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Idiopathic Pulmonary Fibrosis: Current Pathogenetic Insights and Emerging Therapeutic Strategies

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Abstract: Idiopathic interstitial pneumonias (IIPs) comprise a heterogeneous group of diffuse parenchymal lung disorders, with idiopathic pulmonary fibrosis (IPF) being the most prevalent subtype. Despite its rarity, IPF is associated with a high mortality rate, driving substantial research into its etiology, pathogenesis, diagnostic strategies, and therapeutic interventions. In recent years, multiple novel agents, including the anti-fibrotic candidate PRM-151, have been explored as potential treatments aimed at modifying disease progression and improving patient outcomes.

Keywords: Idiopathic Pulmonary Fibrosis; Idiopathic Interstitial Pneumonias; Pathogenetic Insights; Emerging Therapeutic Strategies.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease in which the lungs become fibrotic, making breathing difficult. IPF is a subgroup of idiopathic interstitial pneumonia (IIP)[6], which represents a group of diseases with unidentified causes[53]. In recent years, there has been increasing interest in understanding the pathogenesis, diagnosis, and treatment of IPF. However, the main challenge faced by researchers is the lack of effective treatments. Therefore, more effort needs to be made for IPF patients.

This essay aims to demonstrate the epidemiology, etiology, clinical manifestations, pathogenesis, pathophysiology, diagnosis, and advanced treatments of IPF.

2. Epidemiology

IPF is a rare disease. In the UK, the prevalence and incidence of the IPF are estimated at 0.78 and 0.14 per 10000 persons, respectively [52]. It is also rare worldwide, with reports indicating incidences of 0.09-1.30 and prevalences of 0.33-4.51 per 10000 persons [25]. Moreover, the estimated incidence and prevalence increased by 80% from 2000 to 2012 in the UK [52]. This suggests that despite extensive research and clinical trials, the progression of disease has not seen the big improvement. Additionally, the epidemiology of IPF should consider age and gender.

IPF often affects old people aged 60 to 70, with a survival time of around 2 to 4 years after diagnosis without the lung transplantation [5]. Furthermore, much of the literature found that males have a higher incidence of IPF [36][39][9], but a study among veterans found no obvious difference between the sexes [18]. In addition to age and gender, smoking is also a significant risk factor for IPF, with tobacco prevalence ranging from 41% to 83% among IPF patients [40].

3. Etiology

3.1. Genetic Factors

There are two types of IPF: familial IPF and sporadic IPF.

In familial IPF, genetic mutations are associated with surfactant protein and telomere [35], as **Table 1** shows. For instance, mutations of SFTPA1, SFTPC, and ABCA3 may influence surfactant production or endoplasmic reticulum stress (ERS), ultimately leading to epithelial mesenchymal transition (EMT) [27]. Additionally, telomere-related genetic mutations, such as TERC and TERT, can impact genome stability, leading to familial IPF [54]. However, only 30% of familial IPF patients are affected by genetic mutations in surfactant protein and telomeres, many genes remain unknown [35].

Sporadic IPF can also be associated with surfactant protein [21], as **Table 1** shows. The most closely related variant is rs35705950, located in the MUC5B gene [35]. Importantly, this variant can increase protein expression and cause airway mucus production, which accounts for a 30% increased risk of developing fibrosis [19].

Table 1. Gene mutations in Familial IPF and Sporadic IPF. The information is adapted from Pardo and Selman, 2021[35]

Familial		Sporadic IPF
SFTPC SFTPA2 ABCA3 TERC	Surfactant proteins related	MUC5B DEPTOR MAD1L1 KIF15
TERT DKC 1 PAR N	Telomere related	

3.2. Aging Factors

Aging is a significant risk factor of IPF, affecting telomere function and proteostasis. For example, telomere dysfunction can lead to abnormal DNA repair and reduced genetic stability [49]. One study indicates that patients in susceptible environments with shorter telomeres are more likely to develop fibrotic diseases [30].

Additionally, proteostatic functions are affected in IPF lungs, leading to protein unfolding, abnormal autophagy, and elevated ERS [35]. One study proposed that ERS occurs in alveolar epithelial cells (AECs) and may be related to AEC apoptosis [20]. Moreover, another study revealed that damaged autophagy stimulates mTORC1, which increases resistance to fibroblast apoptosis in IPF lungs [44].

