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Review

Research Progress of Pericytes in Pulmonary Fibrosis

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Abstract

Pericytes, a specific type of mesenchymal cell that surround the basement membrane of pulmonary venules and capillaries. They are crucial pathological features observed in individuals with the severe lung disease of pulmonary fibrosis (PF). The presence of pericytes leads to inflammation and fibrosis in the lung interstitium and alveolar space due to the release of various cytokines and chemokines. Pericytes also stimulate the proliferation and activation of fibroblasts, thereby promoting the progression of PF. Previous studies examining the mechanism of action of pericytes have primarily focused on cell signal transduction pathways, cell growth and death processes, and the synthesis and breakdown of extracellular matrix (ECM). Notably, the transforming growth factor-β (TGF-β) and Wnt signaling pathways have been associated with the action of pericytes in driving the progression of PF. It is therefore clear that pericytes play an essential role in the development of PF, while also offering possible avenues for targeted therapeutic intervention against this condition. The current article provides a comprehensive review on how pericytes contribute to inflammatory responses, as well as their importance for understanding the mechanism of PF. In addition, this review discusses the potential use of pericyte-targeted approaches for the treatment of patients affected by this debilitating lung disease.

Keywords: pulmonary fibrosis; pericytes; myofibroblasts; transformation

1. Background

Pulmonary fibrosis (PF) is a type of interstitial lung disease that arises due to various causative factors, both inside and outside the lungs. It is characterized by the infiltration of inflammatory cells such as macrophages and lymphocytes, the proliferation of myofibroblasts, and the accumulation of extracellular matrix (ECM) within the interstitial space. Most interstitial lung diseases ultimately result in PF, which seriously affects patient health and can even lead to death. The etiology of idiopathic PF (IPF) is unknown [1]. IPF often exhibits chronic progression, massive fibroblast proliferation, ECM deposition, restrictive ventilatory dysfunction in the lungs, and eventually death because of respiratory failure [2]. The prevalence rate of IPF ranges from 0.5 to 18 cases per 100,000 individuals, while the average lifespan after diagnosis is typically only 2–3 years. At present, there are few effective approaches for the prevention and treatment of IPF [1,2]. Hence, there is an urgent need to investigate the development of PF, and especially the molecular mechanism underlying IPF. This should lead to the discovery of more effective drugs for the prevention and treatment of PF.

Abnormal myofibroblast proliferation and massive ECM secretion are prominent features of PF [3,4]. The classic pathogenesis of fibrotic diseases defines resident fibroblasts as the main source of myofibroblasts. However, recent studies suggest that pericytes are one of the essential sources of myofibroblasts [5–10]. Studies on liver and kidney injuries have confirmed the role of pericytes in fibrosis [6,7]. Moreover, studies on spinal cord injuries suggest that pericytes are direct effector cells in fibrosis [8,9]. Kuppe *et al*. [10] employed single cell RNA sequencing (RNA-seq) to comprehensively map the entire human kidney. They profiled the transcriptomes of both proximal and non-proximal tubule cells in healthy and fibrotic kidneys. This approach identified all matrix-producing cells with high precision, revealing distinct subpopulations of pericytes and fibroblasts as the primary cell types responsible for generating scar-forming myofibroblasts during fibrosis in the human kidney. Studies conducted on different organs and employing cell-fate mapping have provided support for pericyte-myofibroblast transition (PMT) in PF. Pericytes may therefore be a novel target in the treatment of fibrotic diseases [5–7]. Wang *et al*. [11] found that regulation of the Lysine-specific demethylase 5B (KDM5B)/platelet-derived growth factor receptor alpha or beta (PDGFRα/β) signaling pathway through overexpression of growth arrest-specific transcript 5 inhibited transforming growth factor-β1 (TGF-β1)-induced pericytomyoblast differentiation, thereby reducing bleomycin-induced PF in mice. Hannan *et al*. [12] found that pulmonary pericytes were myofibroblast progen-

itors in a bleomycin-induced model of lung injury. Sun *et al*. [13] reported that inhibition of fucosyltransferase 8 expression effectively impeded the transdifferentiation of pericytes into myofibroblasts. Finally, pericytes have also been shown to participate in airway remodeling and to transform into myofibroblasts in a mouse model of chronic allergic asthma [14]. In light of the above findings, we herein describe the characteristics of pericytes and their possible mechanism of involvement in PF. We also provide a theoretical basis for the use of pericytes to treat PF.

2. The Epidemiology of Pulmonary Fibrosis

Interstitial lung disease refers to a group of diseases in which cell proliferation, interstitial inflammation and fibrosis occur after alveolar wall damage due to various causes. Idiopathic interstitial pneumonia, specifically IPF, is widely recognized as the most prevalent and severe form within this category [1,2]. IPF is a fatal, irreversible, progressive, and chronic fibrotic respiratory disease of unknown etiology. This non-cancer-related lung disease has poor prognosis and a high prevalence. Because of similar risk factors, the 2019 coronavirus disease pandemic has further increased the burden of IPF [15]. The prevalence of IPF has been increasing over the years, with estimates ranging from 2.8 to 18 cases per year per 100,000 individuals in Europe and North America. Although data on global variation is limited, the occurrence of IPF is thought to be comparatively lower in Asia and South America, with estimates ranging from 0.5 to 4.2 cases per 100,000 individuals annually. IPF tends to affect males more frequently and is uncommon in individuals aged $<$50 years, with the typical age at diagnosis being about 65 years [2]. This disease exhibits a range of outcomes and is difficult to predict, with an average survival period of 2–3 years following diagnosis. Respiratory failure typically ensues as a result of the illness. IPF has an unfavorable prognosis and does not respond well to conventional medications used in fibrosis treatment. Individuals with IPF may encounter sudden episodes of the condition due to unknown causes, leading to high mortality rates [16]. Hence, in order to promptly diagnose IPF it is important to understand the underlying cellular and molecular mechanisms, thereby also facilitating appropriate drug discovery.

