Development of idiopathic pulmonary fibrosis and its pathogenic inhibition by drugs: An overview

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and incurable inflammatory and fibrotic interstitial lung disease (ILD) of unknown etiology having ahigh rate of morbidity and mortality throughout the world. The pathophysiology indicates the persistent or repetitive injury of lung epithelial cells through the involvement of genetic and / or environmental factors predominantly in the older population, and the subsequent activation of fibroblasts to differentiate into myofibroblasts followed by the deposition of extracellular matrix (ECM) components such as collagen and the expressions of other genes and proteins and aberrant lung repair through the various signalingsignallingpathways leading to scarred and stiff tissue (e.g. parenchymal lung alveoli, interstitium, and capillary endothelium) -formation and irreversible loss of lung function making breathing trouble in transferring oxygen and carbon dioxide between the alveolar space and the blood stream. A few drugs either FDA approved or under clinical trials are being applied to slow / arrest disease progression and relieve symptoms partially, mainly through the inhibition of receptor / non-receptor tyrosine kinases, phosphodiesterase 4B, a pro-apoptotic corisin peptide, and a pro-fibrotic β-galactoside-binding lectin galectin 3 (Gal-3) as anti-fibrotic and anti-inflammatory agents. In recent decadesdecade, the emergence of anti-fibrotic therapies has improved the survival of the patients via a cure to some extent. However, it is required further investigations on the mechanistic disease developments and their inhibitions by new drugs with the reflections of clinical phenotypes. This

review elucidates the recent data on approved therapies, the key pathogenic information to develop new anti-fibrotic agents, and new compounds in theclinical development. Moreover, future directions / strategies for the developmentofdeveloping efficient vectorized anti-fibrotic agents for specific targeting with leastthe least side effects are depicted.

Keywords: Idiopathic pulmonary fibrosis; Mechanism of disease development; Anti-fibrotic and anti-inflammatory drugs

Introduction

The diffuse parenchymal lung diseases (DPLDs), the heterogeneous group of diseases, cause progressive fibrosis and remodeling of the pulmonary structure through the chronic inflammation and / or the epithelial damage including idiopathic interstitial pneumonias,and also called IPF [1,2]. As the incidences of IPF are beingincreased and having poor prognosis in the middle-aged and older people, their median survival time denote 3-5 years from the diagnosis [3,4]. Usual interstitial pneumonia (UIP), the histological counterpart of IPF, is provisionally heterogenous with regions of matured fibrosis and scarring and honeycomb alterations (clusters of dilated, mucin-filled epithelial-lined airspaces) directly adjacent to almost normal zones [5-7]. In general, the key factors, such as environmental stressors and genetic susceptibility may activate and promote the development of pulmonary fibrosis [8,9].Genetic deficiency, environmental factors (such as smoking and dust exposure including industrial), infections (e.g. herpes, EB and cytomegalo viruses), aging, and other particulars interact with adjacent cells to induce sustained micro-injuries of alveolar epithelium [10-12,8,13]. Pulmonary macrophages distinguish epithelial injuries, augment inflammatory responses, produceplatelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and other cytokines,

recruit fibroblasts to the injured site/s, convert fibroblasts into myofibroblasts, trigger alveolar epithelial cells for undergoing epithelial-mesenchymal transformation (EMT), while myofobroblastsliberate extracellular matrix components (ECM), following an eventual manner for the occurrence, development and maintenance of pulmonary fibrosis [14-17]. Different types of cells and signaling pathways may be associatedin the process of pathogenesis of alveolar fibrosis marked with epithelial repair disorder, immune response and cell senescence disorder, lacking the effective treatment for the progressive stage of IPF [17]. The persistent epithelial injury in genetically susceptible candidates may cause mutations in surfactant proteins C and A, and the genes encoding the contents of telomerase (TERT/TERC), resulting in short telomeres in the development of IPF [18-20]. The eventual huge epithelial regeneration, the revival of the developmental pathways, unrestrained fibro-proliferation and the increased number of fibroblasts may lead to progressive scarring of the lung [18,19,21].

The primary symptoms of IPF include a wet or dry cough, shortness of breath (dyspnea) and eventually respiratory failure accompanied with declined lung function including weakness, fatigue, weight loss, declining exercise tolerance, tightness and chest discomfort, resulting in aggravation to severe chronic obstructive pulmonary disease (COPD), and / or inflammation-related cancer [22-25]. The common co-morbidity in patients with IPF includes gastro-esophageal reflux disease (GERD), osteoporosis, hypothyroidism, anxiety and depression [26-28].

The treatment strategies cover supportive measures, oxygen supplementations as needed, antifibrotic medications, and lung transplantation in extreme cases. Though FDA approved antifibrotic drugs (pirfenidone and nintedanib) with anti-inflammatory and anti-oxidant activity may diminish the risk of acute exacerbation in IPF subjects with mild to moderate

pulmonaryfunction impairments, these drugs also exhibit adverse side effects/reactions such as dizziness, nausea and vomiting, skin photosensitization and liver dysfunction [13]. Moreover, owing to the restriction in delivery of donor organ and the limitations of chronic allograft rejection, some patients can gain only this intervention [29]. On the other hand, the most of the trial drugs, especially in phase II and III, also have been unsuccessful to meet the primary end point as well as curative activity [30]. Therefore, it would be emphasized for taking a strategy on the maximal amelioration of symptoms, improvement of health status and preservation ofimproving health status and preserving lung function for IPF patients. This review elucidates the recent advances in the pathogenesis of IPF with the inhibitory therapeutic target strategies by the effective/emerging drugs.

