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Review Article

Advances in the research and application of stem cell therapies for idiopathic pulmonary fibrosis

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal lung disease primarily affecting the elderly, marked by lung tissue scarring and impaired function. Current treatments, such as pirfenidone and nintedanib, slow disease progression but do not halt it and are associated with side effects. Lung transplantation is limited by donor shortages and surgical risks. Stem cell-based therapies, particularly mesenchymal stromal cells (MSCs) from bone marrow, adipose tissue, and umbilical cord, offer promise due to their low immunogenicity, homing capacity, and paracrine signaling. Preclinical models show that MSCs or their miRNA-bearing extracellular vehicles (EVs) can inhibit the TGFβ/Smad pathway, reprogram macrophage polarization, and promote tissue regeneration through anti-inflammatory and repair factors (e.g., IL-10, HGF, VEGF). Genetic modifications like CXCR4 overexpression may enhance MSC efficacy. Early clinical trials suggest favorable safety and preliminary efficacy, though long-term validation is needed. Additionally, alveolar type 2 (AT2) cells derived from induced pluripotent stem cells (iPSCs) and lung epithelial cells from embryonic stem cells (ESCs) offer potential for alveolar repair. Bioengineering advancements, including hydrogel scaffolds and 3D lung organoids, enhance stem cell retention and provide platforms for IPF research and drug screening. This review explores the therapeutic potential of stem cell therapies in IPF, integrating recent bioengineering developments and clinical prospects.

Keywords: IPF, stem cell therapy, MSCs, ESCs, iPSCs

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease marked by lung scarring, dyspnea, and eventual respiratory failure [1-3]. It typically affects individuals aged 65-70 [4], with a higher prevalence in males [5, 6]. Despite research, its etiology remains unclear [7], and treatment options are limited [8]. Current management includes pharmacotherapy [9], lung transplantation, and cell-based therapies [10]. Although pharmacotherapy and transplantation can slow progression, they do not halt lung function decline. Drugs like pirfenidone and nintedanib decelerate deterioration but are not curative [11, 12]. Lung transplantation improves survival but is constrained by organ shortages and surgical risks [13].

Stem cell therapy, with self-renewal, multipotency, and immunomodulatory properties, holds promise for IPF treatment [14, 15]. This review summarizes recent advancements in stem cell-based therapies, focusing on the potential of various stem cell types (mesenchymal, induced pluripotent, and embryonic) for lung tissue repair and disease progression attenuation.

Understanding idiopathic pulmonary fibrosis

IPF overview

Idiopathic pulmonary fibrosis (IPF) is one of the most prevalent interstitial lung disease (ILD), characterized by chronic inflammation, aberrant tissue repair, destruction of normal parenchymal, progressive functional impairment, and poor prognosis [16]. Its higher incidence in individuals over 60 suggests a potential link with aging [17]. Smoking constitutes a major risk factor; environmental exposures (e.g., wood dust, viruses, asbestos, silica) also

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contribute to pathogenesis [16]. Global epidemiology indicates an annual IPF incidence of 0.09-1.30 per 10,000 and prevalence of 0.33-4.51 per 10,000. Key pathological features include fibroblast proliferation/differentiation, inflammatory cell infiltration, abnormal extracellular matrix (ECM) deposition, and alveolar structural damage [18]. Repetitive injury to alveolar epithelial cells, particularly type II alveolar cells (AT2), leads to dysfunctional repair mechanisms [19], promoting the proliferation and migration of fibroblasts within the interstitium, driving their phenotypic transition into myofibroblasts [20, 21]. This process results in excessive ECM production, leading to tissue scarring and stiffening. Cellular senescence involves epithelial cells exhibiting a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory and pro-fibrotic mediators (e.g., IL-6, IL-1, TGF-β) [22, 23]. Molecular pathways implicated in IPF include TGF-β/Smad, WNT/β-catenin, PI3K/Akt/mTOR, Notch, and Hippo/Yes-associated protein [24], regulating proliferation, differentiation, programmed cell death, remodeling the fibrotic microenvironment, and driving progression.

IPF treatment strategies

Current IPF pharmacotherapy aims to alleviate symptoms and slow progression but cannot halt the disease process. Untreated median survival is approximately 4 years [25]. Pirfenidone and nintedanib are the sole approved antifibrotic drugs for IPF [26]. While they decelerate progression, they cannot arrest lung function decline [27]. Real-world data reveal significant adverse effects, underscoring the need for more effective and tolerable therapeutics [28]. Recent years, numerous novel drug trials target fibroblasts, alveolar macrophages, epithelial cells, senescence, oxidative stress, and mitochondrial dysfunction [7], acting through multiple fibrotic pathways [29]. However, their inability to reverse disease highlights the necessity for regenerative approaches. Lung transplantation currently offers the sole life-extending intervention for IPF but is restricted by stringent eligibility criteria, age limitations, and donor scarcity, limiting it to a minority of patients [24]. Thus, developing alternative regenerative therapies is critical. Owing to their properties of self-renewal and multipotent differentiation, stem cells have been established as a pivotal research platform in regenerative medicine. Accumulating preclinical and clinical evidence in recent years further indicates that stem cell-based therapeutic strategies demonstrate considerable potential for IPF treatment [14] (**Figure 1**).