3. Growing Focus on the Involvement of Pericytes in the Development of Pulmonary Fibrosis

PF is a consequence of various genetic and environmental risk factors, including but not limited to patient exposure to tobacco smoke or asbestos, autoimmune disorders, and inflammatory conditions [17]. Infection, trauma, cellular stress, and inflammation serve as triggers for wound healing, which tries to restore the normal functions of damaged tissues before eventually ceasing. Prolonged or recurrent injuries lead to excessive production of angiogenic factors alongside the inflammatory and fibrotic cytokines. This dysregulated and unresolved wound-healing response results in fibrosis, which is characterized by the replacement of normal tissues with scar tissue, and leads to a pathological decline in organ function [18–20]. After sustaining an injury, lung epithelial cells release a variety of potent factors that can stimulate fibroblasts, including TGF-β, connective tissue growth factor, prostaglandin E2, sonic hedgehog, Wnt1-inducible signaling pathway protein 1, and interleukin-1α (IL-1α) [18,21]. Myofibroblasts play a crucial role in fibrotic diseases as they are primarily responsible for constructing and modifying the ECM. The expression of alpha-smooth muscle actin (α-SMA) by myofibroblasts distinguishes them from other cell types. It is well established that fibroblasts produce collagens and numerous other proteins that form the ECM of fibrous connective tissues. Vimentin, collagen triple helix repeat containing 1, and fibroblast-specific protein 11 have served as markers to identify fibroblasts by immunohistochemical techniques [22,23]. Due to their abundance in active scar lesions and their rarity in healthy organs, myofibroblasts have emerged as a significant therapeutic target for fibrotic diseases. Consequently, extensive research has been conducted to investigate the origin of myofibroblasts. Various cell types have been proposed as potential sources for their generation, including pericytes, interstitial α-SMA-fibroblasts, epithelial cells, endothelial cells, and hematopoietic fibroblasts [17]. Additionally, ECM increases pulmonary ischemia and hypoxia, thus further promoting PF [24].

Using a bleomycin-induced mouse model of fibrosis, previous studies have shown that most pulmonary myofibroblasts are derived from pericytes. Pericytes can be distinguished from fibrotic cells in many organs. Recent analysis has revealed that pericyte-like cells are important myofibroblast progenitors [24]. Other findings also support the notion that pericytes are an important source of myofibroblasts [25]. Researchers have recently applied genetic fate mapping technology to investigate whether pericytes are an important source of pulmonary interstitial myofibroblasts [17]. The mechanism underlying pericyte activation and the subsequent molecular biological effects could provide new intervention strategies for the treatment of PF. Research suggests that several cell types release cytokines such as TGF-β and platelet-derived growth factor (PDGF) including alveolar epithelial cells, vascular endothelial cells, and macrophages. These cytokines then activate signaling pathways in pericytes. Consequently, downstream proteins are phosphorylated, ultimately leading to pericyte activation [26–29]. Zhao *et al.* [29] reported that myofibroblasts cause scar formation during healing. TGF-β is a fibrogenic cytokine, and TGF-beta-induced phosphorylation of Smad2 and Smad3 in the nucleus mediate pro-fibrotic gene expression. Siedlecki *et al.* [28] found that PDGF signal transduction was crucial for pericellular cells. The recruitment of

these cells induced vascular maturation, which was mainly dependent on PDGF. Pericellular cells migrate to new blood vessels along the PDGF gradient, proliferate, and then bind to the inner duct to achieve vascular stability via physical contact. The above studies show that excessive activation of multiple signaling pathways can cause pericyte activation. The potential treatment of PF could thus involve targeting pericytes to effectively inhibit the progression of this condition.

4. Biological Characteristics of Pericytes

The Definition and Origin of Pericytes

The lung plays a vital role in various biological processes, including the exchange of gases, immune surveillance, and the maintenance of a protective barrier. This highly vascularized organ receives blood supply from both the pulmonary and bronchial arteries. Therefore, pericytes are likely to have significant involvement in lung physiology due to their strategic positioning within the perivascular niche [30]. Pulmonary pericytes play a crucial role in the development of blood vessels and ensure the integrity of endothelial cells, thereby contributing to the maintenance of organ homeostasis [31]. Clark *et al*. [32] first reported the existence of pericytes in 1925 when they observed that connective tissue components of tadpole larvae formed pericytes on capillaries. Subsequent investigations employing chicken-quail chimeras and specific markers for individual cells demonstrated that pericytes originate from the neural crest and are predominantly found in the head region and central nervous system [33,34]. Fate-mapping analysis in mice utilized gene reporters to demonstrate that pericytes in the gut, liver, heart, and lung originate from cells derived from the mesothelium through processes such as epithelial-mesenchymal transition (EMT), stratification, and migration [35]. Pericytes are vascular wall cells within the basement membrane and are connected to endothelial cells. They are a heterogeneous cell population that vary greatly depending on the tissue type [36]. As pericytes come into contact with the microvascular endothelium, they play a crucial role in promoting vascular maturation and ensuring its stability. This includes capillaries, arterioles before capillaries, venules after capillaries, and collecting venules [30]. Pericytes function in the regulation of blood vessels, and they are key cells in cardiovascular diseases.

