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REVIEW

Bi et al: Roles of integrins in lung fibrosis

Integrins and pulmonary fibrosis: Pathogenic roles and therapeutic opportunities

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ABSTRACT

Characterized by the formation of fibrotic scars, pulmonary fibrosis (PF) involves a complex pathogenesis, limited treatment options, and a high mortality rate. Integrins—heterodimeric transmembrane proteins composed of α and β subunits—mediate extracellular matrix remodeling and regulate the physiological functions of epithelial, mesenchymal, and immune cells through "inside-out" and "outside-in" signaling pathways. These molecules play a critical role in the initiation and progression of PF. Due to their central regulatory functions, a range of integrin-targeted therapies has been developed. However, the complex pathophysiology of PF and the structural diversity of integrins pose significant challenges to targeted treatment. In this study, we systematically delineated the signaling networks mediated by the full spectrum of integrin family members and uncovered the molecular mechanisms by which they contribute to PF through immunoregulatory pathways. We also reviewed the development of integrin-based therapies from preclinical studies to clinical trials and discussed current priorities in clinical, basic, and translational research. These insights may provide new perspectives for the diagnosis and treatment of PF.

Keywords: integrin; pulmonary fibrosis; PF; targeted therapy.

INTRODUCTION

Pulmonary fibrosis (PF) represents the final stage of a diverse array of diffuse interstitial diseases, including nonspecific interstitial pneumonia, fibrotic hypersensitivity pneumonitis (fHP), connective tissue disease-associated interstitial lung disease (ILD), and idiopathic pulmonary fibrosis (IPF). PF is pathologically characterized by the degradation of lung tissue structure, which frequently leads to impaired lung function, dysfunction in gas exchange, and ultimately, respiratory failure and mortality. According to studies, patients with IPF exhibit a 5-year mortality rate ranging from 30% to 50%, with a median survival of 2 to 3 years [1]. The median

survival for patients with fHP is reported to be 7.1 years [2]. The interaction between cells and the extracellular matrix (ECM) significantly influences the onset, progression, and prognosis of PF [3]. Integrins are heterodimeric transmembrane glycoproteins composed of two subunits, α (120-185 kD) and β (90-110 kD). In mammals, more than 20 functionally distinct integrin molecules have been identified (Figure 1). As adhesion receptors, integrins possess the unique ability to signal bidirectionally across the plasma membrane, playing a crucial role in cellular interactions with the extracellular environment[4]. In an outside-in signaling cascade, integrins specifically recognize and bind to extracellular ligands, leading to conformational changes in intracellular structural domains that recruit and activate a range of intracellular signaling molecules. The activation of these signaling pathways can regulate various biological behaviors of cells, including proliferation, differentiation, migration, and invasion. In the context of inside-out signaling, intracellular activators bind to the intracellular structural domains of integrins, inducing conformational changes. This transition allows integrins to adopt a high-affinity state, enabling them to bind more readily to extracellular ligands. This process promotes cell migration and induces changes in the extracellular environment.

In the progression of PF, integrins facilitate the proliferation, activation, and migration of pathological cells by mediating abnormal signaling among epithelial, mesenchymal, and immune cells, as well as the ECM. This process subsequently triggers the secretion of pro-fibrotic factors and leads to excessive ECM deposition. The integrin- transforming growth factor β (TGF-β) axis, integrin-mechanotransduction, and integrin-immunity axis are the primary regulatory pathways involved. For instance, αv and α2β1 integrins specifically activate TGF-β signaling. Additionally, αvβ3, αvβ5, α2β1, α4β1, and α5β1 integrins facilitate epithelial-mesenchymal transition (EMT), as well as fibroblast migration, invasion, and differentiation by transducing mechanical signals when the ECM is applied to the cells. Furthermore, integrins such as α4β1, αLβ2, αMβ2, αXβ2, and αE on the surface of immune cells synergistically enhance their pro-inflammatory and pro-fibrotic effects by activating signaling cascades, including RhoA/Rho kinase (ROCK). Therefore, modulating integrin-mediated signaling

pathways presents a promising strategy to attenuate the harmful cascade response, thereby reducing the risk of developing and progressing PF. Currently, several integrin-based therapeutic agents are being investigated in clinical studies to assess their safety, tolerability, and efficacy. Additionally, numerous lead compounds and drug candidates are undergoing preclinical studies in both academic and industrial settings, resulting in the accumulation of substantial and meaningful data. Here, we searched PubMed as the primary database using the following keyword combinations: ("integrin" OR "αvβ6" OR "αvβ1," etc.) AND ("pulmonary fibrosis" OR "IPF" OR "lung fibrosis"). We focused on the period from January 2014 to March 2025 (one month prior to the submission deadline) and included original research (both preclinical and clinical), high-quality reviews, and clinical trial registry records (https://clinicaltrials.gov/). we presented a comprehensive review of integrin-mediated pathogenesis during PF (Table 1). In particular, we summarized integrin-mediated signaling across seven specific cell types (Figure 2). We outlined the mechanisms of action of integrin inhibitors and discussed promising integrin inhibitors currently in clinical trials (Tables 2 and 3). Finally, we addressed the major challenges and future prospects for exploring mechanisms and developing therapeutics that target integrins.

ROLE OF INTEGRIN-DEPENDENT SIGNALING AXIS IN PF

Integrin/TGF-β signaling pathway in PF

The integrin αv subunit can combine with integrin β1, β3, β5, β6, and β8 subunits to form integrin molecules with diverse functions, which are central to the development of fibrosis. Researchers have found that αv integrins activate latent TGF-β, a known classical pro-fibrotic cytokine, to promote the development of PF in several different experimental models[5]. Scholars have discovered that galectin-3 binds to αvβ1 integrin and TGFβRII in a glycosylation-dependent manner, promoting the spatial co-localization of the two. This interaction enhances TGF-β1 activation and its downstream signaling pathways [6]. In lung fibroblasts, αvβ3/β5 integrins interacted

with periostin and activated the TGF-β/Smad3 signaling pathway, contributing to the up-regulation of the expression of lung fibrosis-associated molecules, such as SERPINE1, CTGF, IGFBP3, IL - 11 [7]. Integrin αvβ6 interacts with TGF-β to exert physiological and pathological effects. TGFβ1 regulated the expression of the ITGB6 gene through the smad signaling pathway, which subsequently influenced the expression of integrin αvβ6[8]. The activation of the αvβ6/TGF-β pathway is one of the mechanisms that promote TGF-α-induced pleural fibrosis, as well as PF induced by influenza infection[9,10]. Further studies demonstrated that OGN knockdown and increased levels of developmental endothelial motif-1 (Del-1) effectively inhibited the binding of integrin αv, particularly integrin αvβ6, to latency-associated peptide (LAP), thereby suppressing the activation of the TGF-β/Smad signaling pathway[11,12]. Following an injury, IRE1α was upregulated and modulated the quantity and function of injury-associated transient progenitor cells (DATPs). It enhanced the expression of αvβ6 in DATPs and contributed to lung fibrosis through the activation of TGF-β [13]. Studies have demonstrated that thrombin can promote fibrosis through the protease-activated receptor-1 (PAR1)/ αvβ6/TGF-β pathway. In vitro experiments have shown that PAR1 induces αvβ6-mediated TGF-β activation via RhoA and ROCK, thereby providing a novel target for lung fibrosis[14,15]. ITGB8 gene was significantly downregulated in IPF dogs. Following stimulation with TGF-β, integrin β8 expression was decreased in MRC-5 cells [16]. TGF-β may play a role in the progression of IPF in dogs by modulating the expression of integrin β8.