Stem cell therapy in IPF research and application

Stem cell therapy, leveraging advantages of self-renewal, multipotency, and paracrine immunomodulation [30], is emerging as a core platform in regenerative medicine for diverse diseases. The primary stem cell types relevant to IPF include mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs). A direct comparative analysis of their key characteristics is summarized in the table below. And subsequent sections elaborate on their therapeutic and research value (**Table 1**).

Mesenchymal stem cells (MSCs)

In recent years, MSC-based therapies have been used to treat diverse diseases because of their ability to potently repair tissue and locally restore function [31], which also have garnered significant attention for IPF therapy. Encouraging findings on their mechanisms and efficacy, coupled with entry into clinical research, warrant their focus herein.

Sources and biological characteristics: Mesenchymal stem cells (MSCs) can be isolated from multiple tissue sources - including bone marrow (BM), adipose tissue (AT), and umbilical cord (UC) [32]. Compared to BM-MSCs and adipose-derived stem cells (ADSCs), UC-MSCs exhibit greater primitiveness and higher proliferative potential [33]. Although bone marrow is a traditional source, MSC yield decreases markedly with donor age, and extraction is invasive [34]. The non-invasive harvesting of umbilical cord mesenchymal stem cells (UC-MSCs) significantly reduces procedural risks for donors and may enhance cellular availability for allogeneic transplantation, thereby improving clinical feasibility [35]. Despite procurement flexibility from diverse sources, biological property variations necessitate careful source selection based on therapeutic goals and patient status.

MSCs readily expand in vitro and possess significant immunomodulatory properties, inhibit-

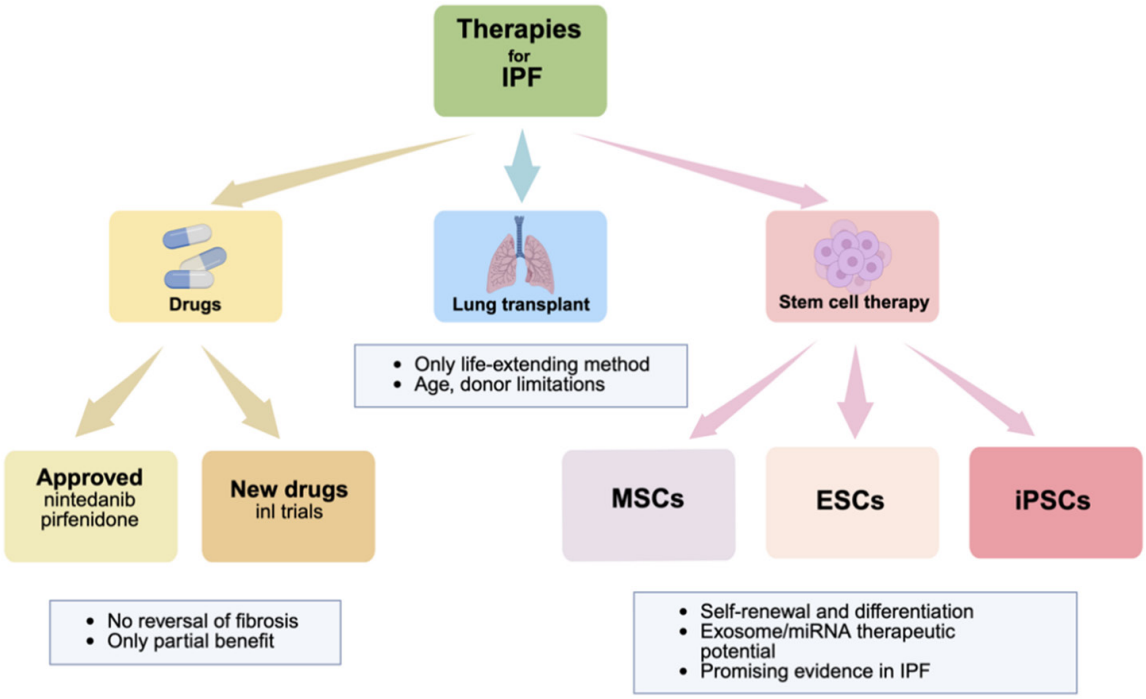

Figure 1. This slide provides a general classification of current and potential therapies for Idiopathic Pulmonary Fibrosis (IPF).