In addition, pericytes may serve as progenitor cells for tissue regeneration [37,38]. According to Birbrair *et al*. [39], two distinct pericellular subtypes exist in the interstitium of skeletal muscle: type 1 ($Nestin^-/NG2^+$) and type 2 ($Nestin^+/NG2^+$). Their findings indicate that type 2 pericytes are involved in muscle regeneration following injury, without the generation of fat tissue. Conversely, type 1 pericytes do not contribute to muscle formation, but instead play a role in the accumulation of adipose tissue. This implies that both type 1 and type 2 pericytes have the ability to regenerate, and that their differences may arise from the equilibrium between myogenic and non-myogenic processes. However, further investigation is required to determine whether the transplantation of type 2 pericytes enhances physiological performance and the repair and regeneration of skeletal muscle [39]. Another study showed that pericytes exist in the small blood vessels of skeletal muscle and promote the growth and regeneration of skeletal muscle after birth [40]. Type 1 rather than type 2 pericytes exhibit fibrogenic properties both *in vitro* and *in vivo*, and are involved in the accumulation of fibrous tissue within various organs such as skeletal muscle and lungs [41]. *In vivo* pericyte lineage tracking studies showed that endogenous pericytes can differentiate into osteoblasts and osteoblasts, thereby serving as a source of osteoblasts for the promotion of fracture healing [42]. This suggests that pericytes are potential candidates for the treatment of bone diseases. In addition to their involvement in skeletal muscle, recent research suggests that $CD146^+$ pericytes derived from microtia tissue could be a valuable cell source for the regeneration of ear cartilage [43]. Type 1 and type 2 pericytes have distinct roles in neurogenesis. While type 1 pericytes generate α-SMA pericytes, they do not give rise to nerve cells. Conversely, under optimized culture conditions, type 2 pericytes can produce neural progenitors that resemble brain neuron-glial antigen2 ($NG2^-$) glial cells [44]. Teichert *et al*. [45] demonstrated the significance of pericyte-expressed Tie2 receptor in regulating angiogenesis and vascular maturation. In contrast to type 1 pericytes, type 2 pericytes play a significant role in angiogenesis in tumors including lung cancer and glioblastoma [46,47]. Together, these studies suggest that pericytes have unique regenerative capabilities, which could lead to the development of new therapeutic strategies.

5. Physiological Functions of Pericytes

5.1 Pericyte biomarkers

Pericyte characteristics include pericyte/endothelial cell coverage, shape, and several markers that validate pericyte heterogeneity [31]. These cells are commonly identified using markers such as α-SMA, NG2, alkaline phosphatase, and PDGFRβ. Additional markers linked to pericytes include desmin, vimentin, aminopeptidase N, CD13, CD133, and CD146 [37,48–50]. Novel pericyte identifiers include the regulator of G protein signaling 5, endosialin, and delta-like homolog 1. Expression of the key pericyte markers is dynamic and varies according to developmental stage, disease, and specific tissue [35]. Marker levels also vary depending on the stage and location of the pericyte. For example, pericytes expressing α-SMA are frequently observed in the retina and retinopathy. The expression of NG2 and PDGFR-β is elevated in pericytes associated with cardiac fibrosis and PF [51]. Furthermore, increased levels of G protein signaling 5 were consistently observed in angiogenic pericytes, indicating the extent of vascular remodeling [52]. However, due to the nature of pericytes as

potential progenitors, none of the markers examined was specific. Moreover, pericytes share common markers with neighboring cells. For example, PDGFR-β is a well-known pericyte marker, but is also expressed in smooth muscle cells, myofibroblasts, stem cells, and neuronal progenitor cells [53]. NG2 is also a well-known pericyte marker, but has been found in adult skin stem cells, adipocytes and oligodendrocyte progenitors [54,55]. α-SMA serves as a common marker for pericytes with contractile properties, smooth muscle cells within blood vessels, and myofibroblasts [56]. Currently, there are no specific markers for identifying pericytes, and use of the above markers is not a reliable way to track pericytes. However, a seminal report by Yamaguchi *et al*. [57] showed that simultaneous positivity for PDGFRB and chondroitin sulfate proteoglycan 4 detected only pericytes in the mouse brain. It should therefore be emphasized that the markers described above are expressed not only in pericytes but also in other cell types. Therefore, it is often necessary to combine multiple markers in order to identify and verify the presence and function of pericytes. Further study of pericytes should lead to the discovery of new markers, or refinement in the use of existing markers.