Some researchers have investigated the heterogeneity of mesenchymal stromal cells and their role in the process of PF in greater depth. Sciurba et al. demonstrated that ITGAV promoted type 17/TGF-β-driven PF as evidenced by reduced collagen deposition in a bleomycin(BLM)-induced ITGAV$^{flox/flox}$ (Pdgfrb-cre+) mice[17]. Yi et al. found reduced secretion of TGF-β1 activity, suppressed expression of p-Smad2/3, and attenuated radiographic lung fibrosis in ITGAV$^{loxP/loxP}$;Pdgfrb-Cre mice receiving radiation[18]. Interestingly, α-SMA-directed deletion of αv integrin did not protect mice from BLM-induced PF, whereas PDGFRβ-Cre-mediated deletion of αv integrin

did. These results suggest that α-SMA-positive cells represent only a subset of PDGFRβ-positive cells in PF and are not the primary cell type involved in αv integrin-mediated TGFβ activation[19].

Integrin-mediated mechanotransduction in PF

The mechanism of integrin-mediated mechanotransduction in PF involves multiple levels of cellular signaling regulation. In PF, various integrins centered on the αv subunit facilitate connections to the actin cytoskeleton by recognizing the RGD sequence in the LAP. This integrin-mediated mechanical tension acts on the LAP-TGF-β complex, inducing a conformational change that leads to the rupture of the disulfide bond between LAP and TGF-β. Consequently, active TGF-β molecules are released from the complex, initiating downstream signaling pathways. When lung tissue is damaged, ECM components such as collagen and fibronectin (FN) increase, resulting in heightened tissue stiffness. Integrins function as transmembrane receptors that link the ECM to the intracellular cytoskeleton, allowing for the sensing of mechanical signals (e.g., ECM stiffness and tensile forces) and their conversion into biochemical signals. Integrin-mediated mechanotransduction signaling pathways, involving focal adhesion kinase (FAK), Src family kinases, and Rho GTPases, facilitate fibroblast cell migration, invasion, and transformation. This process is further exacerbated by increased ECM secretion, creating a vicious cycle. In response to platelet-derived growth factor BB (PDGF-BB) stimulation, FAK binded directly to integrin β1, and fibroblasts migrated toward FN. α5β1 and α4β1 were the primary integrins involved in FAK-mediated fibroblast migration[20]. The integrin-β1/FAK/ERK1/2 signaling pathway facilitated the transformation of fibroblasts into myofibroblasts within a fibrotic ECM microenvironment[21]. It was found that senescent fibroblasts and fibroblasts from patients with IPF (IPF-HLFs) secreted more extracellular vesicles(EVs), which carried more FN, and that interactions with α5β1 integrins on fibroblasts activated signaling pathways associated with invasion, including FAK and Src family kinases[22]. Interestingly, IPF-HLFs overexpressed urokinase-type

fibrinogen activator receptor (uPAR), resulting in a higher migratory capacity of these cells. Upon binding of uPAR to the urokinase receptor binding domain, the integrin signaling pathway switched from the lipid raft-independent FAK pathway to the lipid raft-dependent caveolin-Fyn-Shc pathway. This signaling pathway switch is a novel pathway for high migration of fibrotic fibroblasts in IPF patients[23]. As a mechanosensing molecule, α6-integrin regulates the invasion ability of myofibroblasts and fibroblasts in response to matrix sclerosis. The sclerotic matrix activated the c-Fos/c-Jun transcriptional complex through a ROCK-dependent mechanism, which increased the expression of α6-integrin, mediated MMP-2-dependent hydrolysis of basement membrane collagen IV, and promoted myofibroblast invasion[24].

Increased matrix stiffness and cellular stretch activate integrin β3, which plays an important role in vascular remodeling, as found by modifying a computational network model of pulmonary artery adventitial fibroblasts (PAAFs) [25]. During fibrosis, αvβ3 integrin enhanced fibroblast activation and mechanical conduction by binding to a temporary matrix such as FN [26]. In addition, periostin / integrin αvβ3 played a key role in lung fibroblast proliferation [27]. Thy-1, a cell surface glycoprotein, is able to physically couple to inactive αvβ3 integrins, resulting in reduced adhesion of integrins to FN. Further studies indicated that the lung environment of mice deficient in Thy-1 facilitated the sustained activation of αvβ3 integrins in fibroblasts, resulting in the persistence of a pro-fibrotic myofibroblast phenotype in vivo[28,29]. Normally, integrins bind to high-affinity ligands and induce Rho signaling and rigidity sensing under physiological conditions. Deletion of Thy-1 caused rapid aggregation and elevation of c-Src signaling downstream of integrin αvβ3 and induced enhanced and stiffness-insensitive RhoA activity, leading to activation of lung fibroblasts as well as contraction of the collagen matrix [30]. In addition, Src kinase interacted primarily with integrins αvβ5 and αvβ3 to regulate fibroblast migration [31].

Integrin-mediated inflammation and fibrosis in immune cells

The inflammatory response plays a crucial role in the early stages of PF [32]. Mice

that received intratracheally administered lipopolysaccharide (LPS) showed increased expression of very late antigen-4 (VLA-4, α4β1) in their lungs. Furthermore, VLA-4 was significantly correlated with the expression of several inflammatory markers, including nitric oxide synthase-2 (NOS-2), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) [33]. Myeloid ATP-binding cassette (ABC) cholesterol transporter (ABCG1) deficient multiwalled carbon nanotubes (MWCNTs) mice exhibited efferocytosis, as indicated by increased expression of MFG-E8 and integrin β3. This response can aggravate the inflammatory response in the lung and continue to produce pro-fibrotic cytokines such as TGF-β [34]. It was shown that the expression levels of integrin-inflammasome pathway genes (ITGAM, ITGAL, ITGB2L, ITGB2, NAIP6 and NAIP5) were significantly increased in lung tissues in high-fat diet (HFD) fed mice. Deletion of p16 down-regulated multiple integrin pathway genes (e.g., ITGA4, ITGA7, ITGAL, ITGAM, ITGAX, ITGB2 and ITGB2L). These results suggested that p16 may affect the progression of PF by regulating the integrin-inflammasome signaling pathway[35].

In addition, integrins promote the abnormal secretion of pro-fibrotic mediators and induce pathological deposition of the ECM by modulating multiple signaling pathways in immune cells, such as macrophages, neutrophils, and T lymphocytes. Studies have found that long-term pulmonary complications in patients following COVID-19 are associated with elevated concentrations of sITGaM and sITGb2[36]. Database-based analyses revealed elevated levels of gene expression of RHOA, ITGB2, and ITGAM in alveolar macrophages, indicating mechanical activation of lung macrophages within the highly remodeled fibrotic tissue microenvironment of human IPF lungs[37]. The investigators found that BLM-induced α4 mutant mice had reduced PF and defective M2 macrophage differentiation. Integrin α4β1 may promote alternative activation of pro-fibrotic phenotypic M2 macrophages through activation of Rac2[38]. It has been demonstrated that hypoxia increases the expression of αM and αX integrin subunits in neutrophils, promotes the release of neutrophil extracellular traps (NETs), and fosters a pro-fibrotic environment. The dose-responsive release of NETs induced by αMβ2-

specific agonists strongly indicates that integrin activation serves as a crucial mechanistic link between hypoxia and NET generation. The co-localization of NETs with mesenchymal remodeling suggests that sustained NET release may directly exacerbate fibrosis [39].Through repeated exposure to fungal antigens, the researchers observed two distinct subpopulations of CD4+ TRM cells, which played opposing roles in PF. CD4+ TRM cells characterized by $CD69^{hi}CD103^{lo}$ promoted lung fibrosis by producing effector cytokines, including IL-4, IL-5, IL-13, and IL-17A. In contrast, CD4+ Treg cells marked by $CD69^{hi}CD103^{hi}$ expressed genes such as Foxp3, which inhibited the fibrotic response[40].