3.3. Environmental Factors

Environmental factors involving smoking, farming, and

viral infections are associated with IPF. Smoking is suspected to be the main risk factor for IPF [51] because it induces epigenetic reprogramming, such as DNA methylation, which influences transcription, protein metabolism, and signal transduction, and may lead to pulmonary and heart diseases [15].

4. Clinical Manifestations

Symptoms of IPF include dyspnea, cough, connective tissue disease (CTD), and clubbing fingers. Clubbing fingers are defined as the enlargement of the fingertip (**Figure 1**), but the reason is unknown [31]

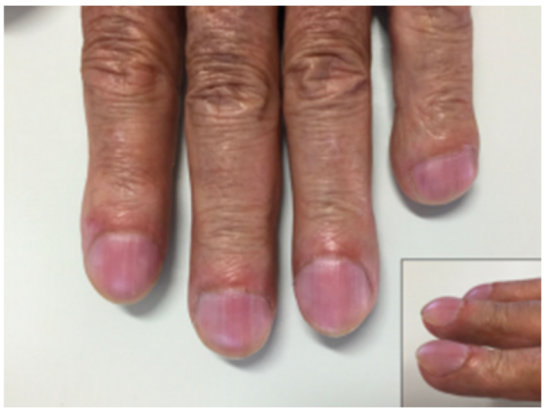

Figure 1. Clubbing fingers. Clubbing finger is the enlargement of fingertip, often associated with heart or lung problems. The image is adapted from Nakamura and Suda, 2015[31]

5. Pathogenesis

There are three crucial factors involved in the pathogenesis of IPF, including genetic (**Table 1**), environmental, and aging factors.

Three factors contribute to the damage of epithelial cells and the aberrant repair process. Activated epithelial cells produce various pro-fibrotic mediators, especially transforming growth factor-beta (TGF-β) which induce fibroblast proliferation and promote fibroblast differentiation into myofibroblasts. Myofibroblasts can produce excessive extracellular matrix (ECM), causing ECM deposition (**Figure 2**).

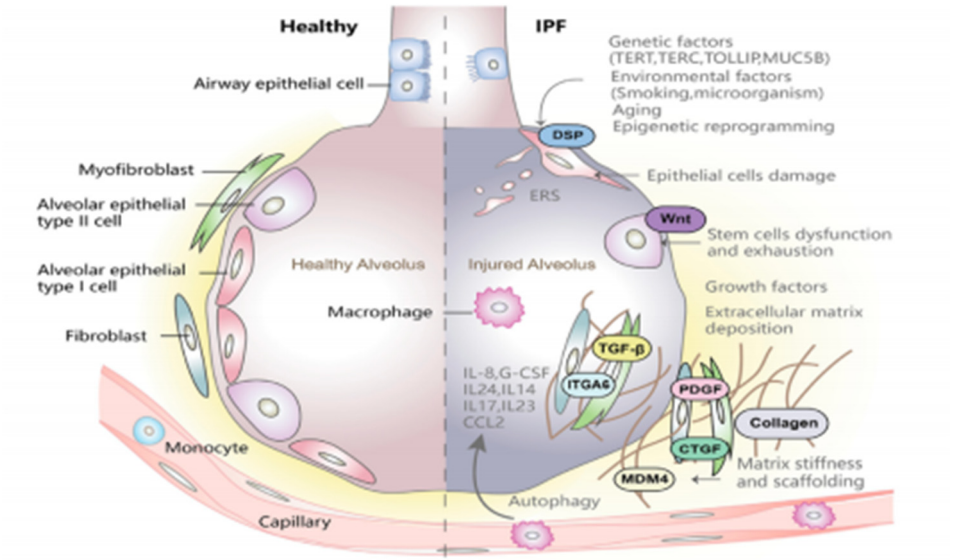

Figure 2. Pathogenesis of IPF. Genetic, environmental, and aging factors cause damage to the epithelium. Moreover, various cell types, including epithelial cells, fibroblast, myofibroblast and macrophage, contribute to lung fibrosis. The image is adapted from Mei et al., 2022[26]

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5.1. Aging

Aging involves telomere mutations, proteostasis dysfunction, and cell senescence. Telomere mutations can trigger cell senescence by damaging DNA or activating p53 [26]. Moreover, literature reveals that alveolar epithelial type II cells (AT2s) express increased markers of cell senescence, such as MDM2 and CDKN1A [23]. Furthermore, many aging-related changes are also observed in AT2s, including telomere shortening [47].