Table 1. Comparison of stem cell types for IPF therapy

Feature	Mesenchymal Stem Cells (MSCs)	Embryonic Stem Cells (ESCs)	Induced Pluripotent Stem Cells (iPSCs)
Source/ Accessibility	Relatively wide range of sources; can be obtained from adult tissues (e.g., bone marrow, adipose) or perinatal tissues (e.g., umbilical cord).	Limited to the inner cell mass of early embryos. Source is restricted and involves ethical controversies.	Obtained by reprogramming somatic cells (e.g., skin fibroblasts); sources are wide-ranging and bypass ethical concerns.
Differentiation Potential	Limited multipotency; primarily differentiates into mesenchymal lineages (e.g., osteoblasts, adipocytes). Therapeutic action relies mainly on paracrine effects rather than direct differentiation into lung epithelial cells.	Pluripotent; can differentiate into all cell types of the body, including functional alveolar epithelial cells.	Pluripotent, similar to ESCs; can differentiate into various cell types, including alveolar epithelial cells. Ideal tools for disease modeling and regenerative medicine.
Major Safety Risks	1. Low tumorigenic risk. 2. Main risks include cellular heterogeneity, low post-transplant survival rates, and potential unintended effects due to immunomodulation (e.g., pro-inflammatory or pro-fibrotic effects).	Tumorigenicity is the primary risk, potentially leading to teratoma formation after transplantation. Also carries a risk of immune rejection.	Tumorigenicity is a major risk, stemming from potential genomic mutations/instability due to integrating reprogramming factors and the presence of residual undifferentiated cells.
Clinical Readiness	Highest. Several Phase I/II clinical trials for IPF have been completed, preliminarily demonstrating safety and tolerability. This cell type is closest to clinical application.	Lowest. Due to ethical and safety constraints, currently confined to basic and preclinical research. No clinical transplantation protocols for IPF exist.	Intermediate. Undergoing active preclinical research, holding significant value for disease modeling and drug screening. Application as a cell therapy for IPF still requires resolving safety and standardization issues.

ing excessive immune responses and promoting tolerance [36]. Their multipotency, including differentiation into lung-associated cells, facilitates tissue repair. Low immunogenicity enables allogeneic transplantation, circumventing costly patient-specific cell preparation and enabling "off-the-shelf" therapy [37]. Homing to injury sites and secretion of beneficial bioactive factors further augment therapeutic value [37, 38]. Owing to this multifaceted potential in immunomodulation, anti-inflammation, and tissue regeneration, MSCs represent a promising candidate for complex diseases like IPF.

Mechanisms of action in IPF: By inhibiting the TGF-β/Smad signaling pathway - which plays a central role in IPF fibrogenesis - MSCs reduce myofibroblast differentiation and extracellular matrix (ECM) production. This regulatory capacity directly underpins their therapeutic potential [39]. Secondly, MSCs modulate immune responses by inhibiting Th17 cell differentiation/proliferation (associated with IPF pathogenesis) [40] and promoting macrophage polarization from pro-inflammatory (M1) to anti-inflammatory/repair (M2) phenotypes [41], thereby inhibiting fibrosis. Furthermore, MSCs primarily function via paracrine mechanisms, secreting factors (e.g., anti-inflammatory IL-10, reparative HGF, angiogenic VEGF) [42] that synergistically reduce inflammation [40], promote repair, and improve lung function. Elucidating specific factor contributions will enable more precise enhancement of MSC-based strategies, suggesting application prospects for therapies based on the MSC secretome. MSC-derived exosomes are small extracellular vesicles rich in bioactive molecules [43], including miRNAs, which deliver specific miRNAs (e.g., miR-30b-5p, miR-29a) to target cells to regulate gene expression (e.g., miR-30b potentially alleviating fibrosis via Spred2/Runx1) [44]. Compared to whole-cell transplantation [42], MSC exosomes offer a safer, more targeted cell-free option, with miRNA delivery showing significant potential for regulating profibrotic pathways like TGF-β.

MSCs exhibit tropism for injury sites, such as lungs in IPF models [42]. Animal studies demonstrate enhanced engraftment of mesenchymal stem cells (MSCs) in bleomycin (BLM)-induced lung injury models, a process partially mediated by the SDF-1/CXCR4 axis [45], which is critical for efficacy (e.g., CXCR4 overexpression enhances it) [46]. However, survival and long-term engraftment in the fibrotic lung microenvironment may be limited [45], indicating a need for strategies to improve pulmonary retention to maximize therapeutic benefit (**Figure 2**).

Research progress

In BLM-induced pulmonary fibrosis models, MSC therapy significantly reduces lung collagen deposition, fibrosis scores, histopathological damage, and improves survival [47] while diminishing inflammatory marker expression [48]. Some studies observed MSC differentiation into AT2-like cells [49] within damaged lungs, suggesting a tissue regeneration mechanism. These findings strongly support the translation MSC therapy into IPF clinical trials [45]. However, such models may not fully recapitulate complex human IPF pathological physiology [50] and primary therapeutic benefits likely stem from paracrine effects rather than direct engraftment/differentiation [45], a mechanistic distinction requiring further investigation.