Fibrocytes are circulating mesenchymal precursor cells derived from hematopoietic stem cells that can be recruited to fibrotic areas to produce ECM components[41]. Periostin is a matrix protein produced by fibrocytes that regulates the interaction of cells with ECM components[42]. It was discovered that β 1 integrin levels in fibrocytes (CD45+col 1+) of periostin-deficient mice were considerably decreased and lung fibrosis was attenuated after BLM treatment. Periostin may activate fibroblasts through the β1 integrin signaling pathway in a paracrine or autocrine manner, release CTGF and other pro-fibrotic mediators, and promote the synthesis of collagen I [43]. Pilling et al. showed that TNF-α-stimulated fibroblasts secrete lumican to promote fibrocytes differentiation. The integrins α2β1, αMβ2, and αXβ2 are essential for lumican-induced fibrocytes differentiation [44].

THE ROLE OF INTEGRIN MOLECULES IN PF

Integrin α1β1-α11β1

The integrin subunit β1 can form heterodimers with integrin subunits α1–α11 and αv, which have several fibrogenic functions in the PF process [45]. It was found that integrin β1 was significantly expressed in the fibrotic foci of fibrotic animal models, demonstrating upregulation at various stages (2 and 4 weeks) [46,47]. Cairns et al. discovered that at one year of age, ELK1-deficient mice developed spontaneous lung

fibrosis, which was accompanied by a marked decrease in ITGB1 mRNA and an increase in collagen deposition [48]. LI et al. discovered that ILK/Snail pathway protein expression was reduced and EMT was enhanced in BEAS-2B cells that had ITGB1 knockdown and silica addition [49].In lung fibroblasts, MWCNTs induced tissue inhibitor of metalloproteinase 1 (TIMP1) to form a complex with CD63 and integrin β1, activating the Erk1/2 pathway to promote cell proliferation. This discovery clarified the molecular mechanism underlying pro-fibrosis[50].

Integrin α1β1

Altered expression of integrin α1, a collagen receptor, may affect cellular interactions with the ECM. Adenoviral vector and BLM were demonstrated to significantly upregulate integrin α1 mRNA expression, causing lung fibrosis, inflammation, and damage in mice[51]

Integrin α2β1

There was a substantial two-fold increase in ITGA2 expression in IPF samples, indicating a very strong correlation between integrin α2 and PF[52]. It has been demonstrated that mice with fibroblast-specific deletion of α2 integrins exhibit protection against fibrosis. Further studies indicate that collagen I enhances TGF-β-mediated activation of collagen synthesis (COL1A1, ACTA2) and promotes myofibroblast activation through the α2β1 integrin in fibroblasts. Collagen I/DDR2 signaling negatively regulates the expression of α2 integrin, suggesting that α2 may function as a compensatory receptor to sustain fibrosis in the absence of DDR2[53]. The α2 integrin in alveolar epithelial cells (AEC) demonstrated potential for bidirectional regulation of PF. Treatment with methotrexate (MTX) markedly raised ITGA2's mRNA and cell surface expression in A549 cells, raising the mRNA expression levels of genes linked to EMT [54]. However, mice with AECs-specific deletion of α2 integrins exhibited increased lung injury and a more severe fibrotic response[55]. Molecular mechanisms indicate that collagen I inhibits caspase-3/7 activation and apoptosis in AEC cells through the α2β1 integrin pathway. Collectively, these findings suggest that the function of α2 integrins is highly dependent on cell type and microenvironment, including factors such as stromal composition and pathological

stage. Variations in downstream signaling pathways can result in seemingly contradictory phenotypes.

Integrin α3β1

ILNEB syndrome includes ILD, nephrotic syndrome and epidermolysis bullosa. Two patients carrying two novel ITGA3 missense mutations in exons 3 and 6 exhibited severe PF and skin problems without nephrotic symptoms and survived to the ages of 9 and 13 years[56].

Integrin α5β1 and α8β1

ITGA5 is highly expressed in IPF fibroblasts and is particularly enriched in fibroblast foci. TNF-α secreted by IPF fibroblasts increased ITGA5 expression in normal fibroblasts and activated the NF-κB pathway, leading to an increased capacity for adhesion and migration on FN [57]. Furthermore, integrin α5 expression is dynamic during mesenchymal cell differentiation. During the differentiation of stromal progenitor cells (SPCs) into myofibroblasts, the expression of genes such as FN1, Col1a1, and ITGA5 was upregulated; however, the proportion of ITGA5-producing cells decreased with cell maturation[58]. It was further demonstrated that silencing ITGA5 led to a decreased proliferation rate and migration capacity, increased cell death, and induced the transformation of fibroblasts to myofibroblasts in IPF-HLFs. This was accompanied by an increase in ITGA8, FN1, TGF-β, α-SMA, and collagen I levels[59]. ITGA8 is primarily distributed in fibrotic regions where dense collagen is deposited and elastic fibers are abundant [59,60]. However, in the BLM-induced PDGFRβ-Cre;ITGA8$^{flox/flox}$ mice, the deletion of ITGA8 did not lead to significantly more severe fibrosis. ITGA8 expression in PDGFRβ+ cells does not seem to play a major biological role in lung fibrosis[61].

Integrin α6β1

Amphiregulin (AREG) is a ligand for the epidermal growth factor receptor that plays a crucial role in tissue repair and fibrosis. Recombinant AREG in bone marrow-derived CD11c+ cells significantly increased the expression of α6 integrins on lung fibroblasts, enhanced lung fibroblast motility and invasiveness [62]. In silica dust-induced PF mice and TGF-β1-stimulated fibroblasts, the expression of miR-542-5p was

downregulated, while ITGA6 mRNA levels were significantly increased. Further molecular mechanisms indicated that miR-542-5p inhibited the expression of ITGA6 by directly targeting its 3'-UTR and suppressed the proliferation and migration of fibroblasts [63].

Integrin α10β1

Integrin α10 mRNA levels were significantly elevated in rats with BLM-induced PF. Inhibition of macrophage migration inhibitory factor (MIF) can decrease the expression of ITGA10, suggesting it may serve as a potential therapeutic target for PF[64].

Integrin α11β1

The expression level of ITGA11 was significantly upregulated in samples from patients with IPF[52]. Further study demonstrated that ITGA11 expression was also significantly elevated and co-localized with α-SMA-positive myofibroblasts in lung tissues from IPF patients [65].

Integrin αvβ3 and αvβ6

Integrin αvβ3

The β3 subunit can bind to αv and αIIb subunit to form the αvβ3 and αIIbβ3 molecules. Integrin αvβ3 was significantly elevated in different subtypes of human ILD and in BLM-induced PF in mice [66]. In vitro experiments showed that lipopolysaccharide (LPS) inhibited autophagy in lung fibroblasts and promoted lung fibrosis formation by reducing the binding of Thy-1 to integrin β3 and activating the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) pathway[67]. Downregulation of integrin β3 attenuated mechanical ventilation(MV)-induced aerobic glycolysis and subsequent PF, accompanied by a decrease in pyruvate kinase M2 (PKM2) and lactate dehydrogenase (LDHA) in lung tissue and lactate levels in BALF[68]. Interestingly, binding of αvβ3 integrin to fibronectin induced a shift in pericytes to a myofibroblast phenotype in BLM-treated mice [26].

Integrin αvβ6

αvβ6 is predominantly expressed in epithelial cells. Elk1 dysregulation is observed in the epithelium of patients with IPF. In vitro experiments demonstrated that Elk1 protein binding to the ITGB6 promoter inhibited the transcription of the ITGB6 gene, leading to a reduction in the expression of integrin αvβ6[69].

INTEGRIN-BASED THERAPIES

Therapeutic agents that target integrins have been actively developed due to their diversity and potential for targeted therapy. Currently, seven medications that target integrins have been successfully marketed [70]. Unfortunately, there are no approved integrin-targeted drugs specifically for PF. However, the favorable therapeutic efficacy of integrin drugs observed in both clinical and preclinical studies offers a compelling example and instills confidence in the use of integrin-based therapy for PF. A variety of integrin therapeutics, including small molecules, antibodies, synthetic mimetic peptides, and natural chemicals, have been evaluated and developed (Figure 3).