Aging epithelial cells can secrete numerous mediators, including interleukins (IL)-1, IL-6, and TGF-β, to enhance the inflammatory response. Additionally, aging fibroblasts can inhibit apoptosis, as shown by the increasing utilization of glucose [26].

5.2. Epithelial Cells

The pathogenesis of IPF is initiated by the damage to epithelial cells. In IPF lungs, genetic mutations, repetitive injuries (smoking or microorganism), and aging damage the integrity of epithelial cells. Additionally, ERS, reactive oxygen species, and inflammation also contribute to repetitive injuries to epithelial cells [33].

5.3. Lung Stem Cells

In IPF lungs, AT1s are destroyed by genetic mutations, but damaged AT2s cannot repair AT1s [26]. Moreover, abnormal alveolar epithelial cells can activate signaling pathways, such as the Wnt signaling pathway, which inhibits the differentiation of stem cells into AT1s and affects the activity of alveolar type II stem cells [29]. Additionally, the lack of Cdc42 in AT2s also impairs differentiation and increases exposure to TGF-β, thus increasing fibrosis [59].

5.4. Fibroblasts and Myofibroblasts

In IPF lungs, there is a positive feedback loop between the ECM and fibroblasts. Fibrotic mediators produced by fibroblasts can activate other fibroblasts, which then produce ECM and differentiate into myofibroblasts [58]. Myofibroblasts play an essential role in collagen production and express collagen remodeling proteins such as fibroblast activation protein (FAP) [55]. The level of FAP is elevated in IPF lungs, indicating increased collagen remodeling activity compared to that in normal lungs [12].

In healthy lung, fibroblasts can be removed through the apoptotic pathway. However, in IPF lungs, fibroblasts are resistant to apoptosis and have increased proliferation capability [60]. Furthermore, one study has illustrated that periostin, a protein mainly found in fibroblast foci, enhances the proliferation of fibroblasts and is increased in IPF [61].

5.5. Growth Factors

Several important growth factors involved in IPF are presented in **Table 2**.

Table 2. Growth factors in IPF. The information is adapted from Mei et al., 2022 [26].

CTGF	Promotes ECM deposition and fibroblast differentiation
PDGF	Mediates fibroblast proliferation and migration
IGF1	Regulates cell senescence

5.6. Inflammation

Numerous inflammatory cells and mediators also participate in IPF (**Table 3**), playing a significant role in pathogenesis of IPF.

Table 3. Inflammatory cells in IPF. The information is adapted from Sgalla *et al*., 2018[48].

Macrophages	Produce pro-fibrotic cytokines and recruit fibroblasts and epithelial cells
Neutrophils Monocytes	Produce ROS
Th-1 cells	Produce IL-1, PDGF, TNF-α
Th-2 cells	Produce IL-4, IL-5,IL-13, and TGF-β, and recruit macrophages, mast cells and mesenchymal cells
Th-17 cells	Increase TGF- β level

6. Pathophysiology

6.1. Lung Function Tests

In IPF lung, the results of the lung function test almost decreased, such as forced vital capacity (FVC) and total lung capacity (TLC). (**Table 4**).

Table 4. Alterations of lung function tests in moderate and severe IPF. The information is adapted from Plantier et al., 2018[37]

Lung function tests	IPF	Description
FVC	Decrease	Reduction of lung volume
FEV1/FVC	Normal or increase	and compliance
TLC	Decrease	Reduction of lung volume and compliance
PaO2	Decrease	
PaCO2	Decrease	
DLco	Decrease	Reduction of diffusion
VA	Decrease	capacity
Kco	Decrease	
Cough reflex	Increase	
Airway resistance	Decrease	
PAP PCWP	Increase May be increase	Raghu *et al*. (2015) [41] found that among 488 IPF patients with PH: 14% of them did not show an increase in PCWP

6.2. Physiological Process of the Dyspnea in IPF

The cause of dyspnea arises from physiological reactions in the lungs, airways, and vasculature (**Figure 3**).

The reduction in lung compliance in IPF is influenced by changes in the ECM and alterations in surfactant levels [11]. Moreover, Cortes-Telles *et al*. (2014) [3] observed that 98% of IPF patients have reduced lung diffusing capacity. Dysfunction in gas diffusion and ventilation/perfusion (V/Q) mismatch contribute to chronic hypoxemia [1], which increases the ventilatory drive, leading to dyspnea.

