory effects presented by MDSCs, resulting in a positive feedback loop [73]. Studies have shown that in order for the anti-inflammatory effects to take place, there must be cell-cell contact, indicating that the mechanism of action of MDSCs is likely to be conductive through cell membrane receptors [74].

The presence of MDSCs is usually associated with a poor prognosis of cancer, as the presence of such cells indicate suppression of the immune system; MDSCs have also been associated with IPF, as well as other interstitial lung diseases. For a more tangible, comprehensible description of the relationship between MDSCs and IPF, studies indicate that MDSCs presence in the blood in IPF patients is inversely associated with maximum vital capacity. This relationship does not extend to other interstitial lung diseases [75]. The role of MDSCs in the pathogenesis of IPF is currently unknown, as well as its role during disease progression.

A clue into the behavior of MDSCs could be found in the presence of B7H3 (sB7H3), a protein that serves as an immune checkpoint. Cells that have bypassed immune checkpoints, such as malignant cancer cells, exhibit high levels of B7H3 expression. Studies have shown that anti-B7H3 antibodies prevented bone-marrow derived MDSCs (BM-MDSC) recruitment into the bleomycin-induced fibrosis area, indicating that B7H3 is responsible for the recruitment of MDSCs, and hence the recruitment of its anti-inflammatory, immune system evasive effects. This indicates that more research is necessary to investigate the effects of anti-B7H3 in not only IPF, but also other forms of pulmonary fibrosis, as the presence of B7H3 could indicate that the disease(s) has hit a significant checkpoint in its progression [76].

The routes, dosage, and timing of cell delivery

Cell delivery routes

The route of administration for cell-based IPF therapies is currently still one of the major challenges for its application. In the highlighted studies, cells have been administered into the injured lung through different routes, including the intravenous [77, 78], intraperitoneal [59, 77], intratracheal [79], and endobronchial [80] instillations. The method of delivery is of great importance, as the route of cell delivery likely has great effect on the cells' ability to target desired sites of influence within the organ [81].

The intratracheal delivery is given either by injecting cells into the lung, or by dispensing aerosolized cells suspended within droplets via a nebulizer [82]. These methods of intratrache-

al delivery are regarded as the optimal delivery method as they restrain the cells within the alveoli and lungs, preventing them from dispersing throughout the body and reducing the effect on the targeted areas, as may occur with intravenous or intraperitoneal methods. It can specifically aid the regeneration of tissue by concentrating the distribution of cells at the site of injury for an extended period of time and therefore minimizing the pulmonary first-pass effect [82].

The most appropriate dose for cell therapy

A good indicator of the effectiveness of stem cell-based therapy for the IPF is determined by the number of cells that reach the target sites. It is crucial to figure out the effective dosage for cell-based therapy since safety is a priority in clinical trials with humans. In regards to safety and efficiency, the minimum number of stem cells required to produce a significant outcome should be determined. This number is variable among different studies. Determining the minimum stem cell number required for IPF therapy since using excess stem cells can lead to increased cell proliferation in the target area that may result in malfunction of the target site itself. Because of the high variability of the minimum required stem cell number in different studies and trials, pinpointing the precise quantity of stem cells recommended for usage poses a challenge [83].

In one study that measured the dosage of allogeneic BM-MSCs injected in patients with first acute myocardial infarctions, the safe dosages ranged from $5*10^5$, $1.6*10^6$, and $5*10^5$ cells per kilogram [84]. In studies with laboratory mice, the effective dose ranges from $1*10^6$ cells per 30 g mouse. This number rises to $2.3*10^9$, when scaled up for use on humans. However, further experiments are still needed to further ascertain the optimum number of stem cells that can be used in chronic lung diseases, including IPF, in addition to the optimum route and frequency of administration [85].

Appropriate timing of exposure and cell delivery

The timing of cell-based therapy is an important part of the treatment regimen. It has a direct impact on the overall outcome of the treatment. Many preclinical research studies used the bleomycin (BLM)-induced model of the IPF in rodents. Bleomycin possesses unique antitumor properties by inducing DNA-strand breaks that simulate lung injury, leading to subsequent interstitial fibrosis [86-88]. After BLM administration, stem cells can be introduced to BLM-induced IPF model at varying time intervals from immediately thereafter, 15 minutes [55], 2 hours [89], 6 hours [90], 8 hours [91], 12 hours [92], 24 hours [93], 3 days [94], 4 days [95], 7 days [96], 10 days [97], 14 days [98], to up to 2 months after [99]. It appears that cells administered within four hours of IPF induction have the most promising results, likely due to the antiproliferative properties of administered cells reducing damage to lung epithelium and overall inflammation which leads to relatively quick resolution of the IPF [100].