Clinical studies of targeted integrin therapy

GSK3008348 is the first αvβ6 integrin inhalation inhibitor developed for the treatment of IPF. In human lung epithelial cells, GSK3008348 induces rapid internalization and lysosomal degradation of the αvβ6 integrin. It binds to αvβ6 with high affinity and effectively reduces downstream pro-fibrotic TGFβ signaling to normal levels in human IPF lungs, demonstrating good tolerability. Positive effects and safety of GSK3008348 were observed in a Phase Ib clinical study for IPF. However, GlaxoSmithKline terminated the development of GSK3008348 in 2018, primarily due to the failure of its Phase II clinical trial (NCT03069989) to achieve the anticipated efficacy goals, which may have been accompanied by a thorough evaluation of its commercial value [71]. BG0001 is an αvβ6 monoclonal antibody that has demonstrated antifibrotic activity in mouse assays. In the Phase IIb clinical study, The least squares

mean of forced vital capacity (FVC) was found to be -0.097 L in the BG0001 group compared to -0.056 L in the placebo group (p = 0.268). A higher percentage of patients in the BG0001 group exhibited exacerbation of PF on chest CT scans (44.4% vs. 18.2%), as well as serious adverse events [76]. Researchers believe this may be attributed to the long half-life and high targeting efficacy of the antibody, which could lead to excessive suppression of TGFβ1 levels, subsequently triggering acute exacerbations. The development of BG0001 was ultimately terminated early in 2019 due to severe side effects[72]. Development of IDL-2965 (NCT03949530), a pan-αv integrin inhibitor for IPF, was also terminated in 2021 due to operational challenges and emerging non-clinical data[73,74].

Bexotegrast (PLN-74809) is an oral small molecule inhibitor that targets αvβ6 and αvβ1 integrins. In studies utilizing precisely cut lung slices derived from lung tissue of IPF patients, PLN-74809 significantly reduced type I collagen gene expression and TGF-β signaling[75]. In 2022, Pliant Therapeutics, Inc. (PLRX) reported positive results from the INTEGRIS-IPF Phase IIa study. The results indicated a slight reduction in the decline of FVC in the PLN-74809 group compared to the placebo group. Alterations in potential prognostic biomarkers (ITGB6 and PRO-C3) support a dose-dependent effect of the study drug. No drug-related serious adverse events or deaths were reported. PLN-74809 is considered the most promising candidate for success in clinical trials.

Preclinical studies on integrin-based therapy

Targeted integrin therapy

pan-αv

Cilengitide is a potent integrin antagonist. The IC50 values of cilengitide against the integrins αvβ3, αvβ5, and α5β1 were 0.61, 8.4, and 14.9 nM, respectively [76]. Cilengitide inhibited radiation-induced excess collagen and α-SMA production in vivo and reduced the adhesion of lung fibroblasts to fibronectin and hyaluronan in vitro by inhibiting the integrin αv/TGF-β1/Smad 2/3 signaling pathway [18]. Additionally, cilengitide inhibited LPS-induced activation of the PI3K-Akt-mTOR pathway and

suppressed autophagy in lung fibroblasts [67]. In MV mice, cilengitide decreased levels of PKM2, LDHA, and lactate, while also reducing collagen deposition [68].

CWHM-12 is a potent inhibitor of αv integrins, specifically targeting αvβ8, αvβ3, αvβ6, and αvβ1, with IC_{50} values of 0.2, 0.8, 1.5, and 1.8 nM, respectively [77]. CWHM-12 significantly inhibited the expression of fibrotic genes and the secretion of proteins, such as Col1a1 and Wisp1, in a rat precision-cut lung tissue sections (PCLS) fibrosis model[78]. CWHM-12 attenuated the mechanical stretch-induced activation of TGF-β1 and the phosphorylation of Smad2/3 in fibrotic lung strips across a range of inhibitory concentrations [79].

Zhang et al. identified a group of integrin antibodies, MK-0429 and Ab-31, that exhibit unique cross-reactivity in both human and mouse models and demonstrate significant effects in inhibiting PF. In mice, MK-0429 significantly inhibited the progression of PF induced by BLM. In lung fibroblasts derived from patients with IPF, Ab-31 markedly reduced the expression of αSMA. MK-0429 demonstrated strong inhibition of human integrins αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, and α5β1, with IC_{50} values of 0.46, 0.15, 9.9, 3.8, 58.3, and 17.3 nM, respectively. Additionally, Ab-31 significantly inhibited mouse integrin-mediated cell adhesion for αvβ1, αvβ3, and αvβ5, with IC_{50} values of 1.5, 1.0, and 5.6 nM, respectively[80].

αvβ1, αvβ3 and αvβ6

Reed et al. developed a potent and highly specific small-molecule inhibitor of αvβ1, known as C8, which significantly reduced collagen deposition in mice with BLM-induced PF[81]. CP4715 is a strong inhibitor of integrin αvβ3 and effectively inhibits the proliferation of IPF fibroblasts [27]. In addition, CP4715 reduced smad3 activation and PF in BLM-induced mice [7]. Cyclo(-RGDfK) is a potent and selective inhibitor of αvβ3 integrins, exhibiting an IC_{50} value of 2.25 nM [82]. Cyclo(-RGDfK) inhibited the transition of pericytes to myofibroblasts and reduced α-SMA expression in fibronectin-coated Myh11 lineage-positive cells [26]. Anindya Roy et al. designed B6_BP_dslf to selectively inhibit αvβ6-mediated TGF-β activation, achieving IC_{50} values of 1.84 nM for αvβ6 and 32.8 nM for TGF-β. In a human lung-like organ model, B6_BP_dslf significantly reduced pro-fibrotic markers, including α-SMA and

fibronectin levels, thereby demonstrating its anti-fibrotic effects [83].

αLβ2 and αMβ2

Leukocyte functional antigen-1 (LFA-1), an integrin present on the surface of leukocytes, interacts with hyaluronic acid receptors such as CD44 and TLR2, playing a crucial role in the expression of inflammatory cytokines. Lovastatin exhibits a unique ability to bind to LFA-1. It significantly inhibited the low molecular weight hyaluronic acid (LMW HA)-induced expression of MIP-1α and other inflammatory cytokines in mouse alveolar macrophages, while also reducing fibrosis in a BLM lung injury model [84]. Furthermore, the application of blocking antibodies against integrin αM (α-αM) and αMβ2 (α-αMβ2) induced the dedifferentiation of monocytes into myofibroblasts and significantly decreased the profibrotic secretion products produced by myofibroblasts. The conjugation of decorin's collagen-binding peptide (CBP) to these blocking antibodies, such as CBP-α-αM and CBP-α-αMβ2, enhanced the concentration of the antibodies in fibrotic lungs and inhibited the progression of lung fibrosis [85].

α2β1, α3β1, α5β1 and α6β1

BTT3033, an integrin α2 inhibitor, significantly inhibited the differentiation of fibrocytes induced by lumican[44]. It was demonstrated that under specific experimental conditions, TC-I 15 inhibited α2β1 with an IC_{50} value of 0.4 μM for GLOGEN peptides and 26.8 μM for GFOGER peptides[86]. The expression of collagen I and α-SMA was reduced in fibroblasts treated with TC-I15 [53]. The ITGA2 inhibitor E7820 was able to inhibit MTX-induced EMT-associated phenotypic changes, such as cellular morphology and the expression of α-SMA [54]. Integrin α3 plays a key role in the differentiation of monocytes into myofibroblasts. Similar to α-αMβ2, α-α3 reversed myofibroblast differentiation and reduced the secretion of profibrotic products[85]. The antagonist of integrin α5β1, ATN-161, is a short five-amino-acid peptide derived from the synergistic region of fibronectin and has an c value of 4.2 uM[87]. The administration of ATN-161 decreased the expression levels of fibronectin and ETS-1, thereby inhibiting the progression of EMT in A549 cells treated with organic solvent-soluble PMs (OPMs) [88]. ATN-161 also attenuated paraquat (PQ)-induced PF and improved survival in rats[21]. Echistatin, an integrin β1 inhibitor, can

impede EMT and lung fibrosis by obstructing various stages of the integrin β1/ILK/PI3K signaling pathway [89].