Several clinical trials have assessed MSC therapy safety and preliminary efficacy in IPF patients. For instance, the Phase I AETHER trial (NCT02013700) evaluated intravenous allogeneic BM-MSC safety in mild-to-moderate IPF. Results demonstrated favorable treatment tolerability with no treatment-related serious adverse events. The two reported deaths were attributed to disease progression and were not treatment related. Exploratory efficacy endpoints showed the mean decline in forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) within 60 weeks was within expected ranges [51].

Application prospects and challenges: The translation of MSC-based therapeutics into clinical practice encounters significant persistent hurdles. Firstly, delivery and engraftment efficiency is low; systemic administration yields poor lung homing, and transplanted cell survival/engraftment in the fibrotic microenvironment is limited, impacting therapeutic durability [52]. Secondly, cellular heterogeneity: variations among MSCs from different sources and donors directly affect immunomodulatory and antifibrotic functions, leading to inconsistent outcomes [53] - standardization requires overcoming this barrier. Thirdly, precise in vivo mechanisms remain incompletely elucidated, hindering optimization; understanding MSC-lung microenvironment interactions is crucial. Finally, safety: while tumorigenicity risk is considered low, clear assessment is needed [54]. Addressing delivery/engraftment challenges involves exploring gene editing (e.g., CXCR4 overexpression) and biomaterial scaffolds to enhance targeted lung delivery and cell retention.

Comparison of cell-based versus cell-free therapies

The field of stem cell therapy is gradually evolving into two major strategies: traditional cell-