In the airways, several studies have illustrated an increased cough reflex in IPF patients [57][17]. Importantly, evidence suggests that the resistance of the conducting airways decreases [24], and the diameter of the airways increases during the IPF pathogenesis. Another study indicated that the volume of the conducting airways is higher in IPF patients, as assessed using volumetric capnography to predict airway volume [38]. Consequently, the increased volume of the conducting airways results in more dead space ventilation, which enhances ventilatory drive, leading to dyspnea.

The mechanism of IPF-induced pulmonary hypertension (PH) remains unknown, but Bourke *et al.* (1993)[2] proposed that it may be due to the reduction of vessel density. PH contributes to abnormal cardiac output and gas exchange, which enhances ventilatory drive and contributes to dyspnea. Additionally, vascular lesions also contribute to V/Q mismatch, resulting in dead space ventilation.

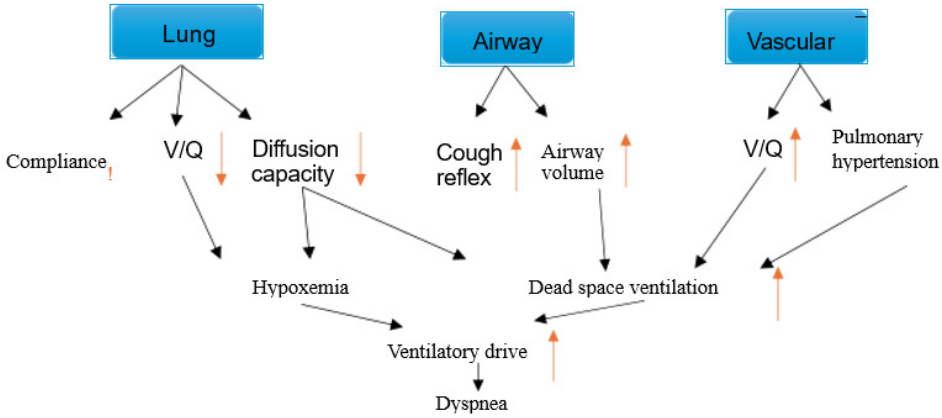

Figure 3. Model of the physiological process of the dyspnea in IPF patients. The figure is adapted from Plantier et al., 2018[37].

7. Diagnosis

7.1. HRCT

High-resolution computed tomography (HRCT) is the primary diagnostic tool for identifying IPF. The main characteristic of IPF on HRCT is the presence of usual interstitial pneumonia (UIP) (**Figure 4**), which is characterized by reticular opacities and traction bronchiectasis [32][16]. Additionally, honeycombing and ground glass opacities are also commonly observed on HRCT [40].

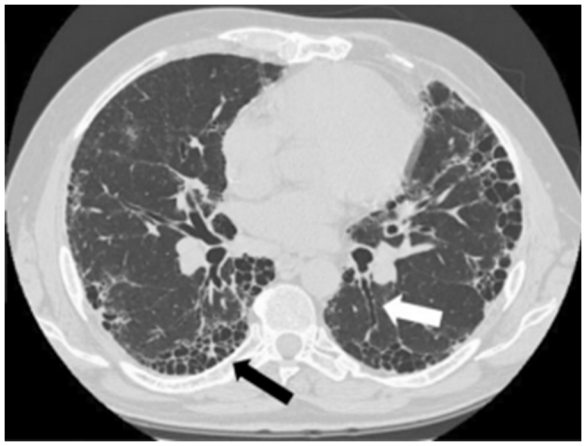

Figure 4. UIP pattern. Black arrow indicates the honeycombing and white arrow indicates the traction bronchiectasis. The image is adapted from Sgalla et al., 2018[48].

7.2. Surgical Lung Biopsy

Lung biopsy is utilized to confirm the IPF diagnosis. The histopathological feature of IPF is UIP, characterized by honeycombing and destruction of pulmonary architecture. Additionally, inflammation is involved in the IPF process, such as hyperplasia of AT2s and epithelial cells, leading to fibrosis [40]. Importantly, fibrotic foci (**Figure 5**), a significant feature defining UIP, consist of excessive fibroblasts and myofibroblasts, which can be observed in the honeycombing lesions within the interstitium [4].

