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Integrin signaling pathways in pulmonary hypertension

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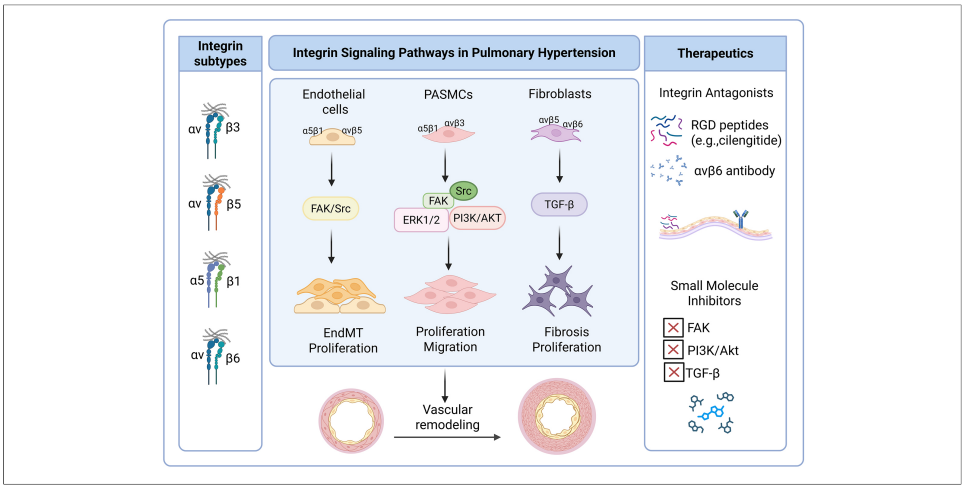

Abstract

Pulmonary hypertension (PH) is a progressive and life-threatening disorder characterized by elevated pulmonary arterial pressure, vascular remodeling, and right ventricular failure. While the pathogenesis of PH involves endothelial dysfunction, inflammation, and excessive extracellular matrix (ECM) deposition, emerging evidence highlights the pivotal role of integrin-mediated signaling in driving vascular cell behavior and tissue stiffness. Integrins, a family of heterodimeric transmembrane receptors, serve as critical mechanosensors and signal transducers between cells and the ECM. The dysregulation of integrins has been confirmed to promote pathological vascular remodeling through the following mechanisms: (1) Activating focal adhesion kinase (FAK) and Src family kinases, driving excessive proliferation and resistance to apoptosis of pulmonary artery smooth

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muscle cells; (2) Enhanced transforming growth factor-beta (TGF-β) signaling leads to the transformation of fibroblasts into myofibroblasts and excessive collagen deposition; (3) Ras homolog gene family, member A/Rho-associated protein kinase-mediated cytoskeletal recombination disrupts the integrity of the endothelial barrier, exacerbating inflammation and thrombosis. These pathways collectively increase vascular hardness and maintain a pro-remodeling microenvironment of pulmonary vessels. This review summarizes the current understanding of integrin signaling pathways in PH, with a focus on αvβ3, α5β1, and β1-containing integrins, their downstream effectors (e.g., FAK, TGF-β), and their interplay with inflammatory and fibrotic processes. We also discuss preclinical and clinical evidence supporting integrin-targeted therapies, including Myocardin-related transcription factor 1 and Cilengitide, as potential strategies for modulating vascular remodeling in PH. However, their clinical transformation remains challenged by limited efficacy, context-dependent signaling, and safety concerns. A deeper understanding of integrin biology may facilitate the development of more precise and effective therapeutic strategies for PH.

INTRODUCTION

Pulmonary hypertension (PH) is a progressive and fatal cardiopulmonary disease characterized by sustained elevation of pulmonary artery pressure. The progression of the disease will gradually lead to right heart failure and even death[1-3]. In clinical diagnosis, a resting mean pulmonary arterial pressure (mPAP) > 20 mmHg measured by right heart catheterization is used as the criterion for diagnosing PH[4]. According to the differences of etiology and pathogenesis, PH is classified into five types: (1) Pulmonary arterial hypertension (PAH), a group of rare and severe vascular disorders targeting pulmonary arterioles; (2) PH due to left heart disease(PH-LHD), the most common subtype caused by left ventricular or valvular heart diseases; (3) PH caused by pulmonary disease and/or hypoxia, mainly induced by chronic obstructive pulmonary disease, interstitial lung disease or high-altitude hypoxia; (4) Chronic thromboembolic pulmonary hypertension (CTEPH), characterized by unresolved or recurrent pulmonary thromboembolism and subsequent vascular remodeling; (5) PH of unknown mechanisms or resulting from multiple factors, involving disorders that cannot be classified into the above four categories[5-7]. Despite of the distinct etiological differences among these types, they collectively exhibit the pathological feature of pulmonary vascular remodeling, including intimal hyperplasia or fibrosis, medial smooth muscle thickening, and adventitial lesions. These changes further lead to plexiform vascular lesions and occlusion of small pulmonary arteries, significantly increasing pulmonary vascular resistance and ultimately causing right heart failure[8].

The core mechanism of PH pathogenesis lies in the pathological remodeling of the pulmonary vascular system, particularly changes in small arteries[9]. This process is not an independent behavior of a single cell type but involves complex dynamic interactions between pulmonary arterial endothelial cells (PAECs), pulmonary arterial smooth muscle cells (PASMCs), fibroblasts, immune cells, and extracellular matrix (ECM) components[10]. It is mainly characterized by abnormal proliferation and apoptosis resistance of PASMCs, leading to medial hypertrophy; endothelial dysfunction-driven intimal hyperplasia and plexiform lesion formation; local coagulation imbalance causing *in situ* thrombosis; and accompanying perivascular inflammatory cell infiltration and interstitial fibrosis[11-13].

Currently, PH treatment strategies mainly focus on improving the imbalance of soluble vasoactive mediators, such as excessive endothelin-1 (ET-1) production, inhibition of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathways, and decreased prostacyclin (PGI_2) synthesis[1,13]. Although these treatments have shown some success in alleviating vasoconstriction, they are still inadequate to reverse structural vascular lesions, suggesting that modulating vascular tone alone is insufficient to effectively halt the progression of PH. In contrast, targeting integrins offers a novel approach that not only addresses

vascular tone but also directly modulates the underlying vascular remodeling in PH. This innovative therapeutic strategy has the potential to reverse pathological ECM deposition and restore vascular homeostasis, representing a significant step beyond traditional vasodilator therapies.