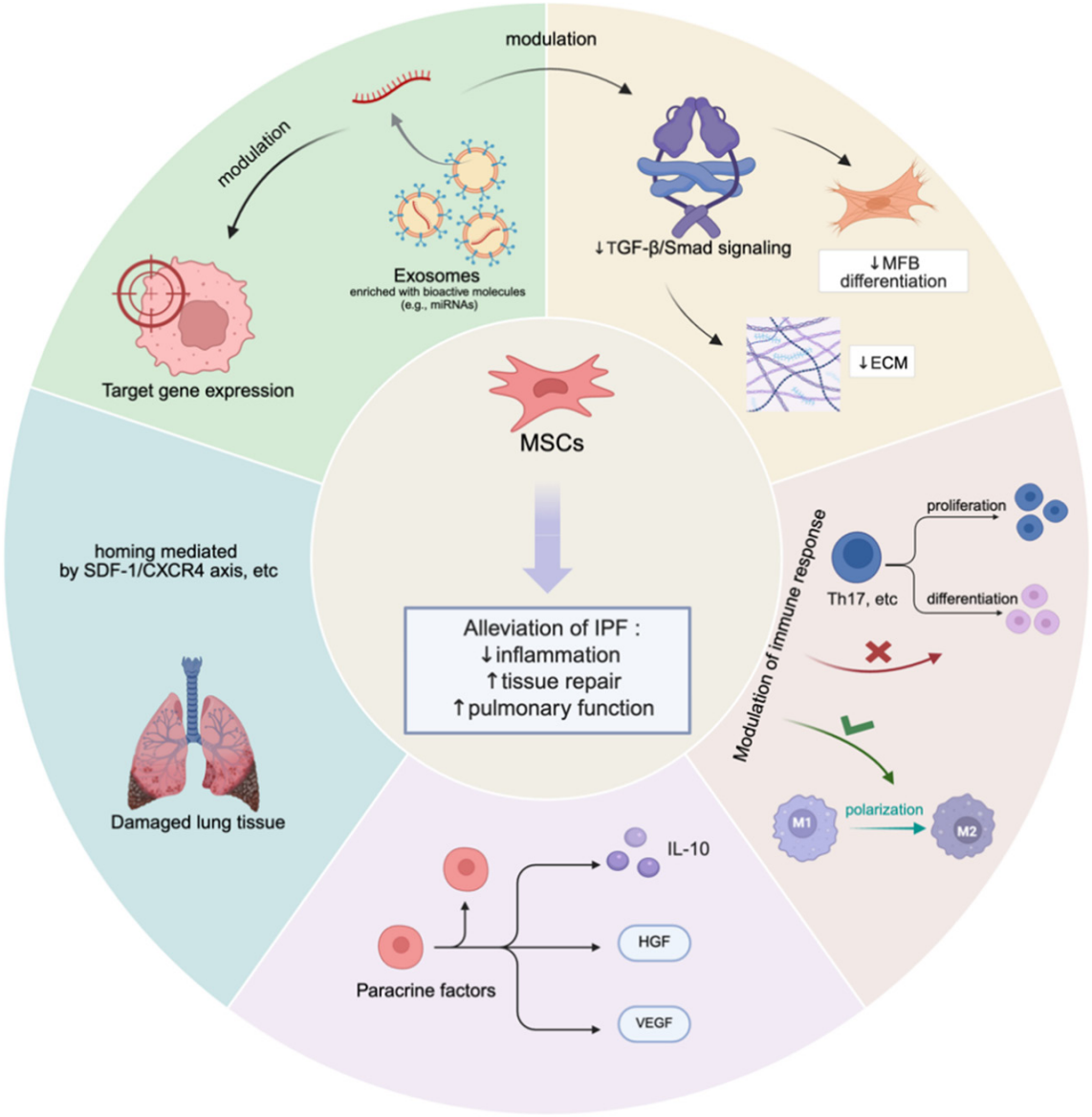

Figure 2. This diagram details the proposed mechanisms by which Mesenchymal Stem Cells (MSCs) alleviate IPF.

based transplantation and emerging cell-free therapies. The latter primarily refers to the use of conditioned medium derived from stem cells or specific active components, such as exosomes and other extracellular vesicles. These two strategies each have their own advantages and disadvantages for treating IPF (**Table 2**).

Cell-based therapies: The core advantage of **cell-based therapies** lies in the ability of transplanted living cells to sense the microenvironment and respond dynamically, exerting synergistic therapeutic effects through the continuous secretion of various factors. However, their greatest challenge is the low survival rate and limited long-term retention of cells within the diseased lung tissue, which restricts the durability of their efficacy. Furthermore, live cell transplantation carries risks of immune rejection (although MSCs have low immunogenicity) and a very low potential tumorigenic risk. Their production and quality control processes are also more complex.

Cell-free therapies: Cell-free therapies (particularly exosome therapy) present unique advantages. Exosomes, as nano-scale vesicles, carry various bioactive substances (e.g., proteins,

Table 2. Comparison of cell-based and cell-free therapies for IPF

Characteristic	Cell-Based Therapy (e.g., MSC Transplantation)	Cell-Free Therapy (e.g., MSC-Derived Exosomes)
Mechanism of Action	Dynamic and multifaceted: homing, differentiation (limited), paracrine secretion (multiple factors), immunomodulation, cell-cell contact.	Relatively singular: primarily relies on carried bioactive molecules (e.g., miRNAs, proteins) to modulate recipient cell function.
Main Advantages	Potentially broader and more sustained action (if cells survive and function long-term).	High safety profile (no tumorigenic risk, very low immunogenicity); easier to standardize for production, storage, and QC; potentially better tissue penetration.
Main Challenges	Low cell survival and retention rates; risks of immune rejection and potential tumorigenicity; complex production, transportation, and QC.	Potentially lower durability and potency of effect compared to live cells; challenges in large-scale production yield; targeting needs improvement; precise definition of active components required.
Clinical Translation	Multiple Phase I/II clinical trials have already verified safety.	Currently primarily in the preclinical research stage, representing a highly promising next-generation therapeutic strategy.

miRNAs) from their parent cells and can mediate intercellular communication, regulating the gene expression and function of target cells. Compared to whole cells, exosomes offer a superior safety profile with extremely low immunogenicity and, crucially, avoid the risk of tumorigenesis due to their inability to proliferate. Their size characteristics may favor distribution within tissues, and they are easier to standardize for production, long-term storage, and quality control, holding promise as "off-the-shelf" products. However, their mechanism of action might be relatively singular, lacking the dynamic and multifaceted regulatory capacity of living cells. Additionally, challenges remain regarding exosome yield, tissue targeting, and the precise definition of their functional components.

Conclusion: Cell-based and cell-free therapies are not mutually exclusive but rather complementary strategies. Cell-free therapies, especially exosomes, offer a safer and more controllable novel approach for IPF treatment. However, the stability and potency of their efficacy still require extensive preclinical and clinical validation. Future research directions may include engineering exosomes to enhance their targeting and anti-fibrotic efficacy or exploring the synergistic effects of combining both strategies.

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)

Due to tumorigenic potential, differentiation inefficiency, and heterogeneity, iPSCs and ESCs remain in preclinical investigation. iPSCs closely resemble ESCs in pluripotency and self-renewal [55]. Consequently, research and clinical applications of MSC-based therapies in IPF treatment will be collectively examined in the following sections.

Sources and biological characteristics: Embryonic stem cells (ESCs) originate from the inner cell mass (ICM) of early embryos. In vitro, they proliferate indefinitely and can differentiate into all three germ layer cell types [56]. However, ESC derivation involves embryo manipulation, raising ethical concerns limiting research/application in some regions. In 2006, Shinya Yamanaka and Kazutoshi Takahashi first successfully reprogrammed somatic cells into iPSCs, a breakthrough inaugurating a regenerative medicine and cell therapy era [57, 58]. In 2007, the same research team successfully induced pluripotent stem cells (iPSCs) by introducing transcription factors - including SOX2, KLF4, and C-MYC - into adult human fibroblasts [59]. The derived iPSCs can be differentiated into diverse cell lineages for multidisciplinary research applications, effectively circumventing the ethical constraints associated with embryonic stem cells (ESCs).

