Review

Advances in mechanisms and signaling pathways of idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown etiology characterized by irreversible pulmonary tissue fibrosis, with a median survival of only 2-3 years and a poor prognosis. Recent studies have revealed abnormal activation of multiple signaling pathways in IPF pathogenesis, including TGF-β/Smad, Wnt/β-catenin, MAPK, and TIME pathways. Additionally, mechanisms such as redox imbalance, cellular senescence, metabolic reprogramming, and epigenetic dysregulation have been implicated in disease progression. Although FDA-approved pirfenidone and nintedanib can delay disease progression, they fail to reverse fibrotic lesions or significantly reduce mortality. This review systematically summarizes recent advances in IPF-related signaling pathways and molecular mechanisms, explores potential therapeutic targets, and evaluates lung transplantation as an end-stage intervention. Future research should focus on identifying novel molecular targets, developing targeted antifibrotic therapies, and optimizing lung transplantation eligibility assessments and perioperative management to advance precision medicine and improve patient outcomes.

INTRODUCTION

With the acceleration of global aging and the impact of the COVID-19 pandemic, chronic lung diseases, including pulmonary fibrosis (PF), have become a significant burden on global health. PF is a severe lung disease characterized by unknown etiology, irreversible progression, dyspnea, dry cough, fatigue, and exercise intolerance. Imaging studies show extensive collagen fiber deposition, alveolar loss, and structural distortion in the lungs, leading to impaired gas exchange and fatal respiratory failure[1]. PF can be categorized into idiopathic pulmonary fibrosis (IPF), secondary pulmonary fibrosis, genetic pulmonary fibrosis, and other subtypes. In China, the number of patients with PF-related diseases increased from 3.3 million to 3.4 million between 2017 and 2020, with IPF being the leading idiopathic interstitial lung disease (ILD) and having extremely high mortality and a median post-diagnosis survival of 2-3 years.

Recent studies indicate that chronic lung diseases, especially COPD and IPF, are predominantly driven by cellular senescence[2, 3]. The senescence-associated secretory phenotype (SASP) transforms senescent fibroblasts into proinflammatory cells, inducing epithelial-mesenchymal transition (EMT) in neighboring cells and contributing to lung fibrosis[4, 5].In senescence-associated pulmonary fibrosis (SAPF), discontinuous epithelial cells are found adjacent to hyperplastic alveolar type II (AT2) cells[2]. Chronic injury to the distal lung leads to functional loss or alteration of AT2 cells, promoting reparative dysfunction and pathogenic activation of fibroblasts[3]. Accelerated aging mechanisms, such as epithelial progenitor cell dysfunction and cellular senescence, are implicated in IPF pathogenesis[6]. Selective clearance of senescent cells has been shown to improve SAPF[7], and the TGF-β1/Smad signaling pathway plays a critical role in fibrogenesis[8, 9]. This review focuses on recent advances in IPF-related signaling pathways and molecular mechanisms, explores potential therapeutic targets, and evaluates lung transplantation as an end-stage intervention.

CLINICAL MANIFESTATIONS AND PATHOLOGICAL ALTERATIONS OF IPF

IPF, a senescence-associated pulmonary fibrosis with unknown etiology, is marked by chronic, progressive, irreversible tissue damage[1]. It poses a significant healthcare burden due to its high morbidity and mortality[2]. As the most common idiopathic interstitial pneumonia[3], IPF primarily presents with nonspecific exertional dyspnea[3], cough (especially in non - smokers or advanced - disease patients[10], and on chest auscultation, bilateral basal inspiratory crackles are often heard, with 30%–50% of patients having digital clubbing[10]. Prognosis is influenced by factors like age (>70), smoking history, BMI, physiological impairment severity, radiographic disease extent, and pulmonary hypertension[8].