Recent studies indicate that dynamic changes of the ECM and the mechanical signal perception system play crucial roles in driving persistent pulmonary vascular remodeling[14,15]. Stimulated by factors such as chronic hypoxia, inflammation, abnormal shear stress, or genetic predisposition, the pulmonary vascular microenvironment undergoes significant changes, manifested as abnormal deposition of ECM components like fibronectin, collagen, and tenascin-C, increased matrix stiffness, and degradation imbalance[16]. These physical and biochemical signals are sensed by cells via specific receptors, especially integrins, thereby activating downstream signaling networks[14,17]

Integrins are key transmembrane receptors that connect cells to the ECM[18,19]. Apart from mediating cell adhesion and anchorage, integrins also act as signaling hubs that regulate cell proliferation, migration, phenotype transformation, and survival[20]. Under the pathological conditions of PH, specific integrin subtypes (e.g., α5β1, αvβ3, αvβ5) are upregulated in PASMCs and PAECs, activating downstream signaling pathways such as focal adhesion kinase (FAK), Src, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), and mitogen-activated protein kinase (MAPK), promoting abnormal cell proliferation and apoptosis resistance[21-23]. Moreover, activation of certain integrins (e.g., αvβ6/αvβ8) may activate latent transforming growth factor-beta (TGF-β), thereby amplifying fibrosis and inflammation[24-27]. Integrins also interact with other mechanosensitive pathways that influence pulmonary vascular remodeling—most notably the Hippo/YAP (Yes-associated protein) pathway. In PH, elevated ECM stiffness promotes integrin activation and downstream FAK signaling, which inhibits the Hippo pathway, leading to nuclear translocation of the transcriptional co-activators YAP/TAZ (transcriptional co-activator with PDZ-binding motif) to promote the transcription of genes related to cell proliferation, survival and fibrosis. Critically, YAP/TAZ also feedback to upregulate integrin and matrix components, increasing ECM stiffness and further amplifying integrin signaling. This bidirectional crosstalk establishes a self-sustaining vicious cycle that continuously aggravates pulmonary vascular remodeling in PH[28-30]. Therefore, integrin-mediated “cell-ECM crosstalk" is not only an important regulatory factor in vascular YAP/TAZ structural remodeling but also provides a potential breakthrough for the development of novel therapeutic strategies targeting structural lesions.

This review comprehensively summarizes the latest research on integrin signaling in PH, discusses the dysregulation of specific integrin subtypes in pulmonary vasculature, introduces the main downstream signaling pathways, explores their interactions with growth factors and inflammatory mediators, and evaluates the therapeutic potential of targeting integrins and their effectors. Additionally, we highlight the challenges in translating these insights into clinical practice and future research directions.

INTEGRIN STRUCTURE AND FUNCTION

Integrins are a group of widely expressed, heterodimeric transmembrane glycoprotein receptors on the cell surface, formed by non-covalent bonding between α and β subunits[31]. Since their discovery in 1980s, research has shown that mammals express at least 18 α subunits and 8 β subunits, which combine to form 24 different integrin subtypes[32,33]. Each integrin subunit typically consists of a large extracellular domain for ligand binding, a single transmembrane helix, and a short cytoplasmic tail that links to intracellular signaling and structural proteins[34] [Table 1].

According to the different ligands identified, integrins are classified into four categories [Table 2][19,103,104]:

Table 1. The 24 known integrin heterodimers

	Main ligand	Expressing cells	References
α1β1 (CD49a/CD29)	Collagen I, IV, Laminin	Fibroblasts, smooth muscle cells, some T cells	[35-37]
α2β1 (CD49b/CD29)	Collagen I, III, IV	Platelets, epithelial cells, fibroblasts	[38,39]
α3β1 (CD49c/CD29)	Laminin, Fibronectin, Thrombospondin	Epithelial, endothelial, fibroblasts	[40-45]
α4β1 (VLA-4, CD49d/CD29)	Fibronectin (CS-1), VCAM-1	Lymphocytes, monocytes, eosinophils	[46-48]
α5β1 (VLA-5, CD49e/CD29)	Fibronectin (RGD), Fibrillin, Thrombospondin	Widely expressed (fibroblasts, SMCs, endothelia, blood cells)	[49-54]
α6β1 (CD49f/CD29)	Laminin isoforms (laminin-111, laminin-511, *etc.*)	Epithelial cells, stem cells, platelets	[40,55]
α7β1 (CD49g/CD29)	Laminin	Skeletal and cardiac muscle cells	[56-58]
α8β1 (CD49h/CD29)	Fibronectin, Vitronectin, Osteopontin	Smooth muscle, neurons, kidney cells	[59-61]
α9β1 (CD49i/CD29)	Fibronectin, VCAM-1, Tenascin-C, Osteopontin, ADAMs	Leukocytes, epithelial cells, endothelial cells	[62,63]
α10β1 (CD49j/CD29)	Collagen I, II, IV	Chondrocytes, fibroblasts	[64,65]
α11β1 (CD49k/CD29)	Collagen I, II, III	Fibroblasts, mesenchymal cells	[38,66]
αvβ1	Fibronectin, Vitronectin, Latent TGF-β	Fibroblasts, smooth muscle cells, epithelial cells	[59,67,68]
αLβ2 (CD11a/CD18)	ICAM-1,2,3	T/B lymphocytes, monocytes	[46,69-71]
αMβ2 (CD11b/CD18)	iC3b, ICAM-1, Fibrinogen	Neutrophils, monocytes, macrophages	[46,70,72]
αXβ2 (CD11c/CD18)	iC3b, Fibrinogen	Dendritic cells, monocytes	[73-75]
αDβ2 (CD11d/CD18)	ICAM-3, VCAM-1	Monocytes, macrophages	[69,70,75,76]
αIIbβ3 (CD41/CD61)	fibrinogen, fibronectin, vWF	Platelets (exclusively)	[59,77]
αvβ3 (CD51/CD61)	Vitronectin, Fibronectin, Osteopontin, Tenascin	Endothelial cells, osteoclasts, tumor cells, smooth muscle cells	[59,78-80]
α6β4	Laminin-332 (laminin-5)	Epithelial cells (localized in hemidesmosomes)	[40,81,82]
αvβ5	Vitronectin	Fibroblasts, epithelial, endothelial, tumor cells	[59,83-87]
αvβ6	Fibronectin, Tenascin, Latent TGF-β	Epithelial cells (low in normal tissue, upregulated in injury/tumor)	[59,88-91]
α4β7	MAdCAM-1, Fibronectin	Gut-homing lymphocytes	[92,93]
αEβ7	E-cadherin	Intraepithelial lymphocytes (IELs), regulatory T cells	[94-96]
αvβ8	Latent TGF-β	Neurons, glial cells, smooth muscle cells, epithelial cells	[97,98]

The table summarizes the 24 currently recognized integrin heterodimers, which are composed of 18 α and 8 β subunits. Each integrin pair displays distinct ligand-binding specificities, recognizing extracellular matrix components such as collagens, fibronectin, laminins, vitronectin, tenascin, osteopontin, and certain members of the immunoglobulin superfamily. Their expression is cell type-specific, observed in endothelial cells, smooth muscle cells, fibroblasts, platelets, leukocytes, and epithelial cells. These unique ligand affinities and cellular distribution patterns underlie the diverse roles of integrins in vascular homeostasis, immune regulation, extracellular matrix remodeling, and pathophysiological processes including pulmonary hypertension.