Factors involved in the development of IPF

Environmental exposures

The exposure of environmental factors such as cigarette smoke (ingredients such as carbon black and cadmium), metal dusts, or other irritant particles / pollutants to lung epithelial cells, and the genetic predisposition synergistically, may induce lung fibrosis and / or enhance both the risks for the sporadic and familial pulmonary fibrosis through inducting miRNA imbalance and endoplasmic reticulum (ER) stress, promoting lung injury, differentiating (such as citrullinated vimentin-induced) fibroblast to myofibroblast, and over-expressing collagen and α-smooth muscle actin (α-SMA) [31-37].

Pathogenic microorganisms such as bacteria, virus and fungi may play a key role in the pathogenesis of IPF [38]. The imbalance in the contents of lung microbiota may act as the sustained stimuli for repetitive pulmonary injury activating fibrotic and inflammatory mediators,

and immune disorders for the development of IPF [39]. Bacterial and viral infection may trigger the disease progression for IPF through the activation of epithelial-mesemchymal transition, the promotion of TGF-β expression, and the initiation of epigenetic reprogramming [40-42]. For the mucociliary clearance of inhaled pathogens and irritants, the epithelial Na^+ channel (ENaC) is modulated by NEDD4-2 via ubiquitination, while NEDD4-2 promotes remodeling of fibrosis via the regulation of the expressions of proSP-C, Smad2/3 and TGF-β signaling axis [43].

Genetical roles

Genetic susceptibility for IPF involves single nucleotide polymorphisms (SNPs) and theconcomitant alterations in gene expressions. Several genes such as Notch, WNT, TGF, Toll-interacting protein (TOLLIP), sonic hedgehog (SHH), and the inhibitor of the Toll-like receptor (TLR) are involved in the response to environmental injury, and the signaling pathways in the process of development of IPF [44,27]. Some genetic factors having contribution to familial cases are surfactant genes (such as SFTPA2), mucin genes (such as MUC5B), and mutated telomerase genes (Such as TERT) involved to coduct to form IPF.Hermansky-Pudlak syndrome, a rare autosomal recessive condition having faults in lysosome-related organelles, may govern to pulmonary fibrosis [45,46]. Genetic variations in familial interstitial pneumonia (FIP) (the autosomal dominant genetic disease) require the maintenance of telomere length (telomerase RNA component-TERC, telomerase reverse transcriptase-TERT, regulator of telomere elongation helicase-RTEL, and poly (A)-specific ribonuclease-PARN) and epithelial barrier function (dipeptidyl peptidase 9-DPP9, desmoplakin-DSP, AKAP13 and CTNNA), while short telomeres diminish the tissue renewal capability correlated with the cellular senescence [47-53]. Mutations in TOLLIP are linked to reduced expression of TLR mRNA and enhanced

inclinationto lung infections through encoding an inhibitor of TGF-β signaling pathway and regulating TLR-mediated innate immunity [49].

A common polymorphism (rs35705950) in the promoter of mucin 5B (MUC5B) enhances the risk in both FIP and sporadic pulmonaryfobrosis, while the over-expression of MUC5B leads to mucociliary dysfunction and augmented fibrosis [53-55].The rs35705950 minor allele mutation may lead to over-expression of MUC5B in small lung epithelial cells associating DNA methylation linked to genetic inclination of MUC5B [56].

Mutations in SFTPC (genes encoding for surfactant protein C (SF-C)) have incriminated their roles in anomalous surfactant processing, resulting in endoplasmic reticulum stress in type 2 AEC and subsequent fibrosis of the pulmonary epithelial cells with usual interstitial pneumonitis (UIP), non-specific interstitial pneumonitis (NSIP) or sporadic cases of IPF [57-60].

Roles of aging and cellular senescence

The genetic pre-dispositions (such as telomere mutations, epigenetic changes, mitochondrial dysfunction and loss of protein homeostasis) may cause pre-mature aging and physiological aging to develop IPF, while the cellular senescence, the form of irreversible cell cycle arrest, may occur naturally or accelerate either with aging or at any stage of life also by the exposure of smoking, infection or occupational irritants [61]. Mutations in telomere in alveolar epithelial type II cells (AT2) may cause abnormal DNA repair and genome instability to trigger cell senescence and promote fibrosis through the activation of p53 and the reduction of mitochondrial biosynthesis [49,62-65]. F-box and WD repeat domain-containing protein 7 (FBW7), an E3 ubiquitin ligase engaged to bind telomere protective protein 1 (TPP1) through degradation and uncapping of telomere, expression of core senescence-related markers (such as CDKN2A/p16,

CDKN1A/p21, TP53, CCND1 and MDM2), dysfunction of stem/progenitor cell renewal, and production of a variation of pro-fibrotic and pro-inflammatory mediators (such as IL-1, IL-6 and TGF-β) cause cell senescence and progressive pulmonary fibrosis correlating the therapeutic target (genetic intervention for p53 activation and senescence) for the treatment of IPF [66-70].