From a pathological standpoint, IPF is defined by abnormal tissue repair post - chronic inflammatory injury, causing excessive ECM component synthesis that displaces normal parenchyma. This persistent ECM buildup leads to structural damage, functional decline, and eventual organ failure[9]. Specifically, in IPF, the pulmonary ECM deposition and parenchyma replacement are key features. Inflammatory and epithelial cells release cytokines/growth factors, driving fibroblasts to migrate, proliferate, and transform into myofibroblasts[11]. In the injured pulmonary microenvironment, myofibroblasts can induce epithelial apoptosis, disrupt the basement membrane, and cause aberrant ECM remodelingg[12].

PATHOLOGICAL ALTERATIONS IN IPF

Fibroblasts and myofibroblasts

Fibroblasts are pivotal effector cells in pulmonary fibrosis and play a central role in IPF pathogenesis through their activation and abnormal proliferation[11]. In IPF, fibroblasts exhibit aberrant proliferation and differentiate into myofibroblasts, which are characterized by high expression of α-smooth muscle actin (α-SMA), robust contractile capacity, and enhanced ECM synthesis capability[13]. The origin of fibroblasts can be traced to the mesenchymal ectoderm. During gastrulation, type 1 EMT generates mesendoderm, which further differentiates into endoderm and mesoderm. The mesoderm forms the true interstitial tissue and gives rise to various cells, including adipocytes, epithelial cells, endothelial cells, pericytes, and bone marrow-derived fibroblasts and fibrocytes. In response to tissue injury, these cells collectively generate fibroblast - like cells alongside mature fibroblasts[14]. The

persistent proliferation of fibroblasts and myofibroblasts, along with ECM deposition, disrupts lung architecture and function, culminating in fibrotic lesion formation[13].

Senescent fibroblasts play a critical role in IPF pathogenesis. During normal wound healing, fibroblasts facilitate repair through proliferation, migration, and contraction[15]. Senescent fibroblasts play a critical role in IPF pathogenesis. During normal wound healing, fibroblasts facilitate repair through proliferation, migration, and contraction[16, 17], and myofibroblast differentiation[18]. Myofibroblasts, the primary producers of ECM, accumulate excessively, leading to tissue stiffening and functional impairment[19]. TGF-β is a master regulator of fibroblast to myofibroblast differentiation. It activates both Smad-dependent and Smad-independent signaling pathways, promoting fibroblast activation and ECM synthesis[20]. Hypoxic microenvironments also strongly stimulate fibroblast proliferation. Studies show that HIF-1α is markedly upregulated under hypoxic conditions, driving fibroblast proliferation and ECM deposition[21]. The aberrant activation, proliferation, and differentiation of fibroblasts into myofibroblasts are core pathological events in IPF, with TGF-β and hypoxia being key drivers and potential therapeutic targets.

Alveolar epithelial cells and bronchial epithelial cells

Alveolar epithelial cells are crucial for maintaining the structural and functional integrity of lung tissue[22]. In healthy lungs, the alveolar epithelium consists of AT1 and AT2 cells. AT1 cells facilitate gas exchange, while AT2 cells synthesize pulmonary surfactant, possess self-renewal capacity, and can differentiate into AT1 cells, making them essential for alveolar epithelial repair and regeneration[23, 24]. In IPF, the disruption of alveolar epithelial integrity and phenotypic alterations are central to disease pathogenesis.[22]. IPF lung tissues show AT2 cell apoptosis, senescence, aberrant differentiation, and impaired self - renewal[25], which are linked to factors like aging, ER stress, mitochondrial dysfunction, and telomere shortening[25]. These changes compromise AT2 cell mediated repair of damaged alveolar epithelium, driving fibrogenesis.

Activated alveolar epithelial cells in IPF secrete pro - fibrotic molecules such as TF and PAI-1/PAI-2, creating a pro-coagulant/anti-fibrinolytic microenvironment and amplifying fibrotic responses[26]. They also release cytokines and growth factors like TGF-β, PDGF, and CTGF, which enhance fibroblast migration, proliferation, phenotypic transformation, and ECM remodeling, thereby exacerbating fibrosis[22]. Recent research highlights YAP1's pivotal role in alveolar epithelial senescence and fibrogenesis in IPF. YAP1, a key Hippo signaling pathway effector, is aberrantly activated, driving alveolar epithelial senescence and dysfunction[27, 28]. Targeted YAP1 inhibition attenuates alveolar epithelial senescence, alleviating clinical symptoms and fibrosis severity in IPF[27].