Non-specific therapy based on integrins

In macrophage-lung fibroblast co-culture microtissues, the inhibition of ROCK2 and integrin αMβ2 by PFD prevented macrophages from undergoing mechanical activation and reduced their capacity to adhere, align, and spread. This inhibition subsequently affected M2 polarization and pro-fibrotic activity [90]. Triptolide is a diterpenoid compound derived from the traditional Chinese medicine Tripterygium wilfordii Hook.f. The study demonstrated that triptolide may inhibit the expression of integrin-β1, prevent the phosphorylation of FAK, inhibit the translocation of YAP1 from the cytoplasm to the nucleus, and attenuate the progression of fibrosis[46]. Artemisinins have potential clinical applications in regulating immune responses and inhibiting inflammation. They inhibited the activity of nuclear factor-κB (NF-κB) by targeting various receptor-coupled signaling pathways, including β3 integrin, and downregulated the expression of numerous genes regulated by NF-κB, such as cytokines, chemokines, and immune receptors [91]. IL-32γ reduced the expression of fibrosis markers by inhibiting the activation of the integrin-FAK-paxillin signaling axis [92]. In aged mice treated with young donor adipose-derived mesenchymal stem cells (yASCs), the expression of αv-integrin mRNA in the lungs was significantly reduced, leading to a decrease in lung fibrosis [93]. PD29 is a 29-amino acid peptide known for its high biological activity and relatively low toxicity, which prevents significant accumulation in the body. PD29 may inhibit the onset and progression of PF through mechanisms such as antiangiogenesis, inhibition of matrix metalloproteinase activity, and suppression of integrin activity. Notably, PD29 significantly reduced the expression levels of integrin αvβ3 and αE, thereby inhibiting the development of PF in rats with BLM induced PF [94].

DISCUSSION

PF is a multifactorial, end-stage lung condition associated with ILD, characterized

by pathological manifestations such as fibroblast proliferation and ECM deposition. This process leads to the destruction of lung structure and a significant loss of function, posing a major threat to global health.

In our exploration of the underlying mechanisms, we discovered that the changes in integrins associated with PF are influenced by time, spatial factors (cellular microenvironment), and cell type, resulting in distinct functional manifestations. Notably, α4β1 integrins demonstrate time-dependent dual functions in PF, exhibiting pro-inflammatory effects in the early stages and pro-fibrotic effects in the later stages. During the transition of fibroblasts into myofibroblasts, we observed a switching phenomenon between integrin α5β1 and integrin α8β1, which conferred spatial characteristics to these integrins in the context of PF. The expression of α2β1 integrins in PF is influenced by ligand proteins in the ECM (laminin versus collagen I) and by cell type (epithelial versus fibroblast). However, the spatiotemporal properties of α2β1 integrin may be associated with the preferential regulation of distinct downstream pathways in various models. In addition, functional compensatory and alternative pathways are present within the integrin family. Both integrin αv and integrin α8 were found to be elevated on PDGFRβ-positive cells. However, knockdown of integrin αv demonstrated a significant inhibitory effect on the progression of PF, while knockdown of integrin α8 had a comparatively lesser impact. This indicates that ITGAV plays a more critical pro-fibrotic role than ITGA8 within the PDGFRβ-positive cell population. Furthermore, the targeted deletion of αv integrins using α-SMA-Cre did not protect mice from BLM-induced PF. In contrast, deletion of αv integrins mediated by PDGFRβ-Cre did provide protection. This indicates that αv integrins, which preferentially target PDGFRβ^{+} precursor cells rather than α-SMA^{+} terminal cells, may offer greater potential for therapeutic intervention in PF. Furthermore, the role of immune cells in the pathogenesis of PF through the integrin pathway is not yet fully understood. Future research should investigate the effects of immune cells on lung epithelial cells and fibroblast lineage cells using co-culture techniques.

The current translational failure of multiple integrin inhibitors from preclinical to

clinical studies highlights the systemic challenges associated with applying this target to IPF therapy. We believe that the mechanisms underlying these translational failures, as well as the potential breakthroughs in future therapeutic strategies, encompass several key aspects, including target validation, biomarker development, and the design of drug delivery strategies.

Currently, the BLM-induced model commonly used in preclinical studies has significant limitations. This model exhibits a self-limiting fibrotic process following acute injury, which fundamentally differs from the chronic progressive characteristics of human IPF. Looking forward, optimization of the model could involve simulating the pathomechanical microenvironment using a dynamic matrix stiffness modulation system, utilizing aged mice or genetically modified models that more accurately reflect the chronic progressive features of human IPF, and constructing lung-like organs derived from IPF patients to evaluate the efficacy of integrin inhibitors.

Second, existing mechanistic studies are primarily limited to phenotypic correlation analyses of integrins and fibrotic progression, while the validation of causal associations through gene editing technologies remains inadequate. Notably, although targeting specific integrins, such as αvβ6, has demonstrated antifibrotic potential in preclinical models, the efficacy of single-target inhibition may be diminished by the activation of compensatory signaling pathways within the complex pathological microenvironment of IPF. In the future, it will be essential to develop more conditional knockout models to establish the causal relationship between integrins and PF. Combining integrin inhibitors with inhibitors of key downstream signaling molecules may provide a synergistic approach to effectively inhibit fibrosis.

In addition, current clinical trial designs have not established a biomarker stratification system based on integrin expression profiles and lack precise intervention strategies to address spatiotemporal heterogeneity and differences among cell types. This oversight may result in a heterogeneous dilution of efficacy signals. Elevated levels of integrin αvβ6 may be beneficial for patient stratification in clinical trials aimed at assessing the efficacy of new therapies [95]. By comparing integrin levels in the

blood or bronchoalveolar lavage fluid of patients with different ILD types, selecting patients who are more reliant on the integrin mechanism may enhance the success of clinical trials. Practical challenges in integrating biomarkers into clinical decision-making for PF must be addressed. Standardized workflows should be developed, encompassing sample collection, isolation methods, sample processing, and follow-up testing. Additionally, it is essential to address potential sources of bias in data analysis. Combining spatial transcriptomics with single-cell sequencing to identify cellular subtypes exhibiting high integrin expression, and exploring their specific roles in various temporal and spatial microenvironments, could offer new avenues for the treatment of PF. In conjunction with the findings from current mechanistic studies, future research could focus on the development of integrins such as α4β1, α5β1, α8β1, and α2β2.