1. Arginine-glycine-aspartic acid (RGD)-binding integrins (the largest group), such as αvβ3, α5β1, and αIIbβ3, which recognize RGD motif in ECM components like fibronectin, fibrillin, and fibrinogen.

2. Leukocyte adhesion integrins, including β2 integrins (e.g., αLβ2, αMβ2) and members of the α4/α9/αE subfamily (e.g., α4β1, α4β7, α9β1, αEβ7), which mediate adhesion and migration of immune cells.

3. Collagen-binding integrins (e.g., α1β1, α2β1, α10β1, α11β1), which bind to collagen fibers through the GFOGER-like sequence and rely on the organizational structure of collagen fibers.

4. Laminin-binding integrins (e.g., α3β1, α6β1, α7β1, α6β4), which interact with laminin in the basement membrane.

Table 2. Classification of integrins based on ligand specificity

Integrin category	Representative heterodimers	Primary ligands/binding motifs	Key features and notes	References
Collagen-binding integrins	α1β1, α2β1, α10β1, α11β1	Collagens (GFOGER-like motifs), laminins (for α1β1, α2β1)	Different specificities: α1β1 prefers collagen IV, α2β1 binds collagen I-III, α10β1 in cartilage, α11β1 in mesenchymal cells cell adhesion, migration, and angiogenesis	[38]
Laminin-binding integrins	α3β1, α6β1, α7β1, α6β4	Laminins (basement membrane, multiple isoforms)	α7β1 abundant in skeletal/cardiac muscle; α6β1 binds multiple laminin isoforms (e.g., laminin-111, -511)	[99-101]
RGD-binding integrins	α5β1, αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, α8β1, αIIbβ3	Fibronectin, fibrillin, fibrinogen, vitronectin, osteopontin (RGD motif)	Largest group; recognize the conserved RGD sequence; important in cell adhesion, migration, and angiogenesis	[67,102]
Leukocyte adhesion integrins	α4β1, α9β1, αLβ2, αMβ2, αXβ2, αDβ2, αEβ7, α4β7	ICAMs, VCAM-1, MAdCAM-1, iC3b, fibrinogen, E-cadherin	Mediate immune cell adhesion and migration; β2 integrins also bind complement fragments (iC3b) and fibrinogen	[46,69]

Integrins are transmembrane receptors that mediate cell-extracellular matrix and cell-cell interactions. They are classified into four main ligand-specific groups: collagen-binding integrins, laminin-binding integrins (anchor cells to basement membrane), RGD-binding integrins (recognize RGD motif in ECM proteins) and leukocyte adhesion integrins (mediate immune cell trafficking). Their distinct expression patterns and ligand specificities underlie diverse roles in tissue homeostasis and disease.

Notably, some collagen-binding integrins (e.g., α1β1, α2β1, α10β1) also show affinity for laminin, suggesting potential functional overlap[31]. Additionally, integrin expression is tightly regulated by tissue specificity and developmental stage. Apart from canonical ECM mediators, integrins also interact with non-ECM ligands, including pathogen-derived surface proteins, growth factors, hormones, and bioactive compounds[105-107].

The function of integrins depends on maintaining a delicate balance between their active and inactive states through various mechanisms, including protein-protein interactions, conformational changes, and transport[108,109]. In their initial state, integrins exist on the cell surface in an inactive, low-affinity conformation. Integrin activation is typically triggered by intracellular signals, a process known as "inside-out" signaling. During this process, proteins like talin and kindlin bind to the intracellular tail of the β-integrin subunit, disrupting the transmembrane structure and inducing a conformational change in the integrin to form a high-affinity, extended state. In this state, integrins bind specific ECM ligands like fibronectin, collagen, or laminin[110-112].

After ligand binding, integrins aggregate and initiate “outside-in” signaling, a more complex and tightly regulated process. The intracellular domains of aggregated integrins serve as scaffolds for recruiting various adaptor proteins, including talin, vinculin, paxillin, and FAK[113-115]. These proteins typically contain phosphotyrosine-binding domain or four-point-one, ezrin, radixin, moesin domain domains that recognize phosphorylation sites or structural changes at adhesion sites[116-118]. The resulting large protein complexes, known as focal adhesion complexes (FACs), act as central hubs for signal transduction, activating downstream pathways such as FAK-Src, PI3K-Akt, and MAPK. These signaling pathways regulate diverse cellular functions such as adhesion, migration, proliferation, survival, and differentiation[119-121].

Notably, integrin activation in PH is not solely regulated by biochemical cues but is strongly influenced by the mechanical stiffness of the ECM. Progressive ECM remodeling in PH, characterized by excessive collagen and fibronectin deposition, leads to increased matrix stiffness, which enhances mechanical force transmission across integrin-ECM bonds. This elevated mechanical tension stabilizes integrins in their active, extended conformation, promotes integrin clustering, and amplifies outside-in signaling even in the absence of strong inside-out activation. Consequently, mechanosensitive pathways such as FAK, YAP/TAZ,