Additionally, silica-based models for pulmonary fibrosis have been used in many studies, which involve the introduction of silica particles into the lungs of rodents to simulate fibrotic nodules similar to those observed in humans exposed to mineral dust [101]. The delivery of silica can be done through aerosolization, intratracheal administration, or oropharyngeal aspiration [102-104]. The response to silica varies depending on the exact mouse model, with varying fibrotic response between different strains. Silica-induced fibrosis in rats is characterized by chronic inflammation and overproduction of TNF-α, while in mice, it is linked with the transient inflammation and overexpression of IL-10, an anti-inflammatory cytokine [103]. Silica retention in the lung leads to increased alveolar accumulation of proteins and neutrophilia, and increased lactate dehydrogenase activity. Silica-based models provide valuable insights into the processes underlying pulmonary fibrosis [105]. This model of fibrosis offers the advantage of persistent fibrotic stimulation due to the slow removal of silica from the lung, with fibrotic nodules easily identifiable. However, the most common mode of exposure, experimental aerosolization, necessitates niche equipment, and the duration for fibrosis development varies widely between studies (within the first month [104, 106] or 60 days [103]), leading to increased daily costs per experiment.

In general, these Acute Lung Injury (ALJ) models for pulmonary fibrosis stimulate similar results to IPF, with the root difference of their

pathology being known. Despite these differences, these ALJ models provide an effective model for treatment of IPF, as replication of treatments performed on ALJ models with IPF patient human clinical trials provide similar results.

MSCs delivered after fibrosis have been shown to actively participate in fibrosis, likely due to fibrotic signals received at the cellular level [97]. However, cell types, like ACEII cells, show to reduce collagen deposition even after fibrosis has begun, suggesting that ACEII cells are capable of reversing fibrosis while MSCs are capable of preventing it [98].

A recent clinical trial investigated MSC administration in either IPF or acute respiratory distress syndrome (ARDS). Averyanov et al. found significantly increased lung function compared with baseline and placebo in patients receiving two intravenous doses of MSCs every three months for a total of six months. This study also demonstrated that high doses of MSCs (4 million cells 3 months apart) are safe to use in humans [36].

Current trials

Although promising results in some clinical studies, there is not currently an effective cure for the IPF. While there are many ongoing investigations, there is no consensus on the most effective treatment for the IPF. The only approved treatments for the IPF are Nintedanib and Pirfenidone.

Stem cell-based therapy is still undergoing many clinical trials [99, 100, 107]. However, there are some major concerns for cell-based treatment of the IPF such as oncogenesis, efficacy, and immune response. A major concern is the oncogenic properties of stem cells and their safety in treating the IPF and other diseases in humans. Another major concern is the possibility of malignant transformation or oncogenesis that can occur during stem-cell based therapy of these diseases. This is particularly important since many of IPF risk factors overlap with those for lung cancer [108] and, therefore, transplanting stem cells into an environment that is already at-risk for mutations poses additional risks. Indeed, several studies have presented indications for the oncogenic properties of stem cell-based treatment in the IPF animal models *in vivo* [42].

Furthermore, the efficacy of treatment and the administration method are another major concern in stem-cell based therapy of the IPF. While paracrine properties of stem cell-based treatment are potent, the ability for these stem cells to target the intended area still need further investigation. However, there are several published articles on the intravenous delivery of stem cells in humans [100], and other delivery methods such as the intratracheal, intraperitoneal, and endobronchial methods of delivery in the IPF murine models *in vivo* [80-99, 110, 111]. Additionally, the window in which stem cell treatment is effective is another important consideration. Many current clinical stem-cell therapies are implemented in the inflammation phase of the fibrosis [99]. The efficacy of this implementation during the later fibrotic phase of the IPF is currently under investigation.

MSCs are commonly used in clinical trials given their immunogenic, anti-inflammatory, anti-proliferative, and anti-apoptotic properties. They were extensively used not only in *in vivo* tests, but also in human clinical trials [98]. In addition, there is progress in the transplantation of basal cells (BCs) in human subjects for regenerating alveolar function because these cells have regenerative abilities that are unique to the respiratory system [98].

There are currently 7 major clinical trials investigating cell therapies for the treatment of IPF. These are evaluated in tabular format in **Table 9**.

An ongoing clinical trial by Xiong and Yun is examining the effects of allogeneic Cell Free Fat Extract (CEFFE) on severe human IPF after promising results from animal models. The trial aims to elucidate the effectiveness and safety of adipose tissue derivatives in the context of IPF treatment. In this trial, CEFFE was synthesized from adipose tissue harvested from healthy donors after liposuction treatment and administered via nebulized inhalation [112].

Bronchial Basal cells in the form of REGEND001 Autologous Therapy Product possess regenera-

Table 9. Summary of current clinical trials involving cellular therapies and associated information