5.2 Interaction between Pericytes and Endothelial Cells

Reciprocal regulation between pericytes and endothelial cells occurs throughout embryonic development, adult homeostasis, and injury responses. PDGF, notch, epidermal growth factor, hedgehog, ephrin, sphingosine-1-phosphate receptor, and stromal-derived factor-1 are thought to establish connections between pericytes and endothelial cells through specific pathways. These interactions play a crucial role in modulating the proliferation, differentiation, localization, and stability of the vasculature during development. Pericytes and endothelial cells work together to deposit and organize the vascular basement membrane. Additionally, pericytes can detach from the endothelium and transform into myofibroblasts, thereby disrupting vascular homeostasis [17]. Endothelial-pericyte communication is generally mediated via specialized intercellular junctions. For example, the peg-socket structure binds to endothelial cells and pericytes, and connects to the endothelial cells and cell matrix [37,48]. The degree of pericyte vascular coverage varies between different organs and anatomical structures, with a relatively high occurrence observed in the lungs. In pulmonary tissue, pericytes are found within the capillary basement membrane and are able to enhance peg-socket interactions with endothelial cells, eventually leading to the formation of adhesions, gaps, and tight junctions between one or more endothelial cells and a pericyte [58–60]. The pericyte-endothelial ratio varies across tissues, and the number and size of pericyte-endothelial contacts also varies widely between different tissues and vessels. The ratio of endothelial cells to pericytes in normal tissues can range from 1:1 to 10:1. The ratio is highest (1:1) in neural tissues and especially in the retina, probably due to their high metabolic activity and the need to control blood flow. The opposite is observed in skeletal muscle tissues, where the ratio of endothelial cells to pericytes is 10:1 [37,61]. Differences in the dispersion and arrangement of pericytes suggest a wide range of microvascular variation and adaptability at the cellular level, probably due to the array of pericyte functions in governing various physiological systems. Close connections exist between endothelial cells and pericytes, and their mutual communication is essential for neovascularization and the maintenance of vascular stability. Endothelial cell-pericyte interactions play a crucial role in the regulation of vascular remodeling and stability, together with various factors such as TGF-β, angiopoietin 1/angiopoietin 2/Tie-2 receptor, PDGF-B/PDGFR-β, vascular endothelial growth factor (VEGF), and sphingosine-1-phosphate receptor [35]. A previous study found that recombinant fucosyltransferase 8, PDGFβR and TGFβR are key proteins involved in pericyte activation [25]. Interactions between pericytes and endothelial cells trigger activation of the latent TGF-β signaling pathway, thereby facilitating the differentiation and proliferation of both cell types by engaging activin receptor-like kinase 1, activin receptor-like kinase 5, and endorphins as receptors. Additionally, pericytes are stimulated to secrete extracellular collagen via Smad2 signaling [62]. Angiopoietin/iron (Ang/Tie) signals also control the association between endothelial cells and pericytes. Tie2 expressed by endothelial cells is activated by Ang1 expressed on pericytes, thus helping to maintain the static phenotype of endothelial cells. Ang1-driven Tie2 phosphorylation activates downstream pathways that mediate cell survival, proliferation, migration and anti-inflammatory signals [45]. PDGFβ secreted by angiogenic endothelial cells is the most characteristic growth factor and can recruit pericytes that express PDGFRβ. Pericytes migrate and proliferate to neovascularization along the PDGF gradient and bind to the endothelial tube. Vascular stability is achieved through physical contact, VEGF and the Ang1/Tie2 system [28]. The sphingosine-1-phosphate (S1P)/S1P1 receptor signaling axis also plays a crucial role in pericyte coverage by regulating N-cadherin, with pericyte coverage being an important sign of vascular maturation [62].

5.3 Pericyte Secretion

Pericytes release various cytokines, immunomodulatory factors and ECM, which regulate tissue repair and regeneration [63,64]. These cells also contain various pro-inflammatory factors, including IL-6, IL-8, TNF-alpha, and interferon gamma-inducible protein 10 (IP-10) that play a role in triggering inflammation responses and influencing T-cell activity [65–67]. Pericytes also release substances such as leukemia inhibitory factor (LIF), cyclooxygenase-2 (COX-2), and heme oxygenase-1 (HMOX-1) that suppress the inflammatory response during periods of inflam-

Table 1. Pericyte secretion products and functions.

Pericyte secretion products	Functions	
IL-6, 8, TNF-α, IP-10	Induce inflammation and contribute to T cell activity	[65–67]
COX-2, HMOX-1, LIF	Inhibit the inflammatory response during inflammation	[68,69]
Bmp-4, 6, 7	Prevent cell exhaustion and preserve stem cell regeneration	[70,71]
VEGF	Stimulates the differentiation and proliferation of vascular endothelial cells and pericytes, and contributes to the formation and stability of blood vessels	[72]
ECM	Promotes tissue repair and regeneration processes	[73,74]
SPARC	Irritable fibrosis	[75]

IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; IP-10, interferon gamma-inducible protein 10; COX-2, cyclooxygenase-2; HMOX-1, heme oxygenase-1; LIF, leukemia inhibitory factor; Bmp-4, 6, 7, bone morphogenetic protein-4, 6, 7; VEGF, vascular endothelial growth factor; ECM, extracellular matrix; SPARC, secreted protein acidic and cysteine-rich.

mation [68,69]. Furthermore, pericytes prevent cell failure by releasing bone morphogenetic protein-4, 6, 7 (Bmp-4, 6, 7) and preserving the regenerative capacity of stem cells [70,71]. VEGF stimulates the differentiation and proliferation of vascular endothelial cells and pericytes, thereby contributing to angiogenesis and vascular stabilization [72]. Moreover, ECM secreted by pericytes is crucial for tissue repair and regeneration [73,74]. In addition, pericytes contribute to the regulation of ECM formation and fibrosis by producing secreted protein acidic and cysteine-rich (SPARC) proteins [75]. Overall, pericytes secrete numerous cytokines and growth factors, making them pivotal for the maintenance of tissue and organ functions (Table 1, Ref. [65–75]).

6. Possible Mechanism Underlying the Transformation of Pericytes to Myofibroblasts in Pulmonary Fibrosis

6.1 The Connection between Pericytes and Myofibroblasts in Pulmonary Fibrosis

Myofibroblast proliferation and massive ECM secretion are prominent features of PF [3,4]. Resident fibroblasts are considered to be the main source of myofibroblasts. However, studies on systemic sclerosis and on fibrosis in a variety of organs have shown that pericytes act as precursors of myofibroblasts [76–78]. Following tissue injury, pericytes readily detach from the vasculature and differentiate into myofibroblasts. Subsequently, these cells deposit ECM which leads to fibrosis [35,79]. The mechanisms underlying the production of ECM by pericytes remain unclear [80]. Hung *et al*. [4] reported that pericytes expressing myofibroblast markers were present in mouse pulmonary fibrotic lesions. These authors performed functional enrichment analysis of differentially expressed genes identified by microarray experiments and found that Foxd1-derived pericytes expressed the typical markers PDGFRβ, NG2, and CD146 during cell culture. Following treatment with TGF-β, α-SMA expression was upregulated and collagen type 1 was expressed, indicating that peri-pulmonary cells can express these two myofibroblast markers. After bleomycin-induced lung injury in mice, Foxd1 ancestral pericytes account for a large proportion of α-SMA$^+$ myofibroblasts, which proliferate locally and produce collagen in fibroblast foci [4]. Subsequently, Yamaguchi *et al*. [57] reported the presence of pericytes in the fibrotic lesions of IPF patients. These authors also performed cell experiments to show that pericytes could transform into myofibroblasts after TGF-β treatment. The aforementioned results indicate the importance of PMT in the onset and progression of PF.