Bronchial epithelial cell senescence is another critical driver of IPF pathogenesis[29]. Studies show that clearing senescent bronchial epithelial cells reduces SASP factor and ECM marker expression[30]. Senescent bronchial epithelial cells secrete cytokines and chemokines that activate lung fibroblasts, promoting their differentiation into myofibroblasts and enhancing collagen synthesis and deposition[31, 32]. Conversely, eliminating senescent cells mitigates inflammatory responses and tissue injury, ameliorating fibrotic pathology[32].

MECHANISMS AND ASSOCIATED SIGNALING PATHWAYS IN IPF

Imbalance in ECM production and degradation

The histopathological hallmark of IPF is characterized by excessive deposition of ECM, which disrupts normal lung architecture and leads to irreversible loss of pulmonary function[33]. Dysregulation of ECM homeostasis is central to IPF pathogenesis, involving complex cellular and molecular mechanisms.

Cellular senescence plays a critical role in IPF development[34]. Studies suggest that senescence may impair the regenerative capacity of stem/progenitor cells, compromising alveolar epithelial repair[23], thereby preventing effective regeneration of injured lung tissue. Senescent epithelial cells exacerbate fibrosis by secreting pro-inflammatory and pro-fibrotic mediators, such as interleukin-6 (IL-6), IL-1, and TGF-β, components of the SASP[35].

During normal wound healing, apoptotic pathways eliminate excess fibroblasts, a process essential for preventing excessive matrix deposition and fibrosis progression[36]. In IPF, however, fibroblasts exhibit resistance to FAS ligand-induced apoptosis and demonstrate enhanced proliferative capacity when cultured on polymerized collagen[37]. This aberrant phenotype is

closely associated with downregulation of FasL, TNF-related apoptosis-inducing ligand (TRAIL), and caveolin-1 (Cav-1), alongside hyperactivation of the AKT signaling pathwa[37].

The contractile properties of myofibroblasts are pivotal in IPF pathology[38]. This irreversible contraction not only regulates collagen remodeling but also triggers spatial reorganization of collagen fibers, increasing mechanical stress and inducing ECM stiffening[38]. These pathological changes culminate in extensive scar formation, severely impairing gas exchange between alveoli and blood vessels and exacerbating pulmonary fibrosis[33].

These findings underscore the central role of ECM production-degradation imbalance in IPF pathogenesis, providing a theoretical foundation for developing therapeutic strategies targeting ECM metabolism.

Redox imbalance

Studies have demonstrated that disruption of cellular redox homeostasis plays a pivotal role in the pathogenesis and progression of pulmonary fibrosis[39], particularly by promoting the aberrant proliferation of myofibroblasts, which drives persistent, senescence-associated fibrosis[40]. In aged murine models of pulmonary fibrosis, the sustained fibrosis is characterized by the massive accumulation of senescent, apoptosis-resistant myofibroblasts[12]]. This abnormal cellular phenotype is closely linked to the persistent oxidative stress within the fibrotic microenvironment.

Specifically, this pathological state is perpetuated by two interrelated molecular mechanisms. On one hand, the expression of reactive oxygen species (ROS)-generating enzymes, such as NADPH oxidase-4 (Nox4), is markedly upregulated, leading to sustained intracellular oxidative stress[41]. On the other hand, the antioxidant capacity mediated by nuclear factor E2-related factor 2 (Nrf2) is significantly impaired[42]. Nrf2, a master transcriptional regulator, normally maintains redox balance by activating antioxidant response elements (AREs) to orchestrate the expression of multiple antioxidant enzymes[42]. However, during pulmonary fibrosis, dysfunction of the Nrf2/ARE signaling pathway compromises the cellular ability to counteract excessive oxidative stress, ultimately resulting in persistent myofibroblast activation and fibrotic progression[42].