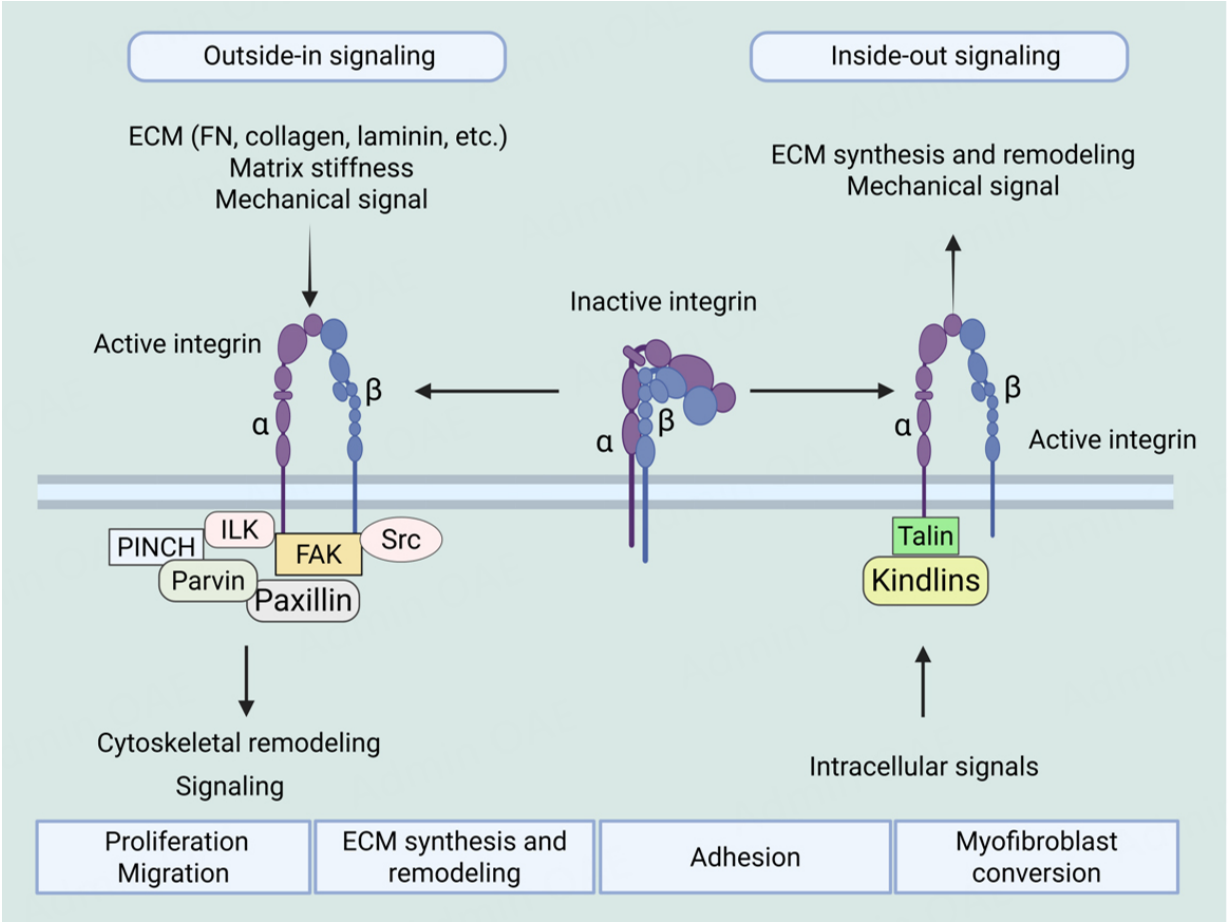

Figure 1. Integrin bidirectional signaling - integrin signaling from the outside in and inside out. In outside-in signaling, abnormal deposition of ECM components, alterations in matrix stiffness, and mechanical stimulation lead to integrin activation and recruitment of adaptor proteins to form integrin adhesion complexes, which trigger cytoskeletal remodeling and conduct or regulate downstream signaling cascades (from outside-in signaling). In inside-out signaling, intracellular signaling activation stimulates talin or kindlin binding to the cytoplasmic tail of integrins, inducing conformational changes in integrins and enhancing their affinity for ECM ligands. ECM: Extracellular matrix, ILK: integrin-linked kinase, FAK: focal adhesion kinase. Created in BioRender. He, S. (2026) https://BioRender.com/1o25dcs.

and TGF-β signaling are persistently activated, driving smooth muscle cell proliferation, endothelial dysfunction, and fibrosis. While these cellular responses further exacerbate ECM remodeling and stiffening, forming a vicious cycle that sustains pathological vascular remodeling in PH.

The complex signaling network formed by integrins and their associated proteins illustrates the multifunctionality of integrins in mediating dynamic interactions between cells and the ECM, and in responding to biochemical and mechanical signals within the microenvironment[20]. Recent studies have further revealed that integrins not only play a key role in cell adhesion and migration, but also participate in many physiological and pathological processes by influencing cell morphology, metabolism, proliferation, apoptosis and other processes, especially playing an important role in the progression of diseases such as PH[111] [Figure 1].

INTEGRINS AND PULMONARY HYPERTENSION: STRUCTURE, FUNCTION, AND SIGNALING MECHANISMS

The unique heterodimeric structure and conformational plasticity of integrin lay the foundation for their dual role as adhesion receptors and mechanosensors. Importantly, these structural features are not merely static properties but are tightly linked to intracellular signaling events. Understanding how integrin

conformational shifts are translated into biochemical signals is therefore essential for elucidating their role in pulmonary vascular remodeling. In this section, we outline the major integrin-mediated signaling pathways that have been implicated in the pathogenesis of PH.

In PH, pulmonary vascular lesions are closely associated with abnormal deposition of ECM components[28]. Under stimuli such as hypoxia, inflammation, shear stress, and genetic predisposition, the pulmonary vascular microenvironment undergoes significant changes, manifesting as abnormal deposition of ECM components like fibronectin, collagen, and tenascin-C, leading to matrix stiffening and increased rigidity[122-124]. This pathological ECM remodeling provides favorable conditions for the overexpression and sustained activation of integrins.

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Studies have shown that in patients with PH and animal models, abnormally upregulated integrin subtypes such as α5β1, αvβ3, and αvβ5 are closely related to pulmonary vascular remodeling[22,125]. However, the expression and dysregulation of these integrins may vary across different PH subtypes. For example, in PAH, characterized by endothelial dysfunction and excessive smooth muscle cell proliferation, αvβ3 and α5β1 are particularly prominent, promoting cell proliferation and resistance to apoptosis[126]. In contrast, in CTEPH, where fibrotic occlusion of large pulmonary arteries predominates, integrin β2 (ITGB2) is increasingly implicated. Recent reports have found that ITGB2 is upregulated in platelets/immune cells in patients with CTEPH, which is related to the formation of neutrophil extracellular trap (NET) and the maintenance of inflammation, which may indirectly promote thrombus solidification and the progression of the disease course[127]. In addition, hypoxia—a key environmental driver of PH—further modulates integrin expression across subtypes via the HIF-1α signaling pathway[128], thereby directly linking external stress to integrin-mediated vascular remodeling. These subtype-specific patterns underscore the need for precision therapeutic strategies that target the most relevant integrin pathways according to the underlying etiology of PH.

Upon activation, integrin not only mediates the physical anchorage of cells to the ECM but more importantly, through the assembly of FACs, initiates a series of complex intracellular signaling cascades[31]. These signaling pathways play a crucial role in the pathological processes of PH, promoting abnormal proliferation, apoptosis resistance, migration, phenotype transformation, and inflammatory responses of PASMCs and ECs, ultimately leading to pulmonary vascular remodeling [Figure 2].

FAK and Src: core signaling hubs

FAK is a non-receptor tyrosine kinase that plays a central role in integrin signaling. When ECM proteins bind to integrins on the cell surface, integrins cluster and activate FAK. This activation triggers FAK to phosphorylate itself at tyrosine 397 (Tyr397). Phosphorylated Tyr397 then serves as a high-affinity binding site for Src family kinases—another group of tyrosine kinases[116]. Once bound, FAK and Src form a signaling complex that further phosphorylates several downstream proteins, such as paxillin, p130Cas, and talin. These proteins help regulate cytoskeletal rearrangement, adhesion dynamics, and cell migration[129]. Furthermore, the FAK-Src pathway activates pro-survival and proliferative pathways such as Ras-MAPK and PI3K-Akt pathways[130,131].