6.2 Fibrosis is Characterized by an Increased Number of Fibrotic Cells and a Build-up of Extracellular Matrix

Fibrotic cells encompass fibroblasts and myofibroblasts. The development of fibrosis is closely associated with pericytes due to the proliferation and transdifferentiation of fibroblasts into myofibroblasts [81]. Numerous cytokines secreted by pericytes have the ability to stimulate the growth and activation of fibrotic cells. For example, TGF-β derived from pericytes plays a critical role in the progression of fibrosis as it enhances ECM secretion and promotes the activation and proliferation of fibrotic cells [82].

In addition to their direct interaction with fibrotic cells, pericytes contribute to fibrosis by assuming a similar role to fibrotic cells. ECM is the primary component of fibrosis and consists of collagen, elastic fibers, and proteoglycans [83]. ECM production is primarily attributed to myofibroblasts, although a recent investigation found that pericytes can also secrete collagen and exhibit comparable functionalities to myofibroblasts [39]. Moreover, pericytes secrete SPARC protein, which is responsible for regulating the ECM [75]. α-SMA, PDGFR-β, and endosialin (CD248) are common markers of pericytes and fibrotic cells. Pericytes possess myofibroblast properties in the fibrotic lung microenvironment [37] and are a critical factor in the fibrosis process due to their similarities with fibrotic cells.

7. Signaling Pathways Associated with the Transformation of Pericytes to Myofibroblasts

7.1 TGF-β Pathway

TGF-β serves as a regulator that promotes fibrosis. Injured epithelial cells generate TGF-β and other signals known as damage-associated molecular patterns (DAMPs) that can be detected by immune receptors on both immune and non-immune cells [84]. Several studies have investigated the effect of TGF-β on PMT and the mechanism underlying the pathogenesis of fibrosis. TGF-β ligand was reported bind and phosphorylate TGF-βR, thus promoting ECM formation. Various downstream regulators are activated during this process, including the Smad2/3 signaling pathway, non-Smad pathways such as the mitogen-activated protein kinase (MAPK) pathway, the rho-like GTPase signaling pathway, and the phosphatidylinositol 3-Kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Smad2 and Smad3 play crucial roles by stimulating pericyte proliferation, differentiation, and migration via TGF-β. The regulation of mTOR activity in pericytes may be influenced to some extent by Akt. These findings suggest that pericyte proliferation and PMT induced by TGF-β are mediated through activation of the Smad2/3 and Akt/mTOR signaling pathways, while TGF-β attenuates laser-induced fibrosis by inhibiting the Akt/mTOR pathway [36].

Castellano *et al.* [85] reported that PMT occurs in a model of lipopolysaccharide (LPS)-induced acute renal fibrosis. Renal pericytes are activated in response to acute stimuli, such as LPS-induced acute kidney injury. In both *in vivo* and *in vitro* settings, PMT can be observed following 9 hours of LPS stimulation. In addition, the regulation of PMT involves interaction between toll-like receptor 4 (TLR-4) and TGF-β signaling. Enhanced fibroblast responsiveness to TGF-β stimulation is observed upon activation of TLR4 signaling. Moreover, LPS increases the phosphorylation of SMAD2/3 and extracellular regulated protein kinase 1 (ERK1), whereas TGF-β directly induces the phosphorylation of SMAD2/3. In summary, LPS-induced pericytes express high levels of TLR-4 and TGF-β, promote the phosphorylation of SMAD2/3 and ERK1, and undergo PMT, thus leading to acute renal fibrosis [85].

Previous studies have also shown that pericytes occur in the abundant microvasculature of the human lung. The production of TGF-β by fibroblasts and resident macrophages in the interstitial space of the lung leads to accumulation of α-SMA$^+$ pericytes in fibrotic lesions. Activation of the Smad signaling pathway is triggered by the interaction between TGF-β and TGF-βR located on the pericyte cell membrane. P-Smad2/3 accumulation in the nucleus increases binding to Smad-binding elements, thereby increasing the transcription of fibrotic genes. Thus, increased secretion of matrix proteins (including type I collagen) leads to increased ECM stiffness. In a stiff environment, focal adhesion kinase increases the translocation of megakaryoblastic leukemia 1, yes-associated protein (YAP), and transcriptional coactivators with PDZ-binding motif (TAZ), thus increasing the expression of α-SMA$^+$ and myofibroblast transformation [5].