Finally, integrin inhibitors encounter the safety challenge of off-target effects. For instance, vedolizumab, eptifibatide, and tirofiban have been successfully marketed for the treatment of Crohn's disease and acute coronary syndromes[70]. These medications are administered intravenously and are associated with systemic toxicities, including viral infections[96], hepatotoxicity[97], and an increased risk of bleeding[98]. In PF, the use of inhalation formulations facilitates localized action within the lungs, enhances targeting, and minimizes systemic exposure, thereby reducing toxicity. However, the development of inhalers presents challenges, as they require precise particle size and stability to ensure effective drug deposition in the lungs. Additionally, improper use by patients can compromise efficacy, and the metering accuracy of inhalers is often inferior to that of systemic administration. Drug delivery systems, as an emerging technological platform, have demonstrated significant potential in the treatment of PF. This is attributed to their precise targeting capabilities, enhanced drug specificity and bioavailability, prolonged duration of action, and reduced toxic side effects [99]. The study synthesized and in vitro bioassessed three new covalent conjugates consisting of the small cyclic peptide c (AmpLRGDL) recognized by the αvβ6 integrin and the tyrosine kinase inhibitor nintedanib. Selective uptake of the conjugates by cells

overexpressing αvβ6 integrins via αvβ6 integrin recognition enhanced the effect of nintedanib [100]. In the field of liver fibrosis treatment, bionanoparticles utilizing hepatic stellate cell (HSC) membrane camouflage (HSC-PLGA-BAY) significantly enhance the enrichment efficiency of the antifibrotic drug BAY 11-7082 in activated HSCs. This enhancement is achieved through active targeting mediated by homologous adhesion molecules, such as integrin αvβ3 and N-cadherin, present on the membrane surface. This approach offers novel insights into integrin-related targeting strategies[101].

CONCLUSION

By enhancing our understanding of integrin specificity across various cell types, their interactions with TGF-β and other signaling pathways, and their engagement with the extracellular environment, we aim to translate these new insights into innovative therapeutic approaches. Integrin-based therapy for PF necessitates a combination of targeted inhibition, precision stratification, and innovative delivery technologies, emphasizing the importance of balanced combinatorial strategies that prioritize safety. Future advancements may depend on thorough analyses of the spatiotemporal dynamics within the fibrotic microenvironment, as well as on interdisciplinary collaborations.

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Table 1. Potential mechanisms of integrin-induced PF

Integrin subunits and molecules	Models	In vivo/in vitro	Main mechanisms	References
αv	cigarette smoke extract -induced and αv-silenced AECs	In vitro	Activated TGF-β1↓	[5]
αv	OGN-knockdown lung fibroblasts treated with or without TGF-β.	In vitro	The binding of integrin αv to LAP↓, p-Smad2↓	[11]
αv	BLM-induced ITGAV $^{flox/flox}$ (Pdgfrb- cre+) mice	In vivo	HYP↓	[17,19]
αv	ITGAV$^{loxP/loxP}$;Pdgfrb-Cre mice receiving radiation	In vivo	Activated TGF-β1↓, p-Smad2/3↓	[18]
β1	BLM-induced mice	In vivo	β1↑	[46]
β1	PQ-induced-PF rats	In vivo	β1↑	[47]
β1	Elk1-knockout mice	In vivo	β1↓, spontaneous fibrosis↑	[48]

β1	BLM-induced mice, accompanied by loss of periostin in fibrocytes; periostin -/- fibrocytes	In vivo and in vitro	β1, CTGF, collagen I↓	[43]
β1	SiO_2-induced and ITGB1-knockout BEAS-2B cells	In vitro	E-cadherin↑, vimentin↓, ILK, Snail↓	[49]
β1	MWCNT-induced PF in mice; lung fibroblasts	In vivo and in vitro	TIMP1/CD63/integrin β1↑, pErk1/2↑, lung fibroblast proliferation↑	[50]
β1	PDGF-BB induced lung fibroblasts with integrin β 1 blocking antibody	In vitro	Fak activation↓, fibroblast migration on FN↓	[20]
β1	Fibroblasts in fibrotic ECM	In vitro	Integrin-β_1/FAK/ERK1/2↑, fibroblasts transforming into myofibroblasts	[21]
β3	ABCG1-deficient MWCNT mice	In vivo	MFG-E8, β3 in BALF cells↑	[34]
β3	LPS-induced β3-specific shRNAs in	In vitro	Activation of the PI3K-Akt-mTOR↓,	[67]

	lung fibroblasts		LC3II/LC3I↓, p62↑	
β3	Integrin β3-deficient MV mice	In vivo	PKM2, LDHA, lactate, collagen deposition↓	[68]
α1	Mice induced by adenoviral vector and BLM	In vivo	α1↑, fibrosis↑	[51]
α2	IPF patients	In vivo	α2↑	[52]
α2	DDR2-deficient mice; lung fibroblasts lacking Col1a1	In vivo and in vitro	α2↑, fibrosis↓	[53]
α2	TC-I-15-treated lung fibroblasts	In vitro	Collagen I and α-SMA↓	[53]
α2	Floxed integrin α2 mice crossed with Col1a2-creERT mice	In vivo	Fibrosis↓	[55]
α2	Floxed integrin α2 mice crossed with SPC-rtTA/tetO-Cre mice	In vivo	Fibrosis↑	[55]
α2	MTX-A549 cells	In vitro	α2↑, mRNA of EMT-related genes↑	[54]
α2, αMβ2 and αXβ2	Lumican-induced PBMC pretreated with α2, αM, αX, and β2	In vitro	Lumican-induced fibrocytes differentiation↓	[44]

	inhibitors			
α3	ITGA3 missense mutation	In vivo	Fibrosis↑	[56]
α4	LPS-induced mice	In vivo	Integrin α4β1↑	[33]
α4	BLM-treated α4Y991A mice	In vivo	Rac↓, M2 macrophage markers (e.g., YM1, Fizz1, CD206) ↓	[38]
α5	Components in the supernatant secreted by IPF fibroblasts affect normal fibroblasts	In vitro	ITGA5, pIκBα↑, adhesion and migration ↑	[57]
α5	Fibroblasts were incubated with EVs	In vitro	Fibroblast invasion↑, activation of FAK and Src↑	[22]
α5	IPF-HLFs	In vitro	uPAR↑, integrin α5↑, caveolin-Fyn-Shc↑in lipid rafts, fibroblast migration↑	[23]
α5	SPCs	In vitro	Fn1, Col1a1, ITGA5↑	[58]
α5	ITGA5-silenced IPF-HLFs	In vitro	Transformation of fibroblasts to myofibroblasts, FN1, TGF-β, α-SMA and	[59]

			collagen I↑	
α6	Human IPF lung myofibroblasts in the sclerotic matrix	In vitro	ROCK↑, c-Fos/c-Jun transcription complex↑, α6 integrin↑, collagen IV↓	[24]
α6	BLM-induced PF in mice; HLF and MLF	In vivo and in vitro	CD11c+ AREG↑, integrin α6↑, lung fibroblast motility and invasiveness↑	[62]
α6	Silica dust-induced PF mice and TGF-β1-stimulated fibroblasts	In vivo and in vitro	miR-542-5p↓, ITGA6↑, proliferation and migration of fibroblasts↑, lung fibrosis↑	[63]
α8	IPF patients	In vivo	CD248 ^{low} ITGA8 ^{high} fibroblast-like cells in the elastic fiber-rich connective tissue	[60]
α8	ITGA5 silenced fibroblasts	In vitro	Transformation of fibroblasts to myofibroblasts, ITGA8 and ITGAV↑	[59]
α10	BLM-induced MIF knockdown in rats	In vivo	α10↓, fibrosis↓	[64]

α11	IPF patients	In vivo	α11↑	[52]
α11	IPF patients	In vivo	α11+ α-SMA myofibroblasts↑	[65]
αMβ2	Human interstitial lung lesions following neococcal pneumonia	In vivo	sITGaM and sITGb2↑	[36]
αM and αX	Neutrophils under hypoxic conditions	In vitro	αM and αX↑, NETs↑	[39]
αLβ2 and αMβ2	HFD-fed mice	In vivo	ITGAM, ITGAL, ITGB2L, ITGB2, NAIP6 and NAIP5↑	[35]
αvβ1	HLFs	In vitro	Galectin-3 binds to β1 integrin, p-Smad2↑	[6]
αvβ3	BLM-induced mice	In vivo	αvβ3↑	[66]
αvβ3	Periostin or integrin silencing in lung fibroblasts	In vitro	Lung fibroblast proliferation↓	[27]
αvβ3 and αvβ5	Knockdown of integrin αv/β3/β5 in lung fibroblasts treated with TGF-β	In vitro	SERPINE1, CTGF, IGFBP3, and IL11↓	[7]
αvβ3	BLM mice lacking Thy-1	In vivo	αvβ3 in αSMA^{+} myofibroblasts↑	[28]
αvβ3 and	PDGF-BB stimulated	In vitro	Src activation, Src	[31]