Role of epigenetic reprogramming

Generally, the prevalence of IPF rises with the aging progress owing to the epigenetic changes, while the familial type of IPF occurs at the younger stage, indicating the incidence of IPF from 2.3 to 5.3 cases /100,000 people / year [71-73]. Epigenetic changes such as histone modifications, DNA methylation, modified expression of non-coding RNA (e.g. microRNA), and enhanced expression of DNA methyl transferase1 (DNMT1) in the alveolar epithelial cells through the environmental stresses may accumulate collagen leading to IPF [74,75]. Regulations of DNA methylation such as methylation in differentially methylated regions (DMRs), binding of MBD2 (macrophages-expressed methyl-CpG-binding domain (MBD) protein) to methylated CpG DNA, and expression of high-mobility group (HMG) AT-hook 2 protein (HMGA2) may control the transcriptional target genes through altering the chromatin structure at the promoter and / or enhancer, and restricting the HMGA2-FACT-ATM-pH2A.X axis of lung fibroblasts in TGF-β-induced key pathogenic IPF [76-84].

Histone modifications by the treatment of drugs (such as SpA and TSA) may affect the level of surfactant protein C (Sp-C), the triggering and proliferation of fibroblasts, the anti-apoptotic capability of fibroblasts, and the expression of histone methyltransferase G9a/chromobox homolog 5 (CBX5)/mehtylated lysine 9 residue on histone 3 (H3K9me) (the key regulators) through the participation in the CBX5/G9a and TGF-β pathway-induced enhancement of ECM

stiffness and the inhibition of anti-fibrotic genes (caveolin 1(Cav-1) and FAS) and expression of PGC1α in lung fibroblasts [85,86].

The expressions of miR-21, miR-145 and miR-424 may induce epithelial mesenchymal transition (EMT) and α-smooth muscle actin (α-SMA), or target Smurf2 for promoting differentiation of fibroblasts to myofibroblasts and secreting TGF-βthrough the inhibition of Smad-7 to induce fibrosis, while Let-7, miR-200, miR301a and miR-29 may regulate the fibrotic process through targeting HMGA2, promoting AT2 to AT1, and controlling fibroblast-activation and ECM production [87-92]. IPF ECM also may regulate the upstream expression of miR-29 at the transcriptional stage, and suppress downstream Dicer1 at the proceeding stage for maintaining the progress of fibrosis [93].

Role of cells and regulators

Regarding epithelial cells injury

Under normal condition, the injury of pulmonary epithelial cells initiates the employment of inflammatory cells, matrix deposition and fibrosis for the repairmen of the injured cells, while the normal pulmonary homeostasis restores fibrosis through the triggering of apoptotic signaling and phagocytosis of macrophages during the injury repairing stage [94]. Repeated stimulation of environmental factors, gastroesophageal reflux and genetical factors may damage more or less the integrity of the lung epithelium through the production of ROS, endoplasmic reticulum stress, mutations of lung epithelial restriction genes (such as ABCA3, SFTPC and SFTPA2) and faulty expression of genes (such as MUC5B) with cellular repairing dysfunction and lung epithelial mucosal barriers dysfunction [95,55]. A subset of fibroblasts, expressing $Lgr5^{+}$ or $PDGFR\alpha^{+}$ participated in alveolar homeostasis through stimulation of Wntsignaling ($Axin2^{+}$),

may be involved in the promotion of alveolar maturation and growth to differentiate into myofibroblasts after alveolar epithelial injury [96,97].

Regarding lung stem cells dysfunction and exhaustion

AT2s, the predominant epithelial progenitor in alveoli, may participate in maintaining lung homeostasis, while the dysfunction of AT2s may restrict the repairing of damaged AT1s caused by genetic and environmental factors [98]. A subset of mature AT2 cells with stem cells property and the overexpression of the Wnt target gene Axin2, associated with the activation of Wnt/β-catenin, Fgf and sonic Hedgehog signaling, block reprogramming of alveolar stem cells into AT1 cells through participation in ancillary AT2 stem cells progenitor cells activity resulting stemness, AT2 depletion and stem cell exhaustion on getting repetitive injury in epithelial cells [99-102]. Additionally, mitochondrial dysfunction, ERS and aging may take a role in AT2 depletion and impaired self-renewal [103,104, 98]. Loss of Cdc42 in AT2s, resulting in defective differentiation in alveolar cells, may trigger enhanced mechanical tension-induced TGF-β signaling to promote lung fibrosis progression [105].

Conversion of fibroblasts into myofibroblasts

Periostin/integrin αVβ3-promoted expressions of cell cycle-related molecules such as cyclin, cyclin-dependent kinase (CDK) and E2F family, and transcription factors (e.g. FOXM1 and B-MVB) may participate in the proliferation of alveolar fibroblasts, while pro-fibrotic mediators produced by the triggered fibroblasts may act on fibroblasts to differentiate into myofibroblasts resulting in ECM and collagen production for the development of pulmonary fibrosis through TGF-β-signaling and enhanced AKT activity, and over-expressions of fibroblast activation protein (FAP) and contractile protein α-SMA, and diminished expressions of FAS-ligand

(FasL),Cav-1 protein and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) to resist apoptosis [106-111].

Activity of basal cells

The expansion of distal basal cells to work as stem/progenitor cells of the pseudostratified lung epithelium may take part asignificant role in the remodeling of epithelial cells in alveolar fibrosis, while the sensitized basal cells are secreted and regulated by Notch signaling through the restriction of differentiation of basal cells by NOTCH2, and the inhibition of secretory differentiation by NOTCH3 [112]. The over-expression of LncRNA MEG3, the differentiation of abnormal epithelial cells, and the regulation of epithelial cells migration-related genes (such as STAT3, TP63, KRT14, AXL and YAP1) may contribute to restructure IPF [113]. The over-expression of MMP-9 through the activation of airway base cells (ABCs) may be regulated by TGF-β activity with the associated expression of type I IFN in ABC-like cells [114].