7.2 The PDGFR Pathway

PDGF plays a crucial role in promoting fibrosis in various organs. Inhibition of PDGF could potentially serve as an effective therapeutic approach for numerous fibrotic diseases. Fibrosis encompasses several pathways, with PDGF signaling being a key mediator. The proliferation, migration, and production of ECM are key processes in fibrosis and are driven by the activation of stromal-mesenchymal cells that express PDGFR-α and -β. The bleomycin model is widely recognized as an effective *in vivo* model for the study of PF. A significant increase in PDGF expression was reported following the induction of PF by bleomycin [3]. PDGF has the ability to promote cell proliferation, movement, and EMT. The various isoforms of PDGFRβ have been implicated in several pathological conditions of mesenchymal cells that contribute to the development of diseases such as PF. Additionally, the expression of PDGF-A and PDGF-C has been observed in other cell types present in injured or fibrotic lungs [86,87]. Moreover, PDGFR-β expression is often increased in glomerular disease [88]. Further study of lung fibrosis and of signaling associated with PDGFRβ is therefore crucial for future intervention strategies [80].

PF is characterized by the conversion of pericytes into myofibroblasts through activation of the TGF-β/Smad2/3 and PDGF-β/ERK signaling pathways. Crosstalk between TGF-β and PDGF signaling is commonly found in endothelial cells and pericytes. TGF-β signaling induces phosphorylation of Smad2/3 proteins, thereby regulating the expression of fiber genes, while PDGF signaling activates ERK1/2 in pericytes. The progression of PF involves the transformation of pericytes into myofibroblasts via stimulation of the TGF-β/Smad2/3 and PDGF-β/ERK signaling cascades. Additionally, Sun *et al.* [25] reported that glycosylation can affect the binding of receptors (TGFβR and PDGFβR) to related ligands. These authors showed that inhibition of the glycosylation modification of TGFβR and PDGFβR can block pericyte activation, thereby alleviating PF. Similarly, Wang *et al.* [11] reported that IPF progression can be delayed by blocking activation of the PDGFRα/β signaling pathway. In IPF, lncRNA growth arrest Specific 5 hinders PMT by suppressing PDGFRα/β expression via demethylation of KDM5B-mediated H3K4me2/3.

7.3 The Receptorless-associated Integration Site (Wnt)/β–catenin Pathway

Wnt signaling is a highly conserved signal transduction pathway that facilitates intercellular communication to regulate various cellular processes. These include the deter-

mination of cell fate, establishment of polarity, promotion of differentiation, and the facilitation of migration. This complex signaling cascade plays a critical role during organ and embryo development. Wnt signaling has also been implicated in the wound healing process. In this particular context, canonical signaling stabilizes the β-catenin complex within the cytoplasm before it is transported to the nucleus. This transportation subsequently triggers gene transcription events that are vital for tissue repair and regeneration. Certain target genes controlled by β-catenin play significant roles in tissue repair and regeneration processes, including cyclinD1, CD44, and VEGF [89]. Wnt/β-catenin as well as atypical Wnt signaling are activated during human renal fibrosis, and this could play a dominant role in the persistence of fibrotic cells [90]. FoxM1 has been recognized as a crucial regulator of the Wnt/β-catenin signaling pathway by retaining β-catenin within the nucleus and enhancing its transcription factor activity through direct binding to the β-catenin promoter region. FoxM1 interacts directly with Smad3 proteins to facilitate their nuclear localization and also binds to specific sequences in the β-catenin promoter, thereby promoting fibrogenesis. Exosomes derived from pulmonary vascular endothelial cells and characterized by low levels of let-7d drive fibrosis in lung pericytes through activation of the TGFβRI/FoxM1/Smad/β-catenin signaling cascade [91].

7.4 Notch Pathway

The communication mechanism known as Notch signaling is a highly conserved process that plays a significant role in maintaining lung function, responding to injury, and facilitating tissue repair [92]. The Notch signaling pathway has been implicated in pericyte differentiation and contributes to the development and progression of IPF. Rat models of lung fibrosis show increased levels of the Notch1 receptor and its ligands. Additionally, Notch1 promotes angiogenesis by stimulating the expression of PDGFRβ in pericytes [16]. Notch1 also regulates the activity of PDGFRβ, which in turn controls various downstream signaling molecules such as Ras, PI3K, and phospholipase C. Moreover, PDGFRβ plays a role in the migration of vascular smooth muscle cells by modulating Rho-related protein kinase 1 (ROCK1). Given that ROCK1 is also implicated in the development of PF, the PDGFRβ–ROCK1 interaction has been speculated to contribute to IPF. In summary, Notch1 induces the proliferation of pericytes and their transformation into myofibroblasts through involvement of the PDGFRβ/ROCK1 pathway [92].

7.5 Other Signaling Pathways

Gui *et al.* [93] reported that mTORC49 and YAP/Taz were activated in TGFβ-induced renal fibrosis. The Hippo pathway is a highly conserved kinase cascade that plays a crucial role in the regulation of cell proliferation and tissue regeneration. Key constituents of this pathway include Mst1/2, Sav1, Lats1/2, YAP, and the coactivator Taz. In response to specific stimuli, YAP and Taz become activated due to a reduction in phosphorylation levels mediated by the canonical Hippo pathway. Recent studies have shown that YAP/Taz can induce fibroblast activation and contribute to renal fibrosis [93]. The mTOR, a member of the phosphatidylinositol-3-OH-kinase-related family, is highly conserved throughout evolution and plays crucial roles in regulating cell growth, proliferation, and survival. Previous research found that mTORC2 signaling promotes fibroblast activation and contributes to renal fibrosis. Moreover, the inhibition of mTORC2 effectively delays fibroblast/pericyte activation and subsequent renal fibrosis by suppressing YAP/Taz activation [93].