αvβ5	fibroblasts		interacted with integrative αvβ3, fibroblasts migration	
αvβ3	Thy-1 neg fibroblasts	In vitro	RhoA activity↑, collagen matrix contraction↑	[30]
αvβ3	BLM-treated mice; CD146+ MACS-enriched primary cells seeded on fibronectin	In vivo and in vitro	Pericytes α-SMA↑, αvβ3↑	[26]
β6	TGF-β1 stimulation of iHBECs	In vitro	Time-dependent increase in ITGB6 mRNA	[8]
αvβ6	TGF-α-induced PF in mice	In vivo	αvβ6↑, TGF-β↑	[10]
αvβ6	Influenza-infected mice	In vivo	αvβ6↑, p-smad2/3↑	[9]
αvβ6	Elk1-deficient BLM-induced mice; Elk1 siRNA IHBECs	In vivo and in vitro	ITGB6↑	[69]
αvβ6	Mice treated with Del-1 following BLM induction; HSAEpC cells incubated with inactive TGF-β were	In vivo and in vitro	αvβ6↓, active TGF-β↓	[12]

	treated with Del-1			
αvβ6	Mice exposed to BLM and treated with the IRE1α kinase inhibitor KRA8.	In vivo	Krt7 and ITGB6 double-positive cells ↓, local TGF-β signaling and fibrosis↓	[13]
αvβ6	SFLLRN-stimulated Immortomouse lung epithelial (IMLE) cells with transformed mink lung reporter (TML) cells + αvβ6 blocking antibody; SFLLRN-stimulated IMLE cells treated with the Rho kinase inhibitor Y-27632.	In vitro	PAR1, αvβ6, TGF-β↓	[14]
αvβ8	West highland white terrier with IPF; TGF-β stimulated MRC-5 cells	In vivo and in vitro	ITGB8↓	[16]
αE	Mice exposed to aspergillus antigen	In vivo	$CD69^{hi}CD103^{lo}$ CD4+ TRM cells: IL5 and IL13↑; $CD69^{hi}CD103^{hi}$	[40]

			Foxp3+ Treg cells: ITGAE, Foxp3↑	

Table 2. Integrin Inhibitors Entering Clinical Studies

Name (sponsor)	Modality	Delivery route	Integrin targets	Highest human dose reported/dose	Clinical Trials.gov identifiers	Safety and efficacy	Study statusa	Population or indication
GSK3008348 (GlaxoSmithKline)	Small molecule	Topical inhalation	αvβ6	1 to 3000 ug	NCT02612051; NCT03069989;	Well tolerated	Phase I (terminated)	IPF and Healthy volunteers
BG00011 (Biogen)	Humanized mAb	s.c.	αvβ6	56 mg weekly	NCT03573505	Toxicity observed	Phase II (terminated)	IPF
IDL-2965 (Indalo Therapeutics)	Small molecule	Oral	pan-αv	/	NCT03949530	/	Terminated	IPF

PLN-74809 (Pliant Therapeutics)	Small molecule	Oral	αvβ6, αvβ1	40 mg daily for 7 days[102]	NCT04396756	Good tolerability	Phase II Recruiting	IPF

Table 3. The potential mechanism of integrin-based therapies in PF

Integrin inhibitor	Targeted integrins	Models	In vivo/in vitro	Main mechanisms	References
Cilengitide	Pan-αv	MRC-5 cells and mice after radiation	In vitro and in vivo	αv, active TGF-β1, Smad2/3 and p-Smad2/3↓, collagen and α-SMA protein↓	[18]
Cilengitide	Pan-αv	LPS-induced lung fibroblasts	In vitro	β3↓, PI3K-Akt-mTOR pathway activation↓, autophagy inhibition↓	[67]
Cilengitide	Pan-αv	MV mice	In vivo	PKM2, LDHA, lactate, collagen deposition↓	[68]

CWHM12	Pan-αv	TGF-β induced PF in PCLS	In vitro	αv↓, Aspn, Col1a1, Csrp2, Fap, Fbln2, Fbn2, Has2, Pappa and Wisp1↓	[78]
CWHM12	Pan-αv	Mechanically stretched fibrotic lung tissues	In vitro	αv↓, TGF-β1↓, p-Smad2/3↓	[79]
MK-0429	Pan-αv	BLM-induced mice	In vivo	Fibrosis↓	[80]
Ab-31	Pan-αv	IPF lung fibroblasts	in vitro	α-SMA↓	[80]
C8	αVβ1	BLM-induced mice	In vivo	Collagen↓	[81]
CP4715	αvβ3	Lung fibroblasts from IPF patients	in vitro	Down-regulation of the expression of proliferation- and cell cycle-related genes	[27]
CP4715	αvβ3	BLM-induced mice	In vivo	Attenuated PF and Smad3 activation	[7]
Cyclo(-	αvβ3	Myh11	In vitro	Inhibition of	[26]

RGDfK)		profile-positive cells cultured on fibronectin-coated Petri dishes		pericyte-to-myofibroblast transformation	
B6_BP_dslf	αvβ6	Fibrotic lung-like organs	in vitro	α-SMA and fibronectin↓	[83]
Lovastatin	αLβ2	BLM-induced mice	In vivo	Inflammation, collagen deposition↓	[84]
α-αMβ2 and CBP-α-αMβ2	αMβ2	BLM-induced mice; Monocyte-derived myofbroblasts	In vivo and in vitro	collagen deposition↓, de-diferentiate mouse myofbroblasts	[85]
BTT 3033	α2β1	Lumican-induced PBMC	In vitro	Lumican-induced fibrocytes differentiation↓	[44]
TC-I 15	α2β1	TGF-β1 stimulated fibroblasts	In vitro	collagen I and α-SMA↓	[53]
E7820	α2β1	In MTX-	In vitro	α-SMA↓	[54]

		treated A549 cells			
α-α3 and CBP-α-α3	α3β1	BLM-induced mice; Monocyte-derived myofbroblasts	In vivo and in vitro	Collagen deposition↓, de-diferentiate mouse myofbroblasts	[85]
ATN-161	α5β1	O-PMs stimulated A549cells	In vitro	Fibronectin and vimentin↓, Ecadherin↑	[88]
ATN-161	α5β1	PQ-induced PF in rats	In vivo	Fibrosis↓	[21]
Echistatin	β1	Silicosis rats	In vivo	Snail, AKT and β-catenin↓, EMT↓	[89]
Pirfenidone	αMβ2	Co-culture of macrophages and lung fibroblasts	In vitro	M2 polarization and its adhesion, α-SMA, active TGF-β levels↓	[90]
Triptolide	β1	BLM-induced mice	In vivo	Integrin β1-FAK activation-mediated nuclear translocation of YAP1↓	[46]
IL-32	/	MRC-5 cells	In vitro	FAK and paxillin	[92]

		treated with TGF-β		activation↓	
yASCs	αv	BLM induced PF in aged mice	In vivo	αv↓, collagen, MMP-2 activity and AKT phosphorylation, Caspase-9, TGF-β, TNF-α, VEGF-A↓, ros↓, nrf2↑	[93]
PD29	αvβ3 and αE	BLM-induced PF in rats	In vivo	αvβ3 and αE↓, TGF-β1/Smad3↓	[94]