Regarding growth factors

The lead role of TGF-β in the development of IPF is not only to promote the transition of epithelial-mesenchyma, migration of epithelial cells, proliferation, activation and differentiation of fibroblasts into myofibroblasts, but also to augment the productions of other fibrotic and pro-angiogenic mediators [108,115,116]. Generally, the over-expressed αvβ6 in lung epithelial cells anchores to the latency-related peptide (LAP) for inducing TGF-β activation, while activated TGF-β anchored with its receptors inducts phosphorylation of Smad3 transcriptional factor, and subsequent interaction with Smad4 for forming a complex to translocate into the nucleus to express target/profibrotic genes (such as, CTGF, α-SMA and ECM collagen 1A1 (COL1A1)) [117-120]. The upregulation of tripartite motif 33 (TRIM33), an ubiquitin ligase, may promote

Smad4 as well as the progression of fibrosis, while the combination of small heat shock protein and TRIM33 may weaken the inhibitory activity of fibrosis [121].

CTGF, the cellular communication network factor 2 (CCN2), the mediator of organ-fibrosis and the target component for anti-fibrosis therapy, may be secreted and triggered by the induction of TGF-β through pulmonary matrix deposition and fibroblast differentiation by the activation of MAPK signaling, and also through the CXCL12-induced expression of CTGF in pulmonary fibroblasts by the activation of MEKK1/JNK signaling involving various transcription factors (such as NF-κB, STAT, AP-1 and SMAD) to affect IPF [122-127].

TGF-β signaling may promote over-expression of PDGF-B in pulmonary fibroblasts via regulatory T cells (Tregs), leading to stimulated PDGF-B-intervened proliferation and migration of fibroblast cells in IPF [128-130].

Insulin-like growth factor (IGF1), the regulator of cellular senescence, relates the weakened repair activity of AT2s in IPF [131]. The main molecules such as IGF1liberated by ATs, the activated surface of the contiguous healthy ATs, IGF receptor (IGFR-1) and the activated PI3K/AKT may take part in senescence and IPF through the release of TGF-β1, CTGF and MMP-9 [132].

Molecular mechanisms

Deposition of extracellular matrix

The deposition of extracellular matrix is caused mainly by the involvement of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), while MMPs are over-expressed in pulmonary epithelial cells and alveolar macrophages, and TIMPs in

myofibroblasts [133]. The extracellular matrix may activate and change the transcriptional profile of pulmonary fibroblasts, and may act on the translation of ECM proteins (such as MMP2, MMP4, MMP10, TIMP2, COL1A1, COL1A2, COL3A1, COL4A2 and COL5A2) for developing IPF [134,135].

Scaffolding and matrix stiffness

Pulmonary scaffolds enhance ECM tissue stiffness through the up-regulation of matrisome proteins such as proteoglycan, collagen, ECM glycoprotein, nidogen-2, periostin, and the down-regulation of specific basement membrane (BM) proteins such as collagen IV and laminin resulting in dysregulated collagen cross-linking and leading to post-trnaslational collagen modification involved in lysyl oxidase (LOXL 2 and 3) for the development of sustained and perpetuated lung fibrosis via the mechanistic interactions of fibroblasts with the stiffened ECM [136-138].

Matrix stiffness controls the capability of pulmonary myofibroblasts for invading the BM through the enhancement of expression of α6-mediated MMP-2-reliant pericellular proteolysis of BM-collagen IV. The mechanotransduction signaling through the involvement of actin cytoskeletal remodeling, Rho/Rho kinase (Rho/ROCK) activity and the transcription factor (megakaryoblastic leukemia 1 (MKL1)) activity may control myofibroblasts differentiation and the disruption of this signaling with the ROCK inhibitor through myofibroblast apoptosis with the down regulation of BCL-2 [138]. Mouse double minute 4 homolog (MDM4), the matrix stiffness-controlled endogenous inhibitor of p53, overexpressed in IPF, may be a molecular target with therapeutics against lung fibrosis [139]. ECM stiffness may inhibit the TGF-β signaling through the inhibition of the interaction of LEMD3 and SMAD2/3, and may impair the

synthesis of PGE2 and expression of COX-2 via p38/MAPK signaling [140,141]. Moreover, matrix stiffness also regulates desmoplakin (DSP) gene expression related to maintain structural integrity and mechanical stability of the epithelium, through alteration of DNA methylation in the DSP promoter, while epigenome editing of the targeted DNA mehtylation by CRISPR/dCas9 or other therapeutics may be another molecular target against over-expressed DSP on mechano-sensitive signaling in myofibroblasts in IPF [50,51,142-144].

Stress effect of endoplasmic reticulum

The sustained endoplasmic reticulum stress (ERS), owing to the imbalance between the demand of cells for protein synthesis and the capability of ER for synthesizing, processing and packaging of proteins, may activate the markers of UPR in AT2 and synergize the inflammation and infection for stimulating and producing fibrotic mediators such as PDGF, CCL2, CXCL12 and TGF-β accompanied with epithelial cell injury to promote fibrosis, while the chaperon protein (GRP78) is the key regulator of ER homeostasis [103,145-148,104]. The up-regulation of ER protein (thioredoxin domain containing 5 (TXNDC5)) in fibroblasts may enhance TGF-β signaling through TGF-beta receptor1 (TGFBR1)-mediated expression of TXNDC5 following ATF6 ER stress pathway to develop IPF [149]. Genetic mutations encoding surfactant proteins (SFTPA2 and SFTPC) may also cause abnormal surfactant folding and ERS to activate epithelial-mesenchymal transition for promoting IPF [150,151].