These findings not only elucidate the critical role of redox imbalance in pulmonary fibrosis but also provide novel insights into therapeutic strategies targeting the Nrf2/ARE pathway. Restoring redox equilibrium or enhancing Nrf2-mediated antioxidant defenses may represent effective approaches to intervene in the progression of pulmonary fibrosis.

Aging

Aging-related biological processes-such as cellular proliferation, apoptosis, senescence, and autophagy, play significant roles in the pathogenesis of IPF[34]. Activation of senescence-associated genes may accelerate IPF progression by promoting cellular senescence, secreting inflammatory factors, and conferring apoptosis resistance[34].

Cellular senescence serves as a key driver in the progression of IPF. Senescent cells contribute to lung tissue matrix remodeling and fibrosis through irreversible cell cycle arrest and the SASP[43]. The SASP comprises pro-inflammatory factors, chemokines, and MMPs, which activate fibroblasts and promote excessive ECM deposition, contributing to fibrotic lesion formation[44]. Studies have shown that senescent cells accumulate markedly in the lung tissues of IPF, with elevated expression of senescence markers (e.g., p16, p21), correlating with disease severity[45].The SASP amplifies inflammatory and fibrotic signaling via paracrine and autocrine effects. For instance, SASP components such as TGF-β, IL-6, and MMPs directly activate fibroblast proliferation and promote EMT through the TGF-β/IGF-1 pathway[43].

Pro-fibrotic signaling

The core pathological features of IPF include abnormal activation of fibroblasts, excessive deposition of ECM, and the formation of fibrotic lesions in the pulmonary interstitium. This process involves aberrant activation of multiple pro-fibrotic signaling pathways, including TGF-β/Smad, Wnt/β-catenin, MAPK, TIME, and PDGF pathways, which collectively drive fibrotic progression by regulating inflammation, fibroblast differentiation, and ECM synthesis.

The TGF-β/Smad pathway is the most critical pro-fibrotic signaling axis in IPF. TGF-β1 activates its receptors (TGF-βRI/II), leading to phosphorylation of Smad2/3 and subsequent formation of a complex with Smad4. This complex translocates to the nucleus to transcriptionally regulate pro-fibrotic genes (e.g., collagen, fibronectin) [46]. Additionally, Smad7, an endogenous inhibitor of TGF-β signaling, is downregulated in IPF[46].

The Wnt/β-catenin pathway, essential for embryonic development and tissue repair, is hyperactivated in IPF. Binding of Wnt proteins (e.g., Wnt3a, Wnt5a) to Frizzled

receptors inhibits the β-catenin degradation complex (Axin/GSK-3/APC), resulting in nuclear accumulation of β-catenin and activation of pro-fibrotic target genes (e.g., MMP-7, cyclin D1)[46].

The MAPK pathway regulates cell proliferation, inflammation, and fibrosis through phosphorylation cascades. TGF-β1 activates ERK1/2, promoting fibroblast proliferation and collagen synthesis[46, 47]. p38 MAPK synergizes with TGF-β to enhance Smad3 phosphorylation, inducing α-smooth muscle actin (α-SMA) expression and driving myofibroblast differentiation[46]. JNK exacerbates ECM deposition by activating c-Jun to amplify TGF-β1 transcriptional activity and cross-talking with the Smad pathway.

The TIME signaling pathway plays a significant role in the initiation and progression of pulmonary fibrosis by promoting cellular senescence, increased secretion of factors, and collagen synthesis. In Bmi-1-deficient murine models, lung fibroblasts and AT2 cells secrete TGF-β1 and IL-11. These cytokines activate MEK, leading to phosphorylation of ERK (p-ERK1/2). The activated MEK/ERK signaling stimulates excessive collagen production by lung fibroblasts, contributing to tissue fibrosis. In AT2 cells, TIME pathway activation promotes EMT, causing loss of epithelial characteristics and acquisition of mesenchymal traits, thereby facilitating fibrotic processes[48].