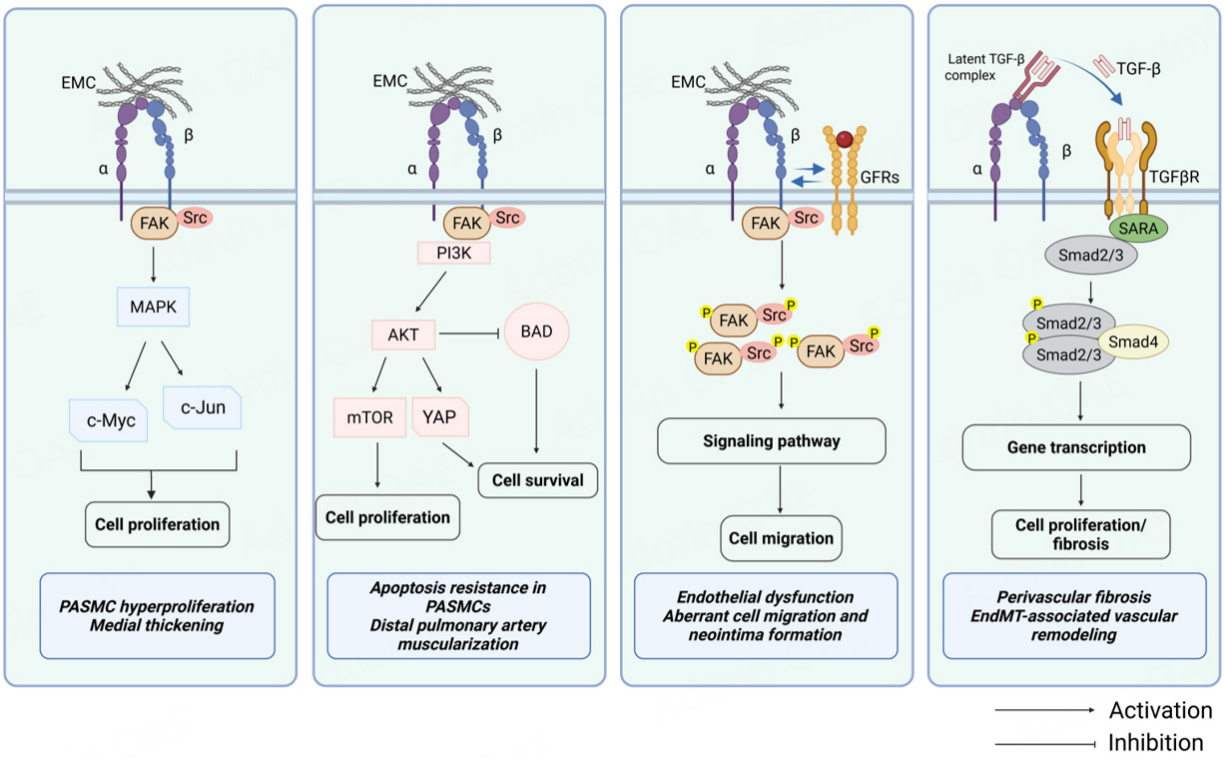

Figure 2. Integrin-mediated signaling pathways in PH. Integrin engagement activates multiple downstream signaling cascades that contribute to pulmonary vascular remodeling. (Left to right) MAPK pathway: FAK/Src-mediated activation of MAPK promotes transcription factors (c-Myc, c-Jun) driving PASMC and PAEC proliferation. PI3K/AKT pathway: integrin-FAK signaling activates PI3K/AKT, which enhances cell proliferation (via mTOR and YAP) and cell survival (via inhibition of BAD and FOXO-mediated pro-apoptotic signaling). Cross-talk with GFRs: Integrins cooperate with GFRs, amplifying downstream pathways and promoting migration and proliferation. TGF-β signaling: integrins mediate activation of latent TGF-β complexes, enabling TGF-β receptor signaling through Smad2/3-Smad4, which regulates cell proliferation and fibrosis. PH: Pulmonary hypertension, GFRs: growth factor receptors, FAK: focal adhesion kinase. Created in BioRender. He, S. (2026) https://BioRender.com/swfm3ic.

In PH, FAK exhibits persistent phosphorylation and high activity in both PASMCs and PAECs, particularly in neointimal and plexiform lesion areas[132,133]. Studies in animal models have shown that gene knockout or pharmacological inhibition of FAK significantly inhibits PASMC proliferation and migration, alleviates vascular wall thickening, and reduces right ventricular systolic pressure, thus improving pulmonary vascular remodeling[134]. This indicates that FAK is not only a central node of integrin signaling but also a highly promising therapeutic target for PH.

PI3K/AKT pathway: promoting cell survival and anti-apoptosis

Integrin-FAK signaling activates PI3K, either directly or indirectly. This activation of PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). The newly formed PIP_3 then recruits and activates AKT[135,136]. Once activated, AKT exerts strong pro-survival and anti-apoptotic effects by phosphorylating a variety of downstream effector molecules. For instance, AKT phosphorylates and inhibits the pro-apoptotic protein Bad, causing it to dissociate from the Bcl-2 complex[137,138]; it also inhibits the nuclear translocation of the transcription factor FOXO, thereby downregulating the expression of pro-apoptotic genes (such as Bim and FasL)[139]. In addition, AKT also promotes protein synthesis and cell growth by activating the mTOR pathway[140].

In PH patients and animal models, phosphorylation of AKT is significantly elevated, particularly in PASMCs. This persistent activation endows the cells with resistance to apoptotic stimuli (such as hypoxia and oxidative stress), contributing to excessive cell proliferation and medial thickening[141,142]. Studies suggest

that inhibiting the PI3K/AKT pathway induces PASMC apoptosis and reverses vascular remodeling, suggesting a key role of this pathway in maintaining the homeostasis of PASMCs[143].

MAPK pathway: regulating proliferation and inflammatory response

Integrins also activate the MAPK family, including ERK1/2, JNK, and p38 MAPK, all of which regulate cell proliferation, stress response, and inflammation.

• **ERK1/2 pathway**: Integrins activate the FAK-Ras-Raf-MEK cascade to promote cell cycle progression (e.g., upregulating cyclin D1, inhibiting p27), driving abnormal proliferation of PASMCs and ECs. In hypoxic PH models, sustained activation of ERK is closely associated with vascular wall thickening[144,145].