Activity on inflammation and immunity

Alveolar injury causes recruitment, infiltration and activation of neutrophils to liberate immunogenic pro-inflammatory cytokines such as IL-8, G-CSF and neutrophil elastase (NE) through TGF-β activation for developing IPF [133,135,152,44]. IL-4 and IL-24 may

synergistically induct M2 program of macrophages to promote and develop alveolar fibrosis, while IL-17 secreted by Th17 cells may directly promote IPF [153]. The treatment with IL-23 antibody may attenuate lung inflammation and fibrosis and diminish the enhanced levels of IL-17 and IL-23 indicating the vital role of IL-23 in the development of lung fibrosis [154]. The highly expressed macrophage-derived SPP1hi (SPP1 and MERTK) may upregulate the expression of MMP2 and collagen-I in the contribution of fibrosis, while NTN1derived from macrophage may participate in the development of IPF via the activity of noradrenaline and α1 adrenoreceptors [155]. Moreover, monocytes/macrophages-derived CCL2 and colony stimulating factor (M-CSF/CSF1) may also contribute to the development of IPF directly [156].

Role of autophagy

Autophagy regulates ECM formation, clears collagen-I in pulmonary fibroblasts, diminishes invasiveness of fibroblasts, and reduces autophagy marker LC3B in alveolar fibroblasts [157-159]. Reduced autophagic signaling (mitophagy and macroautophagy) in pulmonary epithelial cells and fibroblasts aggravates inflammation and fibrosis through Akt signaling to reduce the expression of $FoxO_{3a}$and inhibit the production of LC3B on the collagen matrix directing to fibrotic collagen deposition [160,161].

Treatments for idiopathic pulmonary fibrosis

Recent investigations on the pathogenesis of IPF have promoted remarkable advances in the pharmaco-therapeutic treatments. The progressive pulmonary fibrosis with ILDs develops a decline in pulmonary function tests (Forced vital capacity (FVC) or diffusing lung capacity for carbon monoxide (DLCO)), a worsening of fibrosis detected by high resolution computed tomography (HRCT), or symptoms within one year [162]. Currently, two recommended drugs

(pirfenidone and nintedanib) for the treatment of IPF ameliorate the diseased symptoms as well as subject-survival through slowing down the disease progression but not curing the disease (Table 1). Therefore, a few important novel drugs with their potential molecular targets have been tested in phase II-III trials (Table 2). Moreover, some emerging drugs / strategies, symptomatic adjunct therapy, comorbidities, lung transplantation, and management of acute exacerbation of IPF are under consideration for improving symptoms-control and quality of life [163].

Pirfenidone

Pirfenidone (oral dose: 1800 mg/day in Asia, and 2403 mg/day in Europe and United States), a small molecule, acts after treatment as anti-fibrotic and anti-inflammatory drug, and inhibitsthe epithelial cell transformation, the differentiation of fibroblasts, myofibroblasts, collagen, fibronectin synthesis and the accumulation of ECM through interfering TGF-β1/Smad3, fibroblast growth factor, fibroblast mitogen receptor (PDGF), fibronectin, α-smooth muscle actin (α-SMA), p38MAPK in B lymphocytes, TNF-α, and IL-1,4 and 13, and detoxifying mitochondrial glutathione peroxidase to reduce oxidative stress, while orally administered pirfenidone anchored to serum albumin is metabolized mainly by cytochrome P450, and excreted in the form of 5-carboxy-pirfenidone in the urine (80%) or in the feces (20%) [164-174] (Table 1).

Nintedanib

Nintedanib (NDB, 300 mg/day in 2 divided dosages), a small molecule, acts after exposure as antifibrotic and anti-inflammatory drug, and inhibits the differentiation of fibroblasts into myofibroblasts, epithelial mesenchymal transition (EMT), inflammation, and angiogenesis

through deactivation of tyrosine kinase receptors (such as PDGFR, FGFR, and VEGFR autophosphorylation) and Src family kinases, inhibition of downstream cascade signaling (such as Ras/Raf/MAPK, ERK1/2, and PI3K/Akt), direct inhibition of TGF-β signaling, and inhibition of inflammatory mediators such as IL-2,4,5,10,12p70, 13 and IFN-γ by mononuclear cells or T cells in the system, while orally administered NDB anchored to plasma protein is metabolized through glucuronidation / minor cytochrome p450, and the metabolites are eliminated primarily (>90%) via biliary / fecal, and the residual via renal excretion [175-182] (Table 1).

Table 1. Main drugs applied in the treatment of idiopathic pulmonary fibrosis.