Mechanisms of action: ESCs and iPSCs can differentiate into lung-specific cell types, particularly exhibiting potential for directed differentiation into alveolar epithelial type II cells (AT2), enabling regenerative IPF therapy [60]. By activating critical pathways involved in embryonic lung development (e.g., Wnt, FGF), iPSCs differentiate into functional alveolar type II epithelial cells (AEC2s), forming self-renewing "alveolar spheres" in 3D culture [61]. Bayati et al. observed intravenous iPSCs downregulated Wnt, β-catenin, and LEF expression and upreg-

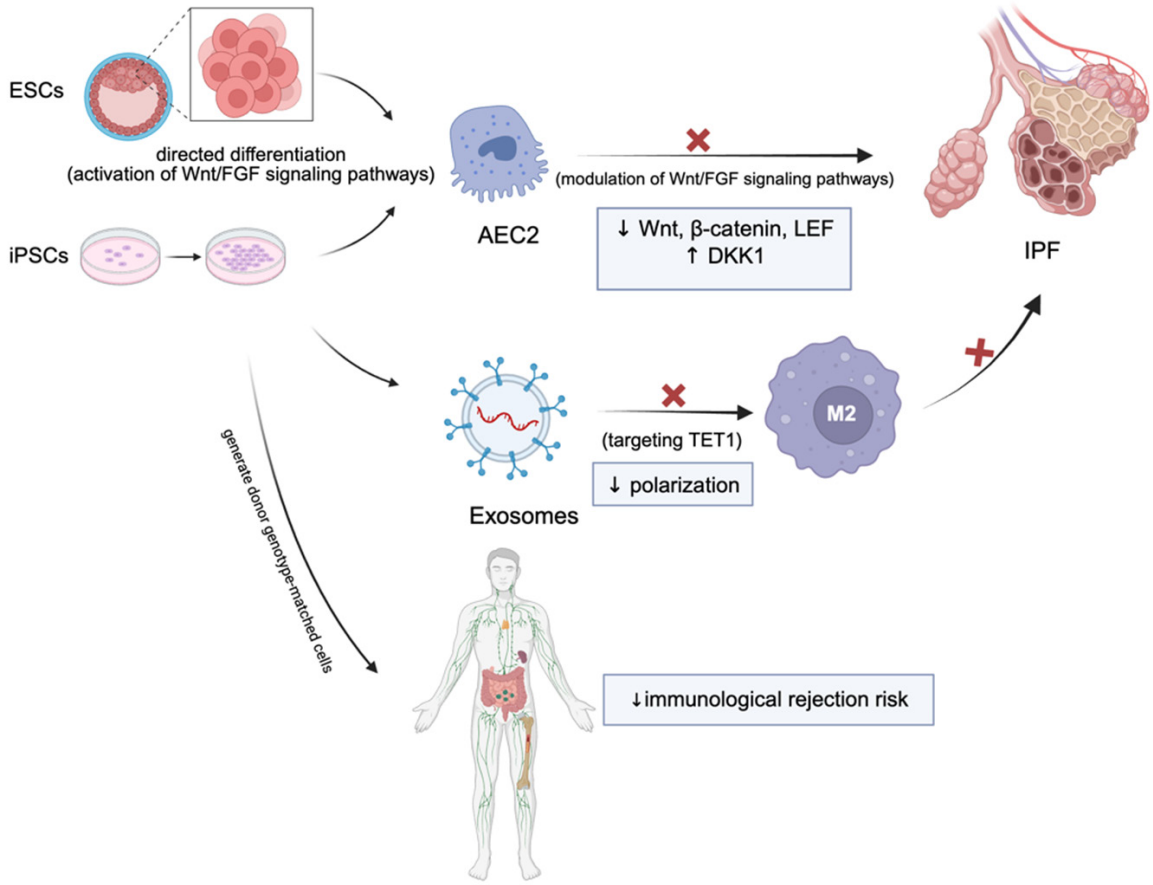

Figure 3. This diagram explains how Embryonic Stem Cells (ESCs) and Induced Pluripotent Stem Cells (iPSCs) could be used to treat IPF.