• **p38 MAPK pathway**: This pathway is induced in response to inflammation and stress stimuli and is involved in the production and secretion of pro-inflammatory factors (e.g., IL-6, TNF-α), enhancing the local inflammatory response[146].

• **JNK pathway**: Activated under conditions of oxidative stress and mechanical tension, JNK regulates the balance between cell apoptosis and survival, and in late-stage PH, it may be involved in right ventricular remodeling[147].

The synergistic effect of these three pathways enables integrins to not only regulate pulmonary vascular structure but also participate in chronic inflammatory responses in PH.

Cross-talk with growth factor receptors: signal amplification and synergy

There is extensive "cross-talk" between integrins and growth factor receptors (GFRs), forming a synergistic signaling network that significantly enhances pathological signal output. This cross-talk occurs through two main mechanisms:

• **Transactivation**: Integrin aggregation promotes the phosphorylation of GFRs [e.g., platelet-derived GFRs (PDGFRs); epidermal growth factor receptors (EGFRs); vascular endothelial growth factor receptor (VEGFR)], initiating downstream signaling even in the absence of ligands. For instance, αvβ3 integrin mediates Src-dependent tyrosine phosphorylation of PDGFR, enhancing its sensitivity to platelet-derived growth factors (PDGF)[148].

• **Co-localization and complex formation**: Integrins and GFRs may form physical complexes on the cell membrane, efficiently, effectively recruiting and activating signaling molecules. For example, co-aggregation of αvβ3 with PDGFR significantly enhances the activation of MAPK and PI3K pathways, synergistically driving excessive proliferation and migration of PASMCs[149,150].

This integrin-GFR synergy explains why single-target therapies (e.g., PDGF inhibition alone) are often ineffective in clinical practice and suggests that combined inhibition of integrin and growth factor pathways could be more effective.

Regulation of TGF-β activation: linking mechanical signals to fibrosis

TGF-β is a key pleiotropic cytokine that drives fibrosis, endothelial-mesenchymal transition (EndMT), and ECM deposition in PH[151-153]. TGF-β usually exists in an inactive "latent complex" form in the ECM and remains dormant by binding to latent TGF-β-binding proteins (LTBPs)[154]. Mechanical activation of latent TGF-β represents a key regulatory node linking matrix remodeling to profibrotic signaling.

Integrins αvβ6 and αvβ8 recognize these latent complexes through their RGD motif and, under mechanical stress, induce conformational changes that release biologically active TGF-β[155,156]. While early work established this activation mechanism, recent preclinical studies have substantially advanced our understanding of its pathological relevance. Emerging evidence published after 2023 demonstrates that genetic or pharmacological blockade of αvβ6 and αvβ8 integrins effectively suppresses TGF-β activation *in vivo*, leading to marked attenuation of fibrotic remodeling and mesenchymal transition programs[25,26,157].

In the context of PH, αvβ6 and αvβ8 expression is markedly upregulated in perivascular fibroblasts and dysfunctional pulmonary endothelial cells, creating a permissive microenvironment for sustained TGF-β activation[155]. Recent experimental studies further suggest that integrin-dependent TGF-β activation not only promotes fibroblast-to-myofibroblast transformation and the secretion of collagen and fibronectin but also induces EndMT in endothelial cells, granting them the ability to migrate and synthesize ECM, thereby directly contributing to perivascular fibrosis and vascular wall thickening[157,158]. Although these mechanistic insights are primarily derived from previous preclinical models, they provide strong support for a conserved integrin-TGF-β axis that links mechanical cues to fibrotic remodeling in pulmonary vascular disease.

These findings indicate that integrin-mediated TGF-β activation plays a critical role in PH, acting as a key bridge connecting mechanical microenvironment changes to tissue fibrosis. Through this mechanism, integrins not only promote vascular fibrosis but also accelerate PH progression, providing a potential new direction for therapeutic strategies targeting integrin and TGF-β pathways.

Collectively, accumulating evidence indicates that distinct integrin subtypes are differentially expressed across pulmonary vascular cell populations and contribute to multiple facets of pulmonary vascular remodeling, including smooth muscle cell hyperplasia, endothelial dysfunction, inflammation, and fibrosis. To provide an integrated overview, the major integrin subtypes implicated in PH, along with their predominant cellular expression, pathological roles, therapeutic relevance, and correspondence with distinct PH phenotypes, are summarized in Table 3.

THERAPEUTIC TARGETING OF INTEGRINS

Integrin inhibitors as potential therapeutic strategies for PAH

Given the central role of integrins in extracellular matrix remodeling, mechanotransduction, and pathological vascular signaling in PH, targeting specific integrin subtypes or their downstream effectors has emerged as a promising therapeutic approach. By directly modulating integrin activity, we can disrupt the aberrant activation of key downstream signaling pathways—namely FAK, TGF-β, and YAP/TAZ—which converge on fundamental processes driving pulmonary vascular remodeling, including abnormal cell proliferation, resistance to apoptosis, dysregulated mechanotransduction, and fibrosis. This approach offers a mechanistically grounded strategy not merely to alleviate symptomatic vasoconstriction, but to reverse the underlying structural pathology of PH. Preclinical studies have evaluated several integrin-directed agents—such as RGD-mimetic peptides and small-molecule inhibitors—with encouraging results in animal models of PH. This section reviews current advances and challenges in the development of integrin-targeted therapies for PH, and the major integrin-targeting therapeutic candidates discussed are summarized in Table 4.

α5β1 integrin inhibitors

Among various subtypes, α5β1 has been the most extensively studied target. Preclinical studies have shown that blocking α5β1 function with research-grade antibodies or small molecule inhibitors like Myocardin-related transcription factor 1 in both monocrotaline (MCT) and Sugen/hypoxia (SuHx) models reverses existing pulmonary vascular remodeling and improves right heart function[22]. Notably, these effects

Table 3. Key integrin subtypes in pulmonary hypertension: cellular distribution, pathological roles, and therapeutic relevance