The Gasdermin (GSDM) family of proteins is involved in regulating innate immune responses and cell death. GSDMD can independently induce the release of inflammatory mediators, such as IL-1β. Previous research has shown that macrophages utilize the GSDMD/IL-1β pathway to secrete IL-1β. Additionally, IL-1β is involved in promoting the conversion of pericytes into fibroblasts. The expression of GSDMD is upregulated in peritoneal fibrosis, whereas knockdown of GSDMD decreases the level of IL-1β in pericytes and peritoneal fibrosis. GSDMD knockdown also inhibits fibrosis and VEGF/PI3K pathways in pericytes. These findings suggest that modulation of the VEGF/PI3K pathway through the GSDMD/IL-1β axis by macrophages can influence the transition of pericytes to peritoneal fibrosis [94].

The release of alarmins or DAMPs by damaged or dying cells can be detected by immune receptors present on both immune and non-immune cells. Recognition of DAMPs by pericytes involves the participation of TLR2 and TLR4 as important pericyte receptors. Extensive studies conducted *in vitro* and *in vivo* have shown that MyD88 present within pericytes is a significant regulator of the injury response. MyD88 can facilitate signaling pathways related to TLR and IL-1. During the development of fibrotic disease, it is crucial that pericytes engage in signaling mediated by MyD88 and IL-1 receptor-associated kinase 4. In summary, DAMPs are released when cells are damaged and bind to TLR2/4 receptors on pericytes. This induces changes in MyD88 and IL-1 receptor-associated kinase 4 signaling, leading to the development of PF [84].

Sirtuin 3 (SIRT3) is the principal regulator of mitochondrial protein deacetylation. It regulates various physiological and pathological processes, including metabolic homeostasis, oxidative stress, apoptosis, and aging. Previous research has shown that SIRT3 plays a protective role in reducing tubulointerstitial fibrosis in hypertensive kidneys, which contain elevated levels of TGF-β and reactive oxygen species (ROS). Decreased expression of SIRT3 was observed during angiotensin II (Ang-II)-induced cardiac fibrosis and PMT. Depletion of SIRT3 enhanced the induction of TGF-β expression and the generation of ROS in response to Ang-II [93,94]. In addition, Feng *et al.* [95]