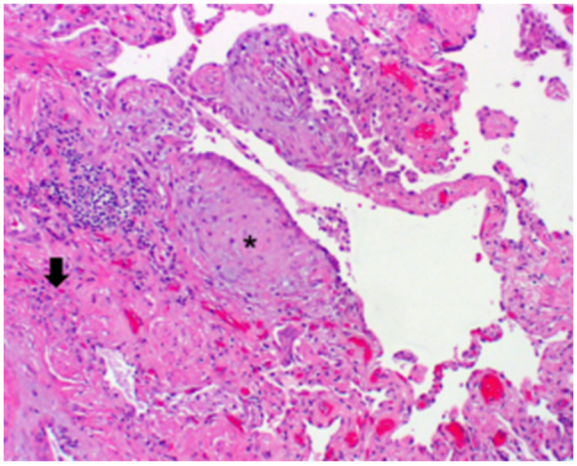

Figure 5. Lung biopsy shows the UIP pattern, with the arrow indicating fibrosis and the asterisk indicating fibrotic foci, characterized by the accumulation of fibroblasts and myofibroblasts. The image is adapted from Raghu et al., 2011[40].

However, in recent years, achieving a correct diagnosis of IPF has been challenging. Literature suggests that approximately 10% of patients are unable to undergo lung

biopsy due to their disease severity or poor health conditions [45]. Additionally, other evidence indicates that the definition of UIP on HRCT is not entirely clear [48]. Therefore, there is a need for a more definitive and consistent approach to diagnosing IPF in the future.

8. Treatments

8.1. Pirfenidone and Nintedanib

Pirfenidone and Nintedanib are currently FDA-approved drugs for the treatment of IPF. Pirfenidone, a small molecule drug, exerts an antifibrotic effect and can regulate the expression of TGF-β [48]. Additionally, nintedanib is a small molecule inhibitor of tyrosine kinase that can suppress vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), thereby reducing fibroblast activity [48]. However, it is crucial to note that pirfenidone and nintedanib cannot improve the symptoms or cure the disease.

8.2. The Mesenchymal Stem Cells (MSCs)

MSCs can differentiate and develop into various cell types within a single lineage. Some evidence suggests that MSC signaling can inhibit fibrosis and inflammation [34][8]. Similarly, Gazdhar *etal*. (2013)[7] demonstrated that MSC administration can regulate the expression of TGF-β and decrease collagen levels. Moreover, intravenous administration of MSCs in IPF patients has been found beneficial in slowing disease progression [10]. However, further research is necessary to fully understand the therapeutic potential of MSCs in IPF.

8.3. Inhaled Drug Administration

Inhaled drugs offer the benefit of enhancing therapeutic exposure at the target site while minimizing side effects simultaneously [50]. A recent study has demonstrated the feasibility of inhaled drug delivery in IPF patients by using the radiolabeled salbutamol [56]. Additionally, a Japanese study suggests that compared to oral pirfenidone alone, the combination of pirfenidone and inhaled acetylcysteine results in a slower rate of decline in FVC [46]. However, another study found contradictory results among 81 patients [46]. Therefore, the clinical application of inhaled drugs should consider patient conditions and drug properties.

8.4. Other Treatments

PRM-151

PRM-151 is a recombinant human pentraxin-2 (PTX2). PTX2 can inhibit the differentiation of monocytes into fibrocytes and the expression of TGF-β [9]. Literature suggests that the level of PTX2 in serum is higher in healthy people compared to IPF patients [28]. Additionally, one study treated 117 IPF patients with PRM-151 or placebo every four weeks for about six months and found that the decline in FVC is much higher in the placebo group [42].

Pamrevlumab

Pamrevlumab is a human recombinant monoclonal antibody that targets connective tissue growth factor, thereby inhibiting fibrosis [22]. One study treated 50 IPF patients with pamrevlumab and 53 with placebo every three weeks for about eight months; they found a slowed decline in predicted FVC in the pamrevlumab group. Moreover, disease progression (death or decline of FVC ≥ 10%) was higher in the placebo group (31.4%) compared to the pamrevlumab group (10%) [43].

TD139

TD139 is an inhibitor of galectin-3, a protein with pro-fibrotic effects [14]. Literature suggests that TD139 is safe in IPF patients in clinical trials and has shown improvement in certain inflammatory markers, such as CCL18 [13].

9. Conclusion

In summary, IPF is a rare disease with multiple causes. The pathogenesis of IPF is very complicated and involves numerous cells and mediators. Significantly, the diagnosis and treatment options for IPF are limited due to its unclear pathogenesis. However, many new treatments, such as PRM-151 and TD139, are being developed. Hence, further research should be undertaken to explore more effective treatments aimed at curing the disease and improving the quality of life for patients.

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