Integrin subtype	Primary cell types in PH	Key pathological roles	Representative signaling pathways	Therapeutic relevance	Main PH subtype association
α5β1	PASMCs, PAECs	Drives PASMC proliferation and migration; promotes medial hypertrophy and ECM stiffening	FAK-Src, PI3K/Akt, MAPK; fibronectin-dependent mechanotransduction	Emerging target; α5β1 blockade attenuates vascular remodeling in preclinical PH models	PAH[22]
αvβ3 / αvβ5	PASMCs, PAECs (plexiform lesions)	Promotes pathological angiogenesis, apoptosis resistance, and hyperproliferation	FAK-ERK, PI3K/Akt; cross-talk with PDGFR/VEGFR	RGD-based inhibitors (e.g., cilengitide); translational lessons from oncology	PAH[126,159], Congenital Heart Disease-Associated PAH[125]
αvβ6	Perivascular fibroblasts, dysfunctional PAECs	Activates latent TGF-β; promotes EndMT-like phenotypic switching and perivascular fibrosis	Mechanical TGF-β activation; Smad2/3 signaling	Small-molecule and peptide inhibitors under investigation in fibrotic diseases	PAH[160]; pulmonary inflammation and fibrosis[155]
αvβ8	Endothelial cells, fibroblasts	Regulates local TGF-β bioavailability; contributes to vascular fibrosis and inflammatory remodeling	TGF-β/Smad signaling; ECM-integrin feedback	Dual αvβ6/αvβ8 blockade proposed to suppress pathological TGF-β activation	PAH[160]
α1β1 / α2β1	PASMCs, fibroblasts	Mediates collagen sensing; reinforces ECM-driven vascular stiffening	Collagen-dependent integrin signaling	Largely unexplored in PH; potential modulators of matrix-cell feedback	Unknown
β1 integrin (general)	PASMCs, PAECs, fibroblasts	Central mechanosensor sustaining proliferative and fibrotic signaling loops	FAK-YAP/TAZ-Hippo axis	Broad mechanotransduction target with translational potential	PAH[161], Hypoxic pulmonary hypertension (PH)[162]

This table summarizes the major integrin subtypes implicated in the pathogenesis of PH, highlighting their predominant cellular expression within the pulmonary vasculature, principal pathological functions, key downstream signaling pathways, and current or emerging therapeutic strategies. Collectively, these integrins contribute to pulmonary vascular remodeling through regulation of smooth muscle cell proliferation, endothelial dysfunction, inflammatory cell recruitment, extracellular matrix (ECM) remodeling, and integrin-mediated activation of profibrotic signaling pathways such as TGF-β.

are comparable or even superior to Sotatercept, an FDA-approved drug for adult PAH[163]. Moreover, the α5β1 monoclonal antibody, volociximab, has undergone early clinical trials in cancer patients[164], showing acceptable tolerability, suggesting that α5β1 is a potential target for disease-modifying therapy. However, specialized clinical validation in PAH patients is still needed.

Small molecule and peptide integrin inhibitors

Various small molecule and peptide integrin inhibitors have shown promise for repositioning. ATN-161, a non-RGD pentapeptide that antagonizes α5β1, has demonstrated safety in phase I oncology trials and alleviates vascular remodeling in cardiovascular disease models[165,166]. Cilengitide, a cyclic RGD peptide targeting αvβ3/αvβ5, has completed several phase I/II clinical trials in oncology with manageable safety[167-170]. MK-0429, a pan-inhibitor of αv integrins, has shown antifibrotic effects in renal and pulmonary fibrosis models[171,172]. Although these molecules have not been tested in PAH patients, their pharmacological characteristics suggest significant translational potential, particularly in PAH patients with fibrotic phenotypes.

αvβ6/αvβ1 inhibitors

Some integrin inhibitors developed for fibrotic diseases may be relevant to PAH with concomitant fibrosis. GSK3008348, an inhaled αvβ6 inhibitor, has been shown to effectively bind the target and inhibit the TGF-β pathway in idiopathic pulmonary fibrosis (IPF) patients[173]. BG00011 (STX-100, αvβ6 monoclonal antibody) and Bexotegrast (PLN-74809, dual αvβ6/αvβ1 inhibitor) have shown anti-fibrotic effects in IPF, with good safety and tolerability in phase I trials[174-176]. Though these drugs have not been tested in PAH, they may have potential value in PAH patients with concurrent fibrosis.

Table 4. Summary of integrin-targeting therapeutic candidates for pulmonary hypertension (PH)

Drug name	Target integrin	Current stage of development	Key findings & potential relevance to PAH	References
MRT1	α5β1	Preclinical	Reverses established pulmonary vascular remodeling and improves right heart function in MCT and SuHx PH models; efficacy comparable or superior to FDA-approved PAH drug Sotatercept	[22,163]
Volociximab	α5β1	Phase I (oncology)	Monoclonal antibody with acceptable tolerability in cancer clinical trials; identified as a potential disease-modifying target for PAH, pending specialized PAH clinical validation	[164]
ATN-161	α5β1	Phase I (oncology)	Non-RGD pentapeptide integrin antagonist; confirmed safety in oncology Phase I trials; alleviates vascular remodeling in cardiovascular disease models, with translational potential for PAH	[165,166]
Cilengitide	αvβ3/αvβ5	Phase I/II (oncology)	Cyclic RGD peptide; manageable safety profile in multiple oncology Phase I/II trials; promising candidate for PAH, especially for patients with fibrotic phenotypes	[167-170]
MK-0429	Pan-αv integrins	Preclinical	Exerts antifibrotic effects in renal and pulmonary fibrosis models; untested in PAH but holds translational value for PAH with fibrotic features	[171,172]
GSK3008348	αvβ6	Clinical (IPF; inhaled)	Effectively binds target and inhibits TGF-β pathway in IPF patients; potential relevance for PAH patients with concomitant fibrosis	[173]
BG00011 (STX-100)	αvβ6	Phase I (IPF)	Monoclonal antibody with anti-fibrotic effects in IPF models; good safety and tolerability in Phase I trials; may benefit PAH patients with concurrent fibrosis	[174,175]
Bexotegrast (PLN-74809)	Dual αvβ6/αvβ1	Phase I (IPF)	Dual integrin inhibitor with anti-fibrotic activity in IPF; favorable safety profile in Phase I trials; potential therapeutic value for PAH with concomitant fibrosis	[176]
EDIL3-αvβ3 Axis Inhibitors	EDIL3-αvβ3 ligand-receptor axis	Preclinical	Blockade downregulates ERK1/2 activation, inhibits PASMC proliferation and migration, and alleviates pulmonary vascular remodeling; provides proof-of-concept for ligand-receptor	[159]

This table outlines promising investigational agents targeting specific integrins involved in pulmonary vascular remodeling, with a focus on their relevance to pulmonary arterial hypertension (PAH). Myocardin-related transcription factor 1 (MRT1), a small-molecule inhibitor of α5β1 integrin, has shown efficacy in reversing established pulmonary vascular remodeling and improving right heart function in preclinical models. BG00011 (STX-100), a monoclonal antibody against αvβ6 integrin, demonstrated anti-fibrotic effects in idiopathic pulmonary fibrosis (IPF) models and favorable safety in Phase I trials, suggesting potential benefit in PAH patients with concomitant lung fibrosis. Bexotegrast (PLN-74809), a dual inhibitor of αvβ6 and αvβ1 integrins, also exhibits anti-fibrotic activity and a favorable safety profile in early-phase studies, supporting its therapeutic potential in PAH with fibrotic components. EDIL3-αvβ3 axis inhibitors, currently in preclinical development, target the ligand-receptor interaction between EDIL3 and αvβ3 integrin; they suppress ERK1/2 signaling, inhibit pulmonary arterial smooth muscle cell (PASMC) proliferation and migration, and attenuate vascular remodeling, providing proof-of-concept for targeting this pathway in PH. All candidates are listed with their current stage of clinical development and key findings relevant to PH.