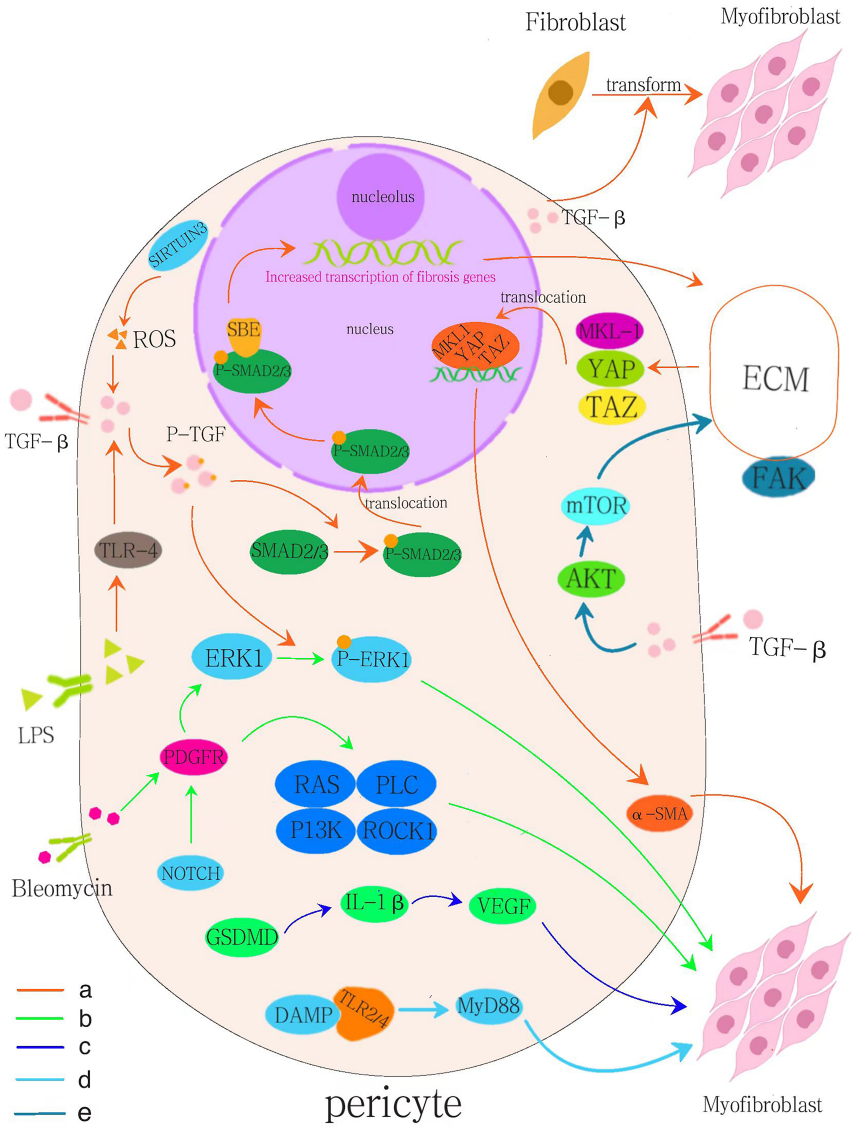

Fig. 1. The mechanism underlying pericyte transformation into myofibroblasts. (a) transforming growth factor-β (TGF-β) production was increased (damaged epithelial cells produce TGF-β; toll-like receptor 4 (TLR-4) and TGF-β were highly expressed in pericytes upon lipopolysaccharide (LPS) induction; and Sirtuin 3 (SIRT3) highly expresses TGF-β by increasing reactive oxygen species (ROS) levels), and then TGF-β with receptor phosphorylation, multiple downstream adjustment factor is activated (e.g., Smad2/3 signaling, and non-Smad pathways). Phosphorylated TGF-β promotes the phosphorylation of Smad2/3 and extracellular regulated protein kinase 1 (ERK1), leading to pericyte-myofibroblast transition (PMT). Phosphorylated Smad2/3 (P-Smad2/3) translocated to the nucleus, and the accumulation of P-Smad2/3 in the nucleus increases the binding to Smad-binding elements (SBE), leading to increased transcription of fibrotic genes, which in turn increases matrix proteins (including collagen type I) leading to increased extracellular matrix (ECM) deposition. Binding of FAK to the ECM leads to increased translocation of MKL-1, yes-associated protein (YAP), and transcriptional coactivators with PDZ-binding motifs (TAZ), which in turn lead to increased α-SMA^{+} expression and myofibroblast transition, leading to idiopathic pulmonary fibrosis (IPF). (b) Notch1 and exogenous bleomycin can regulate platelet-derived growth factor receptor (PDGFR) activity, and PDGFR activation can regulate a variety of downstream signaling molecules, such as Ras, phosphatidylinositol 3-Kinase (PI3K) and phospholipase C (PLC). In addition, PDGFR also regulates Rho-related protein kinase 1 (ROCK1), which is involved in the pathogenesis of pulmonary fibrosis, while PDGF signaling can stimulate ERK1/2 activation in pericytes. (c) Macrophages can modulate the vascular endothelial growth factor (VEGF) /PI3K pathway through the gasdermin D (GSDMD)/ interleukin-1β (IL-1β) axis, thereby altering the transition of pericytes to fibrosis. (d) damage-associated molecular patterns (DAMPs) occur when cells are damaged, bind to receptors TLR2/4 on pericytes, induce changes in MyD88 and interleukin-1 receptor associated kinase 4 (RAK4) signaling and develop pulmonary fibrosis. (e) The mTOR is a member of the phosphatidylinositol-3-OH-kinase-related family, TGF-β binds to its receptor and activates Akt/mTOR signaling pathway to mediate the proliferation of ECM and PMT.

demonstrated that fibrosis induced by Ang-II could be attributed to a reduction in SIRT3 levels and upregulation of the ROS-TGF-β1 pathway, thus facilitating PMT.

Valproic acid (VPA) is a short-chain fatty acid used as a first-line drug for the treatment of epilepsy and depression [1]. A recent study showed that VPA inhibits histone deacetylase (HDAC), thereby increasing the levels of histone acetylation [2]. Other studies have shown that HDAC mitigates cardiac fibrosis in rats, and that differentiation of pericardial cells and myofibroblasts is HDAC4-dependent. HDAC4 can induce phosphorylase, which then dephosphorylates ERK [96]. The MAPK pathway is critical for cell proliferation, programmed cell death, and cellular differentiation. Among the three major MAPKs, ERK1/2 is the primary kinase responsible for growth signaling. The phosphorylation of ERK is tightly regulated by both kinases and protein phosphatases. A significant increase in the level of phosphorylated ERK1/2 protein was observed in a rat model of cardiac fibrosis [96]. Studies have also shown that knockdown of VPA and HDAC4 lead to decreased ERK phosphorylation and inhibition of PMT, thereby reducing organ fibrosis [96].

8. Therapeutic Potential of Pericytes

Although the cause of PF remains unclear, there is growing recognition of the significant contribution made by pericytes to the onset and progression of PF. This cell type is therefore a potential target for the treatment of PF. Several treatment methods involving pericytes have been proposed in recent years, such as TGF-βR and PDGFR antagonists. Through the use of a PDGFR inhibitor, Johnson *et al*. [14] have suggested that pericytes could serve as a reservoir for airway resident mesenchymal cells, thereby playing a role in the airway remodeling process observed in individuals with chronic asthma. The dual effects of TGF-βR and PDGF receptor antagonists on pericellular cells means that further studies are required to clarify the effects of these antagonists.

9. Summary and Perspectives

Pericytes play a crucial role in the pathogenesis of PF and are involved in diverse physiological processes including inflammation, ECM remodeling, vascular homeostasis, and EMT (Fig. 1). The primary function of these cells is to secrete multiple types of inflammatory mediators such as TGF-β, IL-6, IL-1β, together with cytokines including VEGF, PDGF, and Notch. These molecules can effectively induce myofibroblast proliferation and collagen deposition, thereby advancing the progression of PF. To date, TGF-β and PDGF have been extensively investigated as key targets in the progression of PF, providing valuable avenues for the development of novel therapeutics. However, research on related pathways such as the Wnt/β-catenin signaling pathway, VEGF, TLR, MAPK, and the PI3K-AKT pathway is still relatively scarce.

Activation of the Wnt/β-catenin signaling pathway in PF leads to enhanced stability and accumulation of β-catenin within the cell nucleus. This subsequently triggers the activation of transcription factors that promote fibroblast proliferation and collagen synthesis, thereby driving disease progression. β-catenin also plays a role in regulating pathophysiological functions such as EMT and the modulation of inflammation. However, there is a paucity of research on downstream pathways associated with β-catenin. Therefore, further investigation is warranted into the role of β-catenin in the pathogenesis and progression of PF. Despite some encouraging progress in this field, a comprehensive understanding of the intricate mechanisms and regulatory networks that govern the involvement of pericytes in PF requires further research. Future investigations should clarify the precise contribution of pericytes during lung fibrogenesis and seek to obtain novel insights into their potential therapeutic application.

Author Contributions

XH and YF contributed to the conceptualization ideas and writing of the original draft. YL, YY consulted the relevant literature and summarized the literature. YW contributed to the formal analysis, reviewing, and editing of the manuscript. XT put forward insightful opinions on the project and revised the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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