ulated DKK1 in BLM-induced fibrosis, inhibiting fibroblast activation and reducing fibrosis, suggesting modulation of Wnt signaling mediates antifibrotic effects [62]. iPSC-derived exosomes rich in miR-302a-3p can inhibit M2 macrophage polarization by targeting TET1, alleviating BLM-induced fibrosis in mice [63]. Additionally, patient-derived iPSCs generate donor-genotype-matched cells, reducing rejection risk [64]. These properties render ESCs and iPSCs valuable for studying IPF mechanisms, drug screening, and regenerative therapy. Despite the potential of iPSCs and ESCs to differentiate into functional alveolar epithelial type II cells (AEC2s), their clinical application faces several challenges. Current differentiation protocols are inefficient and yield heterogeneous cell populations with limited purity. The derived cells often exhibit functional immaturity, including underdeveloped lamellar body structures, which compromises their regenerative capacity. Furthermore, transplanted cells may undergo phenotypic instability within the fibrotic microenvironment, potentially leading to abnormal trans differentiation and safety concerns. Ultimately, clinical translation requires addressing the critical challenge of scaling up laboratory differentiation methods into standardized, GMP-compliant manufacturing processes (**Figure 3**).

Research progress: Current ESC and iPSC research for IPF is preclinical. Animal models show iPSC, or iPSC-derived AT2 cell transplantation reduces fibrosis and improves function [65, 66]. In a separate study, JayminJ. Kathiriya et al. utilized iPSCs derived from IPF patients to generate alveolar organoids, unveiling the role of aberrant alveolar epithelial repair in fibrogenesis [67]. Alvarez-Palomo et al. differentiated human iPSCs into AT2 cells (iAT2s) and transplanted them into BLM-induced rat fibrosis; transplanted iAT2s secreted surfactant protein C (SP-C), significantly reduced lung collagen

deposition, suppressed TGF-β and α-SMA expression, and restored gas exchange, indicating iAT2 repair potential [66]. ESC-derived lung epithelial cells also demonstrate therapeutic effects in fibrosis models [68]. Successful preclinical application supports the potential feasibility of ESC/iPSC therapy for IPF, providing evidence for future clinical trials requiring safety and efficacy validation.

Application prospects and challenges: Owing to their unlimited proliferative potential, both iPSCs and ESCs carry inherent tumorigenic risks [69], constituting a primary safety challenge for cell-based therapeutic strategies utilizing these platforms. Ensuring safety necessitates complete differentiation before transplantation and effective elimination of residual undifferentiated cells [70]. What's more, ESC derivation involves embryo destruction, raising ethical concerns regarding embryonic dignity and research acceptability [71]. iPSCs circumvent embryo procurement, avoiding associated ethical issues, thus possessing higher ethical acceptability for IPF therapy. However, iPSCs may present reprogramming efficiency and genomic instability challenges [72], posing safety risks requiring stringent evaluation and control prior to clinical translation.

Regulatory and manufacturing hurdles in the clinical translation of stem cell therapies for IPF

The clinical translation of stem cell therapies for idiopathic pulmonary fibrosis (IPF) faces significant regulatory and manufacturing challenges. The core issue lies in the safe and consistent transformation of living cells into standardized pharmaceutical products. Both mesenchymal stem cells (MSCs) and pluripotent stem cells (iPSCs/ESCs) are plagued by source heterogeneity, where variations in donor characteristics, tissue origins, or minor procedural differences can lead to substantial inconsistencies in the final product's efficacy and safety profile.

Establishing standardized processes compliant with Good Manufacturing Practice (GMP) is crucial. This requires comprehensive control over the entire production workflow - from cell isolation and expansion to differentiation - while addressing engineering complexities associated with scalable manufacturing. Quality control presents another major bottleneck. Living cell-based products demand sophisticated release criteria, including identity verification, sterility assurance, and particularly rigorous assessment of tumorigenic risk. Furthermore, developing potency assays that accurately reflect clinical therapeutic effects remains a critical unmet need.

iPSC-based therapies face an additional dilemma in choosing between autologous and allogeneic approaches. Autologous therapies, while avoiding immune rejection, are prohibitively costly and difficult to standardize. Allogeneic "off-the-shelf" strategies enable scalability but introduce immunogenicity concerns and require exceptionally high standards for master cell bank safety and genetic stability. For emerging cell-free approaches such as exosome therapies, challenges remain in defining active components, standardizing manufacturing, and clarifying regulatory classification frameworks.

In summary, overcoming these barriers will require integrated advances in automated GMP production platforms, clinically relevant biomarkers, and adaptive regulatory policies. Only through such coordinated efforts can stem cell therapies evolve into safe, effective, and accessible treatment options for IPF patients.

Technological innovations to enhance stem cell therapy for IPF

Gene editing strategies: In animal models of lung injury, genetic engineering-mediated overexpression of homing receptors (e.g.CXCR4) on mesenchymal stem cells (MSCs) enhances their homing efficiency to damaged pulmonary tissue, consequently amplifying therapeutic efficacy [44]. This strategy addresses low pulmonary homing efficiency post-systemic administration, enhancing MSC therapeutic potential for IPF.