Drugs	**Mechanism of action**	**Effects**	**Side effects**	**Ref.**
Pirfenidone (Esbriet®)	Anti-fibrotic (TGF-β and fibronectin inhibitor)	Anti-fibrinolytic, anti-inflammatory, and reduced mortality; Significant reduction decline in forced vital capacity (FVC) and 6-min walk distance (6MWD)	Photosensitivity, skin rash, gastrointestinal upset, anorexia, nausea, vomiting, dyspepsia, dizziness, facial paralysis, liver dysfunction, and hepatocellular tumor	[173,174]
Nintedanib (Ofev®)	Anti-PDGFR, VEGFR, FGRR (Tyrosine kinase inhibitor)	Reduced mortality; Reduction decline in FVC. Reduction of the time to 1st exacerbation in INPULSIS-2	Diarrhea, nausea, vomiting, nasopharyngitis, and cough	[181,182,175]
Pirfenidone + Nintedanib	Combined anti-fibrotic (TGF-β + Tyrosine kinase inhibitors)	Reduced rate of decrement in lung function	No augment in adverse events	[184]

Combination therapy

As various pathways are involved in the development and progress of IPF, combined synergistic multiple therapies to target different pathways in IPF have been attracted attention, while efficiency evaluation study of combined therapy is required further as both pirfenidone and nintedanib reduce the migration of the fibroblasts resulting in a decline in the accumulation of myofibroblasts through inhibition of the transcription of TGF-β, and FGF, PDGF and VEGF, respectively [183,184] (Table 1).

Novel therapies

Though the current FDA approved anti-fibrotic pirfenidone and nintedanib reduce significantly IPF progression, there is no perfect treatment to stop the disease progression or reverse the decline in lung function. Moreover, the tolerability-issues to anti-fibrotic drug/s by the subject/s have very limited options regarding dosage titration and alternatives. Therefore, a few compounds on new molecular targets and treatment options are under investigations with their ongoing clinical trials to function as the alternate replacement, or add on therapy, even to halt disease progression, or reverse fibrosis potentially, illustrated with their major mechanism/s of action and finding/s (Table 2) [117,185-205].

Table 2. A few novel drugs utilized in the clinical trials for the treatment of idiopathic pulmonary fibrosis.

Drugs	**Mechanism of action**	**Effects**	**Side effects**	**Ref.**
Pamrevlumab (Recombinant human antibody)	Anti-CTGF monoclonal antibody (Anti-fibrotic)	Reduction decline of FVC and attenuation of the progression of IPF	No aggravation of safety and tolerability	[185]
Simtuzumab	Anti-lysyl oxidase (LOX) antibody	Reduction of collagen cross-linking activity	Worsening of IPF, dyspnoea and pneumonia	[186]
GSK3008348	αvβ6	Induction of αvβ6	No aggravation of	[117]

	antagonist	internalization and degradation, and inhibition of activation of TGF-β. Reduction of lung collagen deposition and IPF progression marker serum C3M	safety and tolerability	
Carlumab	Anti-CC-chemokine ligand 2 (CCL2)	Greater decline in FVC, or no treatment effect	One or more serious adverse event/s , or no unexpected serious adverse events	[187]
Lebrikizumab	Anti-IL-13 monoclonal antibody	No association with reduced FVC % decline. Despite of blocking IL-13, no sufficient achievement of lung function benefit in IPF	No aggravation of safety and tolerability	[188]
GLPG 1690 / Ziritaxestat	Autotaxin inhibitor	Improvement of FVC	No significant adverse reactions	[189]
PRM 151 (Recombinant human PTX2 protein)	Inhibitor of the differentiation of monocytes and TGF-β expression	Improvement in reduction of % FVC and 6-min walk distance	No significant side effects	[190,191]
PBI 4050 (G-protein receptor analogue)	Anti-fibrotic, GPR40 activator and GPR84 suppressor	Reduction in fibrosis; Well-tolerated in monotherapy or combined therapy with either pirfenidone or nintedanib. FVC stability at week 12 for PBI 4050 and combined with nintedanib	Altered pharmacokinetics in PBI 4050 with pirfenidone but not with nintedanib; Mild diarrhea, headache, and nausea	[192]

Table 2. Contd. 1.

Drugs	**Mechanism of action**	**Effects**	**Side effects**	**Ref.**
BI 1015550 (PDE type 4B compound)	Phosphodiesterase 4B inhibitor	Reduction in FVC decline	Appearance of GI related symptoms	[193]
PLN 74809 / Bexotegrast	Integrins αvβ6 and αvβ1inhibitor	Reduction in decline in FVC in a dose dependent manner	No significant SAE / Mild diarrhea	[194]
PA 101 (Inhaled sodium	Anti-tussive, anti-mastocytosis and anti-asthmatic	Reduction of daytime cough in IPF at day 14	No significant SAE	[195]

cromoglycate)				
BMS-986020 / BMS-986278	Lysophosphatidic acid receptor-1 inhibitor	Significant reduction decline in FVC / Results awaited	Significant SAE (Cholecystitis) in BMS-986020	[196]
TD 139	Inhaled galectin-3 inhibitor	Lower Gal-3 expression in alveolar macrophages (dose dependent), slower decline in FVC	No aggravation in Safety and well tolerability in IPF patients and healthy subjects	[197]
TRK 250 (siRNA-based oligonucleotide)	Inhibitor of the TGF-β1mRNA	Results awaited	No information available	[198]
Dasatinib / Quercetin; DQ	Tyrosine kinase, senescent cell anti-apoptotic signal inhibitors / Flavonoid	Improvement in 6-min walk distance but no betterment in FVC	Skin irritation, GI discomfort, nausea, headache, weakness, sleep disturbance, sepsis and cholelithiasis	[199]
BG00011 (IgG antibody)	TGF-β inhibitor through targeting integrin αVβ6	Results awaited (NCT01371305)	No information available	[200]
Saracatinib	Src kinase inhibitor	Significant effect in reducing FVC decline; Ongoing investigation (Phase 1b/2a clinical trial, STOP-IPF)	GI discomfort	[201]
Treprostinil	Inhaled form of PDE-5 inhibitor	Improved in 6-min walk distance	Headache, dyspnea, nausea, dizziness, cough, and diarrhea	[202-204]
AP01 (aerosolized pirfenidone)	TGF-β and fibronectin inhibitor	Stable mean % FVC in the 100 mg twice-daily group	Less frequent adverse effects than oral pirfenidone	[205]