Metabolic dysregulation

In IPF, metabolic alterations serve as critical drivers of pro-fibrotic responses. Studies indicate that enhanced glycolysis is a hallmark feature of IPF, where lactic acid accumulation in the pulmonary microenvironment promotes fibroblast proliferation and differentiation, exacerbating fibrotic remodeling[49]. Additionally, mitochondrial dysfunction and oxidative stress are central mechanisms underlying pro-fibrotic reactions[50, 51], while dysregulated iron metabolism (e.g., iron accumulation) worsens lung function by amplifying reactive oxygen species (ROS) production and inflammatory responses[52]. Metabolic reprogramming in macrophages has also been implicated in IPF pathogenesis. For instance, the miR-33 family modulates macrophage pro-fibrotic functions by regulating cholesterol and fatty acid metabolism[50]], whereas activation of the Nrf2 pathway suppresses fibrosis by enhancing antioxidant capacity[53]. Other metabolic pathways, including fatty acid metabolism, MAP3K8 signaling, and mitochondrial metabolic regulators such as PGC-1α, have been shown to closely correlate with IPF progression. These metabolic alterations not only influence macrophage polarization and function but also drive IPF development by regulating inflammatory and fibrotic signaling networks[49]. Consequently, therapeutic strategies targeting metabolic reprogramming—such as miR-33 inhibitors, Nrf2 activators, and iron chelators—may offer novel avenues for IPF treatment.

Mitochondrial dysfunction

In IPF, mitochondrial dysfunction and metabolic reprogramming are critical mechanisms driving disease progression[54]. Mitochondria in various pulmonary cell types (e.g., alveolar epithelial cells, fibroblasts, and macrophages) of IPF exhibit significant alterations, including reduced mitochondrial quantity, diminished biogenesis capacity, imbalanced dynamics (fusion/fission), and impaired mitophagy. The compromised energy metabolism of mitochondria is characterized by decreased oxidative phosphorylation (OXPHOS) capacity[51], reduced ATP production, and elevated ROS generation[54]. These ROS not only directly damage mitochondrial DNA (mtDNA) but also exacerbate fibrotic responses by activating inflammatory signaling pathways, such as NF-κB and the NLRP3 inflammasome[55]. Furthermore, disrupted mitochondrial dynamics (fusion-fission imbalance) lead to abnormal mitochondrial network architecture, aggravating cellular dysfunction[54]. Defective mitophagy prevents the efficient clearance of damaged mitochondria, resulting in their accumulation and the release of damage-associated molecular patterns (DAMPs), which perpetuate chronic inflammation and fibrosis[54, 56]. Oxidative damage to mtDNA and diminished repair capacity also play pivotal roles in IPF, further deteriorating mitochondrial function[54]. Finally, metabolic reprogramming in IPF—such as enhanced glycolysis and dysregulated fatty acid metabolism—amplifies the activity and differentiation of fibrotic cells, accelerating disease progression. Collectively, these mitochondrial alterations synergistically establish a pro-fibrotic pathological microenvironment, offering potential therapeutic targets for interventions aimed at mitochondrial dysfunction[54].

Epigenetic dysregulation

Emerging studies have increasingly established that epigenetic regulation plays a pivotal role in the

pathogenesis of IPF under the combined influence of environmental factors and aging[57]. Epigenetic modifications constitute a complex regulatory network encompassing DNA methylation, histone modifications, RNA methylation, and expression changes in non-coding RNAs (particularly microRNAs). These modifications act as a bridge in gene-environment interactions by modulating gene expression without altering the DNA sequence. In IPF, significant alterations in DNA methylation patterns—including hypermethylation and hypomethylation—have been observed[58]. These aberrant methylation profiles are associated with dysregulated expression of numerous genes in lung tissues. For instance, studies have identified 625 differentially methylated CpG islands in IPF lungs, involving over 14,000 genes, with 53% exhibiting hypermethylation and 47% hypomethylation[58].