Biomaterial scaffolds: Hydrogel scaffolds provide a supportive microenvironment for transplanted stem cells, improving survival and retention [73]. They mimic natural extracellular matrices (ECMs) and facilitate tailored cell-hydrogel interactions [74]. Hydrogels derived from decellularized lung matrix (DLM) demonstrate potential utility for investigating fibroblast behavior in idiopathic pulmonary fibrosis

(IPF) [75]. Biomaterial scaffolds, particularly hydrogels [76], enhance stem cell delivery and survival in the lung, strengthening therapeutic effects. Additionally, hydrogel scaffolds serve as in vitro models for studying pathogenesis [77].

Three-dimensional lung organoid models: Pluripotent stem cell (PSC)-derived 3D lung organoids recapitulate human lung complexity and cellular interactions [78]. These models facilitate IPF pathogenesis study, in vitro disease modeling, and therapeutic screening [79]. Organoids recapitulate fibrotic alterations observed in IPF, including honeycomb cyst-like structures [80], thus providing a valuable tool to overcome limitations inherent in animal models and 2D cell culture systems [81]. This platform enables in-depth elucidation of disease mechanisms and accelerates therapeutic development.

Conclusion and future perspectives

Stem cell therapy exhibits substantial potential for idiopathic pulmonary fibrosis (IPF) research and application. Despite demonstrating efficacy in slowing disease progression, current therapeutic approaches fail to achieve a cure for IPF. Stem cells, particularly MSCs, iPSCs, and ESCs, offer novel therapeutic avenues through their unique biological properties.

MSCs, readily obtainable with low immunogenicity and capable of secreting diverse anti-inflammatory/reparative factors, demonstrate favorable safety in preclinical and early clinical studies. However, key challenges persist, including in vivo homing efficiency, survival rates, and source-dependent heterogeneity. Innovative technologies - including genome editing, biomaterial scaffolds, and three-dimensional (3D) organoid models - are being explored to address these limitations, showing promise for enhancing therapeutic outcomes.

iPSCs and ESCs, as pluripotent stem cells (PSCs), provide an unlimited cell source for regenerative medicine. The potential of iPSC differentiation into AT2 cells and ESC-derived lung progenitor research offer valuable tools for elucidating IPF pathogenesis and developing cell replacement strategies. Nonetheless, tumorigenic risks and ethical considerations remain significant clinical translation barriers. Prospective studies should investigate these complex interrelations and their tissue-specific manifestations to devise comprehensive therapeutic approaches.

Furthermore, current clinical trials of stem cell therapy for IPF remain preliminary, with major limitations including: (1) Small sample sizes: Early-phase trials focused primarily on safety enrolled limited patients, resulting in underpowered studies that struggle to demonstrate efficacy definitively or identify rare adverse events. (2) Lack of protocol standardization: Significant heterogeneity in cell type, dosage, and administration routes across trials makes direct comparison of results difficult and hinders the identification of an optimal treatment regimen. (3) Challenges with endpoint selection: The commonly used primary endpoint of annual forced vital capacity (FVC) decline changes slowly, requiring extended follow-up and large cohorts to detect significant differences. Therefore, future large-scale, standardized Phase III clinical trials utilizing more reliable clinical endpoints are essential to definitively establish the ultimate clinical value of stem cell therapies.

Future research should prioritize: (1) optimization of stem cell source selection and manufacturing standardization, (2) enhancement of pulmonary-targeted delivery efficiency and survival within the fibrotic niche, and (3) comprehensive delineation of the precise mechanistic actions of stem cells in IPF pathogenesis. Furthermore, conducting rigorous clinical trials to evaluate stem cell therapy safety and efficacy in IPF patients is paramount. Through sustained research and innovation, stem cell therapy is anticipated to provide novel therapeutic options for IPF patients, improving quality of life and extending survival.

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Disclosure of conflict of interest

None.

Abbreviations

IPF, Idiopathic Pulmonary Fibrosis; MSCs, Mesenchymal Stromal Cells; EVs, Extracellular Vesicles; TGFβ/Smad, Transforming Growth Factor Beta/Smad; IL-10, Interleukin-10; HGF, Hepatocyte Growth Factor; VEGF, Vascular Endothelial Growth Factor; iPSCs, Induced Pluripotent Stem Cells; ESCs, Embryonic Stem Cells; ILDs, Interstitial Lung Diseases; AT2, Type II Alveolar Cells; ECM, Extracellular Matrix; SASP, Senescence-Associated Secretory Phenotype; IL-6, Interleukin-6; IL-1, Interleukin-1; Th17, T helper 17 cells; M1/M2, M1/M2 Macrophages; BLM, Bleomycin; FVC, Forced Vital Capacity; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; ICM, Inner Cell Mass; AEC2s, Alveolar Epithelial Type II Cells; SP-C, Surfactant Protein C; PSCs, Pluripotent Stem Cells.

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