Adjunctive drug treatment

The efficacies of numerous economical and accessible drugs have been trialed / investigated in IPF patients as mono or combined (adjunctive with anti-fibrotic) therapy:

N-acetylcysteine (NAC)

NAC, an anti-oxidant, acts to provide a precursor of cysteine needed in the production of glutathione (GSH), an antioxidant of hydrogen peroxide (H_2O_2), and enhances the clearance of acetaminophenonfrom the system exposed to acetaminophenon overdose (paracetamol poisoning). The adjunctive oral therapy of NAC (600 mg 3 times daily) with prednisone and azathioprine one year) have shown better preserved vital capacity and DLCO [206]. The follow-up high profile study (PANTHER-IPF) with a combination of azathioprine, prednisolone and NAC, or NAC alone in IPF patients having mild to moderate lung function impairment, have shown an enhanced risk of death in the combination therapy leading to its early termination, while NAC alone has no significant benefits to preserve FVC in patients [207,208]. A post hoc secondary analysis of the trial has suggested the individual's response to NAC through the prediction of their genetic mutation (MUC5B) [209]. Several investigations with inhaled NAC as a mono or combined therapy in IPF patients require evidences still insufficient to utilize them in clinical practices [210-212].

Corticosteroids

Corticosteroids, the anti-inflammatory steroid hormones (glucocorticoids and mineralocorticoids) act through binding with their respective receptor to reduce the expressions of transcription factors activator protein-1 (AP-1) and NFκB,and the subsequent reduced productions of pro-inflammatory cytokines such as IL-1β [213]. The usages of corticosteroids alone or the combination with prednisolone as a supportive treatment in the PANTHER-IPF trial have not exhibited any promising results or any betterment in the clinical outcomes [214-216,207]. At present, corticosteroids are chiefly utilized by the clinicians on the basis of discretion in the acute exacerbation of IPF as a supported therapy [162,217].

Antacids

The exposures of lung epithelial cells to bile acids (glycochenodeoxycholic acid and chenodeoxycholic acid) associated with gastroesophageal reflux disease (GERD) or other related factors such as smoking may lead to pathogenesis of IPF through the enhanced expression of TGF-β and proliferation of fibroblast [218-220]. Three clinical trials on the treatment with a proton pump inhibitor or histamine receptor 2 (H_2) blocker in IPF patients have shown a little decrement in FVC at 30 weeks, while the recent studies for IPF patients on the antacid treatment or having anti-reflux surgery have exhibited no improved outcomes as well as better lung function [221-224,162].

Azithromycin

More advance disease in never smoked IPF patients having debilitating cough has indicated independent predictor of disease progression, lung transplantation, or time to death, while anti-fibrotic drugs may diminish cough-symptoms to some extent, but may persist in a few IPF patients [225-227]. Azithromycin, an immunomodulatory antibiotic, has been utilized successfully to treat chronic cough in COPD patients, while trialed prophylactic azithromycin (500 mg 3 times / week) has yielded disappointing outcomes on the safety and efficacy of drug to treat chronic cough in IPF patients [228,229].

Co-trimoxazole

Based on the activity of pulmonary microbiome in the initiation, progression and exacerbation of fibrosis in IPF subjects, co-trimoxazole, a sulfonamide antibiotic as prophylaxis as well as supportive therapy, has been utilized, and the drug has enhanced the quality of life and reduced the mortality having no effect on lung function [230-232]. The EME-TIPAC trial of co-

trimoxazole in patients with moderate to severe IPF has exhibited disappointed results on reducing the outcomes of transplant, time to death, or non-elective hospitalization [233].

Anti-viral treatment

Infection with virus (herpes virus, CMV, and EBV) causes diversified surfactant protein processing in AEC, resulting in endoplasmic reticulum stress and subsequent fibrosis and disease progression [57]. A phase I clinical trial has disclosed that the adjunctive treatment of valganciclovir with anti-fibrotic pirfenidone in IPF patients has shown well-tolerability with improved FVC at week 12 for a small numbers and short duration, but required the effect on pulmonaryfunction on long-term basis [234]. Another anti-viral agent, ganciclovir (twice daily for 2 weeks) at advanced IPF patients has exhibited its effectiveness in a few patients with not blinded or randomized small sample size [235].

Phosphodiesterase-5 inhibitor

Sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor and lung vasodilator, has been treated orally to IPF patients having pulmonary arterial hypertension to improve exercise capacity [236]. The treatment with sildenafil in IPF patients with right-sided ventricular dysfunction has shown significantly improved exercise capacity and quality of life, while a double blind, randomized, placebo-controlled trial of sildenafil in advance IPF patients has exhibited no benefit on 6-min walk distance [237,238]. The STEP-IPF and INSTAGE trials of the combined therapy of sildenafil and nintedanib have shown no benefits over nintedanib alone in the FVC and SGRQ between IPF subjects with or without signs of right heart dysfunctions at the baseline [239,240]. The INCREASE study with treprostinil, an inhaled form of PDE-5 inhibitor, in patients having interstitial lung disease (ILD) and associated lung hypertension, has exhibited significant

betterment in the mean FVC at 16 weeks for the short term, though needed further investigation for longer clinical trials [202].