DNA methyltransferases (DNMTs) are critical for establishing and maintaining DNA methylation patterns. In IPF, the expression of *DNMT3a* and *DNMT3b* is markedly upregulated, which may partially explain the cell type-specific methylation changes observed[59]. Additionally, the methyl-CpG-binding domain (MBD) protein family, including MBD2 and MECP2, regulates gene transcription by interpreting DNA methylation signatures[58].

Histone deacetylases (HDACs), key enzymes modulating histone acetylation status, influence chromatin structure and gene transcription, thereby impacting diverse biological processes[60]. The HDAC family comprises multiple members (e.g., HDAC1, HDAC2, HDAC3), each contributing distinct roles in IPF pathogenesis. HDAC1 and HDAC2 are significantly overexpressed in IPF lung tissues and primary fibroblasts[60]. This upregulation correlates with STAT3 phosphorylation and activation, which in turn drives fibroblast proliferation, survival, and transformation into myofibroblasts[60]. Notably, HDAC3 has also emerged as a critical player, with studies suggesting that its aberrant overexpression promotes pulmonary fibrosis by activating specific signaling pathways, such as Notch1 and STAT1[60].

THERAPEUTIC APPROACHES FOR IDIOPATHIC PULMONARY FIBROSIS

IPF is a chronic, progressive, fibrosing interstitial lung disease with no current cure. The primary therapeutic goals are to slow disease progression, alleviate symptoms, and improve quality of life.

Pharmacotherapy

Two FDA-approved drugs, pirfenidone and nintedanib, are currently used for IPF treatment.

Pirfenidone is a small-molecule compound with anti-fibrotic, anti-inflammatory, and antioxidant properties. It attenuates pulmonary fibrosis by inhibiting TGF-β activity, thereby reducing collagen production[61]. Clinical trials demonstrate that pirfenidone slows the decline in forced vital capacity (FVC) and delays disease progression[62]. Common adverse effects include gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), skin rash, and photosensitivity[61].

Nintedanib, an intracellular tyrosine kinase inhibitor, targets vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFR 1–3), and platelet-derived growth factor receptors (PDGFR α/β). By blocking these signaling pathways, nintedanib reduces fibroblast activation and proliferation, thereby mitigating fibrotic progression[61]. Nintedanib has also been shown to decelerate FVC decline[62]. Frequent adverse effects include diarrhea, nausea, vomiting, and abnormal liver function[61].

While both agents slow the rate of lung function deterioration, they neither halt nor reverse disease progression nor reduce mortality in IPF. Furthermore, off-target effects (e.g., nausea, fatigue, diarrhea) often compromise long-term tolerability in some patients.

Emerging Therapies

Given the adverse effects of current IPF medications and the lack of curative treatments, identifying novel molecular targets and therapeutic strategies is imperative.

Connective tissue growth factor (CTGF) is a key pro-fibrotic mediator linked to extracellular matrix secretion and aberrant tissue repair. A Phase II clinical trial demonstrated that pamrevlumab, a fully human recombinant monoclonal antibody targeting CTGF, slows IPF progression by inhibiting forced vital capacity (FVC) decline. Notably, pamrevlumab exhibits favorable safety and tolerability, holding promise as a novel anti-fibrotic agent[33].

The αvβ6 integrin is a critical effector for TGF-β activation. GSK3008348, a selective small-molecule αvβ6 inhibitor, binds with high affinity to αvβ6 in human IPF lung epithelial cells, inducing its internalization and degradation, thereby inhibiting downstream TGF-β activation. In a Phase 1 trial, inhaled GSK3008348 was

well-tolerated and safe, suggesting its potential for future anti-fibrotic drug development[33].

Histone deacetylases (HDACs) play a significant role in IPF pathogenesis. By modulating histone acetylation, HDACs regulate gene expression and chromatin structure, influencing processes such as fibroblast proliferation, survival, and myofibroblast differentiation. HDAC inhibitors have demonstrated anti-fibrotic efficacy in preclinical models, highlighting HDACs as potential therapeutic targets[60].