Trial Number	Cell Type	Safety	Cell Source	Delivery Route	Dose	Trial Phase	NCT Number	Reference
1	Cell Free Fat Extract (CEFFE)	CEFFE is safe for use in humans (134)	Allogenic adipose tissue	Inhalation	7 rounds of 2 mL of 3 mg/mL CEFFE given 3 days apart	Phase 1	NCT05883293	[112]
2	REGEND001	Currently under investigation	Autologous Bronchial Basal Cells	Transplantation via Bronchoscopy	Currently under investigation	Phase 1, Phase 2	NCT05657184	[113]
3	Umbilical Mesenchymal Stem Cells	Umbilical Mesenchymal Stem cells are safe for use in humans	Human umbilical cord mesenchymal stem cells	Injection infusion via bronchoscope	Single dose of 6.0×10^6, 3.0×10^7, 6.0×10^7, or 9.0×10^7 cells per person	Phase 1	NCT05468502	[132]
4	Bone Marrow derived Mesenchymal Stem Cells (BM-MSCs)	BM-MSCs are safe to use in humans	Autologous mesenchymal stem cells derived from bone marrow	Endobronchial infusion	10×10^6, 50×10^6, or 100×10^6 cells per person	Phase 1	NCT01919827	[133]
5	Umbilical mesenchymal stem cells	Umbilical Mesenchymal Stem cells are safe for use in humans	Allogenic adult umbilical cord derived mesenchymal stem sells	Intravenous infusion	1.0×10^8 cells per person	Phase 1	NCT05016817	[134]
6	Placenta derived Mesenchymal stem cells	Placenta derived Mesenchymal Stem Cells are safe for use in humans	Allogenic donated placentas (HLA unmatched)	Intravenous infusion	One group receives 1.0×10^6 cells, and if no adverse reaction after 4 months, another group will receive 2.0×10^6 cells	Phase 1	NCT01385644	[135]
7	Adipose Derived Stromal Vascular Fraction & Adipose derived Mesenchymal stem cells	Both cell types are safe for use in humans	Autologous adipose derived stromal vascular fraction & Autologous adipose derived mesenchymal	Intravenous	Single dose of Stromal Vascular Factor OR 3 doses of 2×10^6 cells per kg at weekly intervals	Phase 1, Phase 2	NCT02135380	[114]

tive properties for lung tissue as well. Currently, the efficacy and safety of this novel treatment are being researched by Xu [113].

Cells derived from human umbilical mesenchymal stem cells are undergoing evaluation in two clinical trials to establish the ideal dose to treat IPF. One trial examines injection via bronchoscopy while the other examines intravenous cell administration.

Two other clinical trials focus on mesenchymal stem cells, or stromal cells. The trials aim to learn more about bone marrow and placenta stem cell derivatives. One trial, which uses placenta derived MSCs, is examining the safety and efficacy of using related, unrelated, or mismatched Human Leukocyte Antigen (HLA) donor cells as a possible therapy for IPF.

The last clinical trial is investigating Adipose Derived Stromal Vascular Fraction, which includes a various cells such as endothelial cells, pre-adipocytes, smooth muscle cells, natural killer cells, pericytes, fibroblasts, adult stem cells, erythrocytes, B and T cells, monocytes, macrophages, mast cells, endothelial progenitor cells, hematopoietic stem cells, growth factors, proteins, and more. Additionally, this trial also has Mesenchymal stem cells, and a corticosteroid control group. Of note, the control included drugs such as prednisolone, cyclophosphamide or azathioprine, N-acetylcysteine, and pirfenidone [114].

Conclusions and prospects

IPF is a life-threatening condition. Several mechanisms have been investigated to understand the pathogenesis of the IPF. Additionally, several strategies are being looked at in terms of treatment options for the IPF. In terms of medications, the FDA has approved pirfenidone and nintedanib for treatment of IPF. American Thoracic Society (ATS) recommends against prednisone combined with both azathioprine and N-acetyl cysteine. In addition, the ATS recommends against the use of warfarin, imatinib, ambrisentan, macitentan, bosentan and sildenafil for the IPF patients. However, they recommend the use of N-acetyl cysteine and antacid therapy in the IPF patients without symptoms of gastroesophageal reflux disease.

Lung transplantation is a treatment option for some IPF patients. However, there are several limitations for this treatment, including the lack of donors and poor surgical patient's suitability. Cell-based therapies have been used for the treatment of patients with various diseases and disorders, including MSC in blood disorders, skin stem cells for patients with severe burns, and cord blood stem cells for leukemia. The overall goal of cell-based therapies for the IPF is to replace damaged cells with healthy cells and repair damaged cells with the paracrine effects of administered cells. We have summarized different stem cell types and their preclinical and clinical application for the treatment of the IPF.

The bleomycin-induced lung injury is the most used murine model used for the IPF. However, several recent models have been developed, including 3D lung culture models, decellularized whole lung models, and bioengineering approaches to generate functional lung tissues. The decellularized whole lung model offers a scaffold for 3D networks of different cell types, including mesenchymal, epithelial, fibroblast, endothelial, inflammatory, and neuronal cell types that can function effectively together. Furthermore, the cytokines and signaling molecules on targeted cells can be utilized to improve cell-based therapy.

Viral vectors can be used to produce genetically modified stem cells. These genetically modified stem cells can be delivered to the injured lungs to exert their effects locally. However, there are currently several challenges that should be overcome before applying this treatment method, including the identification of the most appropriate stem cell population for treating injured lungs, and the suitable gene vector that can provide a sustained expression. In addition, the effectiveness and safety of gene therapy are not currently completely well-understood.

Disclosure of conflict of interest

None.

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