Emerging drug targets / therapeutic strategies

A few emerging drug targets as well as therapeutic strategies are depicted below:

ROCKs

Rho kinases (ROCK1 and ROCK2), the serine/threonine kinases, regulate mainly fibroblast apoptosis/survival and mechano-transduction, while their downstream targets are linked to the regulation of stress fiber formation, cytoskeletal stability, focal adhesion assemblage and cell contractility, and biomechanical stress-inducted signal transduction to a feed-forward mechanism in stiffened ECM-fibrosis microenvironment [241,242]. Recent investigation has elucidated that the inhibition of the ROCK-activated pathway may ameliorate fibrosis in IPF subjects as an effectual therapeutic strategy [138]. A phase II study of a ROCK2 inhibitor, KD025 for treating IPF patients orally is being designed to evaluate in fibrotic diseases.

NOX4

NADPH oxidase 4 (NOX4), the TGF-β-responsive and H_2O_2-producing flavoenzyme in lung fibroblasts, may mediate myofibroblast-activation and fibrogenic responses in the biological system through generating oxidative stress, especially in aging / senescence [243-253]. The targeted treatment with a small molecule inhibitor (GKT137831) / intranasal siRNA of NOX4 may reverse the persistent fibrosis including in aged animal, though needed further specific targeted investigation of NOX4 in human IPF [254].

AMPK

AMP-activated protein kinase (AMPK), the metabolic sensor as well as cellular homeostat, may act to mediate antifibrotic action, enhance autophagy and metabolic reprogramming in aging-associated fibrosis and also to extend life span of the animals [255-258]. The anti-diabetic drug, metformin, the potent activator of AMPK, has gained interest as an attractive drug to repurpose in IPF with a favorable safety profile.

Other kinases

Though the targeting of protein kinases with tyrosine kinase inhibitors (TKIs) has been utilized in IPF patients, further investigations for other TKIs are required based on the roles of receptor tyrosine kinases and their therapeutic targetings, and the roles of many non-receptor tyrosine and serine-threonine kinases in pulmonary fibrosis [259-263,115]. Recent investigation has suggested that the restraint of the Src family of non-receptor protein kinases may improve fibrosis [264]. In addition, further studies are needed for getting information whether several kinase-inhibitors already approved or being tested for the treatment of cancers are suitable to repurpose in IPF patients.

RNA inhibition

Micro RNAs (miRNAs) and small interfering RNAs (siRNAs), the regulatory non-coding RNAs, may reduce the levels of target gene transcripts (mRNAs) through mRNAs destabilization and the decrement of translation efficiency leading to the anti-profibrotic or anti-fibrotic milieu [265-267]. The activity of miR-21is familiar to promote fibrosis, while the activity of miR-29usually as anti-fibrotic agent through the suppression of TGF-β stimulation [87,268,269]. Therefore, strategies to enhance the levels of anti-fibrotic miRNAs/siRNAs and diminish the levels of profibrotic miRNAsto treat IPF are being considered for a few miRNA/siRNA-based

therapeutics to treat pulmonary fibrosis, while novel technologies regarding the optimum delivery of miRNAs, siRNAs mimics and anti-miR oligonucleotides are being investigated [270,271].

Nanomaterials mediated targeted delivery strategies

The treatments with conventional chemotherapeutics generally face the obstacles of drug resistance, insolubility, non-specificity, toxicity and biological barriers that may aggravate the diseased state in the biological system. To overcome these barriers, the small amount of cargos may be anchored / loaded to nanomaterial delivery systems/vehicles with / without ligands as the optimized delivery formulations for their sustained delivery and release to the targeted site/s of interest maximally for availing higher therapeutic efficiency in the biological system with least side effects [272-281].

Conclusions and future perspectives

The treatments with FDA approved drugs (nintedanib and pirfenidone) ameliorate the disease state of IPF but cannot cure the disease, persisted with a few side effects. A few emerging drugs, or several other drugs are under phase II trials, or in the early stages of pre-clinical or clinical developments, respectively. Therefore, further investigations are required in the pathogenesis of IPF and its treatments such as genetic and epigenetic changes, inherent heterogeneity, stem cell dysfunction and ECM remodeling, gene corrections/editing based on CRISPR-mediated genome and epigenome, expressions of pathogenic biomarkers, pathogenic stage-based pre-clinical/clinical developments, effect of aging/senescence, new molecular mechanisms/signaling pathways, new drug targets, repurposing of drugs/cargos, and longer periods of clinical trials to avail higher efficacy, safety and tolerability in IPF patients for reducing the rate of mortality and

sufferings. Moreover, cargo-loaded nanomaterial targeted delivery may be another approach to IPF patients to get higher therapeutic efficacy in the biological system. In this context, the thorough investigations regarding the optimization of cargos in the nanomaterial formulations and functionalizations with ligands/other biomolecules, characterizations, and biological interactions in their toxicities, immune responses, biodistribution, elimination, scaled-up productions with batch-to-batch uniformity and route of administrations, are needed to avail their maximal biological effectiveness in IPF before going to clinical translation.

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