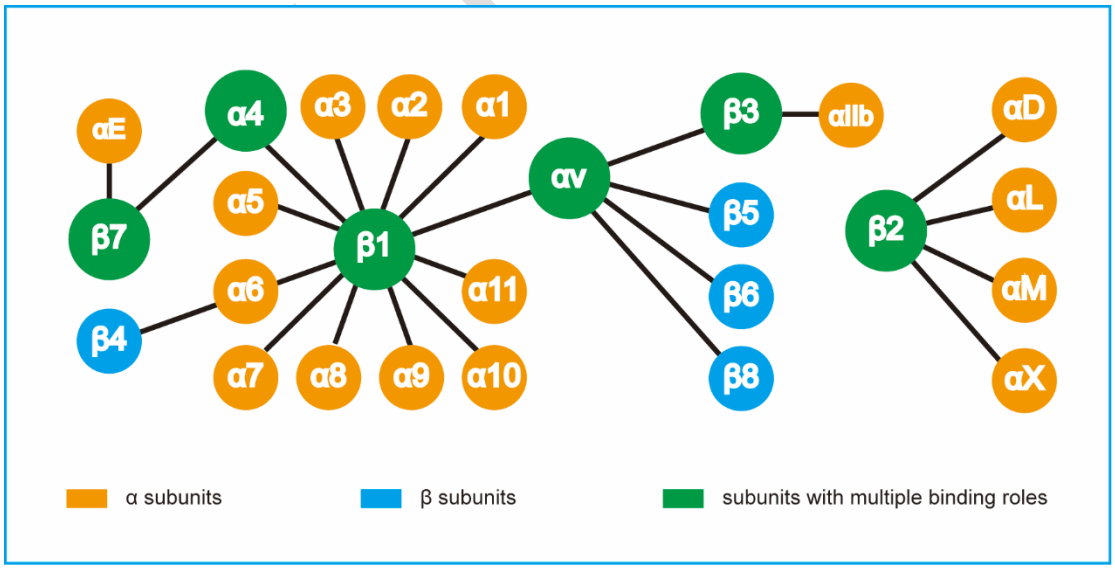

Figure 1. The combination of integrin subunits forms integrin molecules. The orange represents the α-subunit, the blue indicates the β-subunit, and the green denotes

the subunit with multiple binding roles.

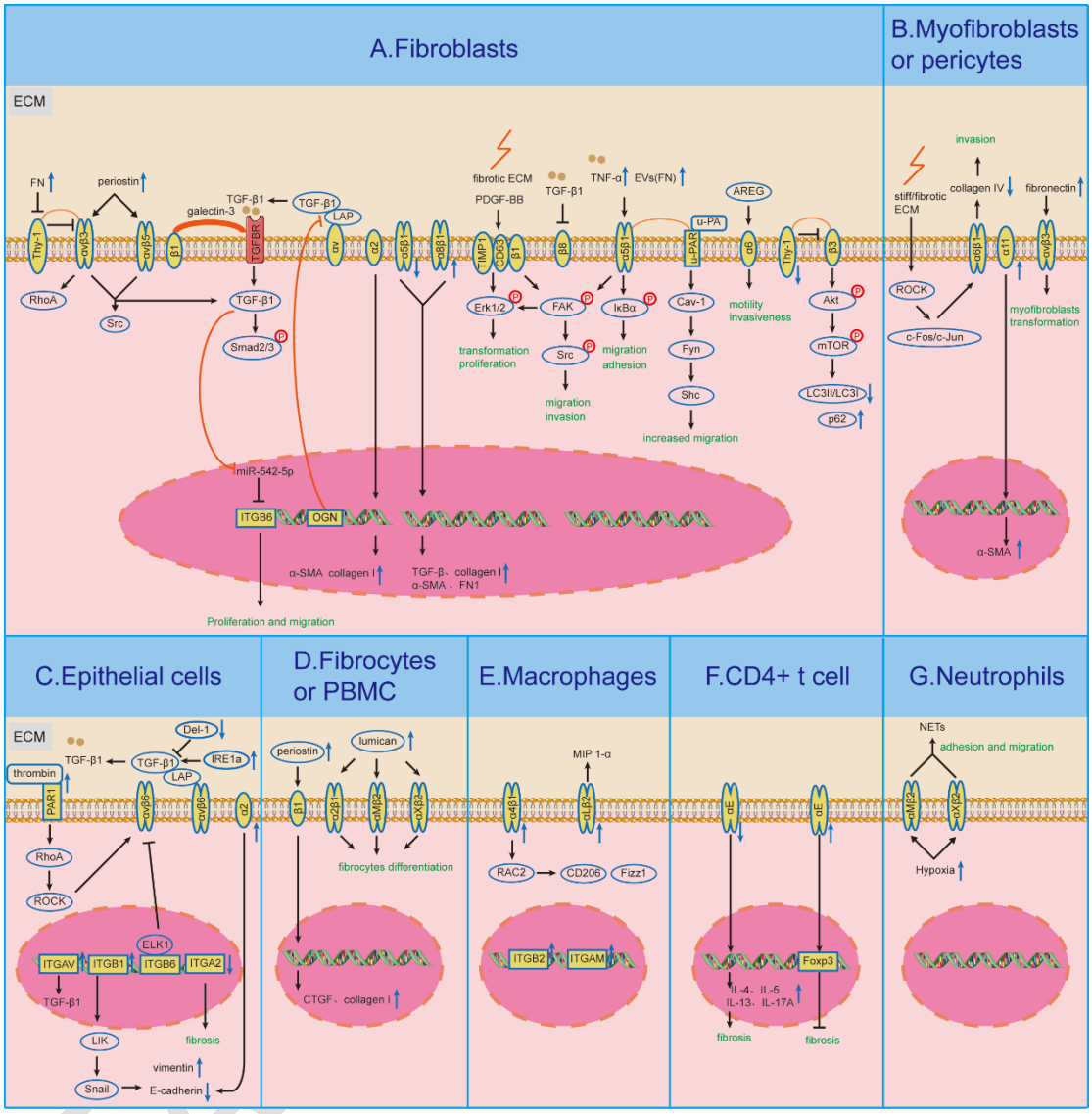

Figure 2. Summary diagram illustrating the role of integrins in the seven specific cell types involved in the pathogenesis of pulmonary fibrosis. The cell types are described as follows: (A) lung fibroblast cells, (B) lung myofibroblasts or pericytes, (C) lung epithelial cells, (D) fibrocytes or peripheral blood mononuclear cells, (E) macrophages, (F) CD4+ T cells, and (G) neutrophils. Arrows indicate the following: ↑ denotes promotion or activation; ⊤ indicates reduction or inhibition. p represents phosphorylation.

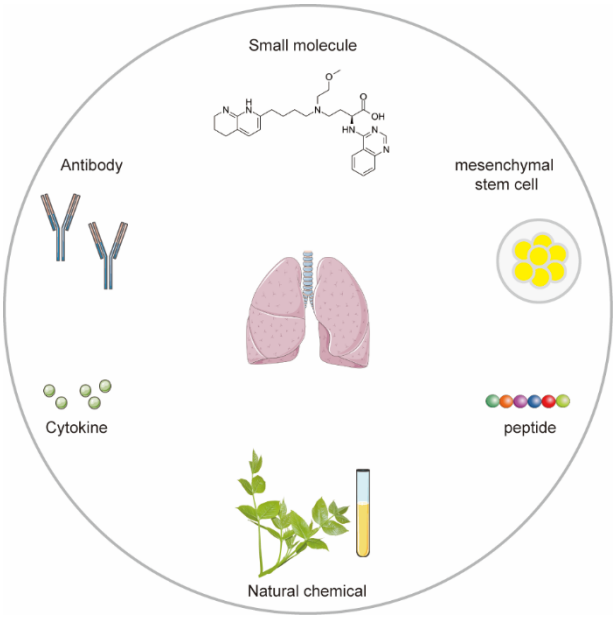

Figure 3. Integrin-based therapies are as follows: Small molecule, antibody, cytokine, natural chemical, peptide, and mesenchymal stem cell.