Ligand-receptor axis intervention

Recent studies have identified the EDIL3-αvβ3 axis as a critical driver of PASMC proliferation and migration. Blocking this interaction downregulates ERK1/2 activation and alleviates vascular remodeling[159]. This provides proof of concept for cutting off pathological signals at the ligand-receptor interface.

Taken together, despite compelling preclinical evidence supporting integrin-targeted interventions in pulmonary vascular remodeling, there is currently a lack of Phase II/III clinical trial data evaluating integrin inhibitors in PAH patients. Future translational efforts should prioritize carefully designed early-phase clinical trials incorporating biomarker-based patient stratification, disease-stage-specific enrollment, and mechanistic endpoints to bridge this critical gap between bench and bedside.

CHALLENGES AND PROSPECTS

With the deepening of research into the pathogenesis of PH, the role of the ECM and mechanotransduction systems in pulmonary vascular remodeling has received increasing attention[15]. As a key molecule linking cells to the ECM, integrins play an important role in the pathology of PH[22]. Although integrin signaling has

been shown to play a crucial role in PH pathogenesis, the current challenge lies in how to translate these findings into effective clinical treatments.

There are many members of the integrin family, and their functions and expression differ significantly across different tissues[31]. Therefore, accurately identifying specific integrin subtypes associated with PH and developing highly selective inhibitors is critical for avoiding off-target effects and reducing side effects. Additionally, it is necessary to gain a deeper understanding of the specific roles of each subtype in different types of PH to achieve precision therapy.

While several integrin inhibitors have made progress in oncology and fibrotic diseases, clinical validation in PH is still in the early stages[177,178]. One major barrier to clinical translation in PH is efficacy concerns, as integrin inhibitors have shown limited success in targeting vascular remodeling in PH. Furthermore, biomarker limitations in PH complicate patient stratification, making it difficult to identify those most likely to benefit from integrin-targeted therapies. Off-target effects, particularly in the cardiovascular system, may also contribute to safety concerns. These challenges highlight the need for further research into integrin inhibitor efficacy in PH and the development of reliable biomarkers to guide patient selection for future trials.

Importantly, the limited success of certain integrin inhibitors in oncology trials offers valuable insights for their potential application in PH. For instance, Cilengitide—a cyclic RGD peptide targeting αvβ3 and αvβ5—exhibited promising anti-angiogenic activity in preclinical tumor models yet failed to deliver significant survival benefits in Phase III clinical trials for glioblastoma. Several key factors have been implicated in this outcome, including inadequate biomarker-guided patient stratification, functional redundancy among integrin subtypes, and paradoxical pro-angiogenic effects at suboptimal dosing concentrations[179]. These clinical experiences hold profound relevance for PH translational research. In contrast to oncology, PH is a chronic progressive disorder requiring long-term therapeutic intervention, where safety profiles, rational dosing strategies, and sustained target engagement are of particular importance. Furthermore, the inherent heterogeneity of PH suggests that only distinct patient subgroups—such as those with marked integrin overexpression or ECM-driven vascular remodeling—are likely to derive clinical benefit from integrin-targeted therapies[180]. Therefore, successful translation of such agents in PH will likely hinge on improved biomarker-based patient selection, disease-stage-specific therapeutic intervention, and meticulous optimization of dosing regimens to mitigate off-target effects or compensatory signaling pathways.

Systemic administration of integrin inhibitors may lead to severe side effects, particularly in the cardiovascular system[181]. Therefore, improving the delivery efficiency of drugs to the lungs and reducing systemic side effects is key to achieving clinical translation. Nanotechnology, liposomes, and other targeted delivery systems provide new approaches to solving this problem. For example, nanoparticles surface-modified with RGD peptides or anti-PECAM antibodies actively targets activated endothelial cells, enabling localized drug accumulation[182,183]. Moreover, inhaled formulations (such as nebulized inhalers) also represent a potential delivery method, directly acting on the pulmonary lesions and reducing systemic exposure[173].

Biomarkers and treatment responses in different types of PH patients show significant differences. For instance, some patients may exhibit overexpression of specific integrin subtypes, while others may rely on different signaling pathways (e.g., PDGF, VEGF)[23,126]. Developing individualized treatment plans based on molecular characteristics remains an urgent challenge.

Looking ahead, the development of imaging-based and circulating biomarkers reflecting integrin expression or activation status may provide powerful tools for patient stratification in PH. While direct clinical evidence supporting circulating soluble integrin ectodomains as validated biomarkers remains limited, increasing attention has focused on ECM-derived peptides—such as collagen degradation neo-epitopes and matrikines—which reflect pathological matrix turnover and vascular fibrosis. Several studies in PH and related fibrotic diseases have demonstrated that these ECM fragments correlate with disease severity and hemodynamic impairment[184-186]. In parallel, integrin-targeted molecular imaging approaches, including αvβ3-directed PET tracers, are being explored to enable non-invasive assessment of regional vascular remodeling and integrin activation in vivo, highlighting an emerging translational framework for biomarker-guided precision therapy.

Despite the multiple challenges currently faced in the study of integrins in PH, their emerging role as a therapeutic target offers unprecedented treatment potential. Through further basic research and clinical trials, we expect to see integrin-targeted therapies become a new option for PH treatment. By combining modern molecular biology techniques and drug delivery systems, integrin-targeted therapies not only have the potential to slow vascular remodeling but also reverse the structural damage caused by PH, offering patients better prognosis.

CONCLUSION

Integrin signaling pathways play a central role in the pathogenesis of PH, driving vascular remodeling through their impact on cell proliferation, survival, inflammation, and ECM dynamics. Dysregulation of integrin expression and abnormal activation of downstream signaling pathways (such as FAK, PI3K/Akt, and MAPK) create a favorable environment for disease progression. While current treatments mainly target vasoconstriction, integrin-targeted therapies offer a strategy to address the structural basis of PH. Integrin-targeted strategies not only alleviate vasoconstriction but may also reverse structural remodeling, representing a paradigm shift in PH therapeutics. Although clinical translation faces obstacles, advances in selective inhibitors and delivery systems hold promising potential. A deeper understanding of integrin biology in PH is essential for developing effective disease-modifying therapies.

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Authors' contributions

Conceptualized the manuscript: He S, Bian JS
Wrote the manuscript text and made a visualization: He S
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Conflicts of interest

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Consent for publication

Not applicable.

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