Cellular senescence has emerged as a pivotal mechanism in IPF. Fibroblasts and epithelial cells in IPF lungs exhibit marked senescence features, including elevated expression of senescence markers (e.g., *p16*, *p21*) and activation of the SASP. SASP factors such as TGF-β, IL-6, and MMPs exacerbate pulmonary fibrosis and inflammation. Preclinical studies show that selective clearance of senescent cells using senolytic agents (e.g., dasatinib and quercetin) significantly reduces fibrosis, improves lung function, and enhances overall health in experimental models[7]. Furthermore, AT2 cells in IPF display senescence-associated transcriptomic signatures. Inhibiting the p53 signaling pathway or administering senolytics to eliminate senescent cells has been shown to attenuate fibrosis in experimental settings[63]. Early intervention targeting senescence pathways and senescent cell clearance may represent a promising strategy for IPF prevention and treatment.

Lung Transplantation

Lung transplantation, while challenging, remains the only definitive therapeutic option to alleviate symptoms and prolong survival in select patients with IPF. Compared to other treatment modalities, lung transplantation offers significant advantages in improving quality of life and long-term prognosis. However, determining patient eligibility for transplantation is a complex process requiring comprehensive evaluation of multiple factors, including mortality risk, post-transplant survival expectations, and comorbidities such as cardiac dysfunction, gastroesophageal reflux disease, diabetes, and obesity[64].

Current referral criteria and contraindications for lung transplantation are primarily based on guidelines from the International Society for Heart and Lung Transplantation (ISHLT). Key candidacy indicators include significant declines in pulmonary function parameters, such as reduced forced vital capacity (FVC), decreased forced expiratory volume in 1 second (FEV1), and rapid deterioration of diffusing capacity for carbon monoxide (DLCO). Additionally, functional assessments like the 6-minute walk test are critical for evaluating exercise tolerance[64].

Lung transplantation may be performed unilaterally (single lung) or bilaterally (double lung). Unilateral transplantation offers advantages such as shorter waiting times, simpler surgical procedures, lower perioperative complication rates, and the potential to benefit two recipients from a single donor. However, the choice between unilateral and bilateral transplantation depends on individualized patient factors and multidisciplinary clinical evaluation[64].

Despite its potential benefits, the feasibility of lung transplantation for IPF is constrained by donor shortages, surgical risks, and the necessity for lifelong immunosuppressive therapy. Thus, the decision to pursue transplantation must be guided by personalized assessment and coordinated through a multidisciplinary care team[64].

CONCLUSIONS AND OUTLOOK

IPF is a chronic, progressive fibrosing interstitial lung disease whose pathogenesis remains incompletely elucidated, involving complex signaling pathways and cellular processes such as ECM remodeling, fibroblast activation and proliferation, immune dysregulation, and cellular senescence. Despite significant advances in understanding IPF pathophysiology in recent years, therapeutic options remain limited. Currently, oral anti-fibrotic agents (e.g., pirfenidone and nintedanib) constitute the primary treatment modality. These drugs can partially improve quality of life, alleviate symptoms, and delay disease progression but fail to achieve a cure. For eligible patients, unilateral or bilateral lung transplantation remains the only intervention capable of significantly prolonging life expectancy; however, its widespread application is restricted by donor shortages, surgical risks, and postoperative complications.

Future research and therapeutic strategies for IPF should focus on the following priorities: First, further elucidation of IPF molecular mechanisms and critical signaling pathways is essential to identify novel therapeutic targets. Second, there is an urgent need to develop more targeted and effective anti-fibrotic agents, combined with personalized treatment strategies to enhance therapeutic outcomes. Additionally, innovative approaches leveraging emerging technologies—including stem cell-based

therapies, gene editing, and immune modulation—show promising potential to revolutionize IPF management. Concurrently, optimizing lung transplantation protocols through improved assessment of transplant candidacy, perioperative management, and postoperative immunosuppressive regimens represents another critical research priority. Ultimately, through multidisciplinary collaboration and the integration of basic research with clinical practice, the therapeutic landscape for IPF is poised to expand significantly, offering patients a broader spectrum of effective treatment options.

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