Review Article

A narrative review of the role of HDAC6 in idiopathic pulmonary fibrosis

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Background and Objective: Idiopathic pulmonary fibrosis (IPF) is a progressive and irreversible condition characterized by the deposition of extracellular matrix resulting from repetitive damage to the alveolar epithelium. These injuries, along with dysregulated wound repair and fibroblast dysfunction, lead to continuous tissue remodeling and fibrosis, eventually resulting in end-stage pulmonary fibrosis. Currently, there is no specific pharmacological treatment available for IPF. The role of inflammation in the development of IPF is still a topic of debate, and it is sometimes considered incidental to fibrosis. Over the past decade, macrophages have emerged as significant contributors to the pathogenesis of fibrosis. M1 macrophages are responsible for wound healing following alveolar epithelial injury, while M2 macrophages are involved in resolving wound repair and terminating the inflammatory response in the lungs. Various studies provide evidence that M2-like macrophages contribute to the abnormal fibrogenesis. In recent years, there has been growing interest in understanding macrophage polarization and its role in the development of pulmonary fibrosis. Histone deacetylase 6 (HDAC6), a member of the HDAC family with two functional deacetylase structural domains and a ubiquitin-binding zinc finger structural domain (ZnF-BUZ), plays a crucial role in pulmonary fibrosis. This article explores the role of HDAC6 in pulmonary fibrosis and evaluates its potential as a treatment approach for IPF.

Methods: PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, China Biomedical Literature Service System (CBMdisc) and Web of Science were searched to obtain researches, published in English and Chinese, until July 2023. The search was performed using specific keywords such as Histone deacetylase 6, HDAC6, Idiopathic pulmonary fibrosis, IPF, fibrosis.

Key Content and Findings: HDAC6 has diverse effects on physiological processes, including the NLRP3 inflammasome, epithelial-mesenchymal transition, the TGFβ-PI3K-AKT pathway, macrophage polarization and TGF-β-Smad signaling pathway, due to its unique structure. HDAC6 has been found to enhance the inflammatory response and fibrosis of lung tissues, contributing to the development of IPF.

Conclusions: In the future, HDAC6 inhibitors are expected to play a crucial role in the treatment of fibrotic disorders and should be studied further deserves to pursue in future research.

Keywords: Histone deacetylase 6 (HDAC6); idiopathic pulmonary fibrosis (IPF); inflammation; macrophage

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease that remains incompletely understood. It is believed to be caused by repetitive injury to the alveolar epithelial cells and subsequent abnormal repair. In China, a country with a rapidly aging population, the number of IPF diagnoses is increasing each year. IPF is an irreversible and chronic interstitial lung disease with a gradual onset, and only 50% of patients have a chance of surviving for 2–3 years after being diagnosed. Currently, there are limitations in the treatment of IPF. Pharmacological therapies such as pirfenidone and nintedanib have shown moderate effectiveness in patients but come with significant adverse effects and high costs. Lung transplantation is rarely an option due to a shortage of donors and the risk of rejection. Recent studies on the pathogenesis of pulmonary fibrosis have focused on an imbalance between fibroblast proliferation and death, as well as the overproduction of extracellular matrix (ECM) components such as collagen (1). Collagen is primarily produced by myofibroblasts, and the regulation of myofibroblasts is influenced by epithelial-mesenchymal transition (EMT) (2,3). EMT is a process in which epithelial cells stimulated by certain factors, acquire characteristics of mesenchymal cells, including changes in cell morphology and expression of specific proteins (4). Approximately one-third of pulmonary fibroblasts originate from epithelial cells (5,6). Myofibroblasts derived from EMT proliferate rapidly and produce excessive extracellular matrix, contributing to the development of IPF. Histone deacetylases (HDACs), including HDAC6, are expressed in different patterns in IPF lungs, with higher expression observed in type II alveolar epithelial cells (AECII) and myofibroblasts within fibroblast foci (7). In order to give some clinical value, this paper presents a brief review of the role of HDAC6 and its inhibitors in pulmonary fibrosis in recent years. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1183/rc).

Methods

For the purpose of integrating search results, all authors independently conducted computerized searches of various databases including the China National Knowledge Infrastructure (CNKI), Wanfang database (WANFANG), China Biomedical Literature Service System (CBMdisc), Cochrane library, PubMed, and Web of Science. The search was performed using specific keywords such as Histone deacetylase 6, HDAC6, Idiopathic pulmonary fibrosis, IPF, fibrosis, macrophage M1, macrophage M2. The aim of this research literature was to investigate the multifaceted role of HDAC6 in pulmonary fibrosis. The time limit for retrieval was set from the beginning in 2020 and ending on July 3, 2023. The search was available in both Chinese and English (*Table 1*, Table S1).

Biological properties of HDACs

HDACs are enzymes that remove acetyl groups from histones and play a crucial role in epigenetic gene regulation by modifying chromatin. Therefore, they are considered essential regulators of gene expression (8). To date, 18 HDACs have been discovered, marking them important regulators of gene expression. They have been divided into four groups based on their similarity to yeast HDACs. Class I HDACs (1, 2, 3, and 8) are generally present in the nucleus and are detected in a wide range of cell lines and tissues. It is related to the Reduced Potassium Dependent 3 (RPD3) protein from yeast. Class II HDACs include HDAC 4, 5, 6, 7, 9, and 10, which are similar in sequence to the yeast HDAC1 protein and are expressed in both the cytoplasm and nucleus (9). Class III HDACs (SIRT1, 2, 3, 4, 5, 6, and 7) require NAD+ for activity and yeast protein homologization. These HDAC classes regulate gene expression based on the cellular redox state (10). Class IV HDACs are located in the nucleus and regulate the expression of interleukin 10 (IL-10) and consist solely of HDAC11, which has a catalytic core similar to that of Class I and II HDACs (11). HDAC6 is a distinct Class II HDAC isoform. The HDAC6 gene is found on chromosome X, Xp11.23, and is responsible for encoding 1,215 amino acids, making it the biggest protein in the HDAC family (9). HDAC6 has two catalytic deacetylase domains (DD1 and DD2) that primarily regulate deacetylase activity. HDAC6's structure also includes a C-terminal zinc-finger ubiquitin-binding domain, which functions as a ubiquitin-dependent mechanism and is essential for HDAC6's non-deacetylase function (12).

The role of HDAC6 in pulmonary fibrosis

HDAC6 may contribute to IPF by increasing inflammatory responses

IPF is primarily caused by damage to alveolar and airway

Table 1 The search strategy summary

Items	Specification
Date of search	July 3, 2023
Databases and other sources searched	China National Knowledge Infrastructure (CNKI), Wanfang database (WANFANG), China Biomedical Literature Service System (CBMdisc), Cochrane library, PubMed, and Web of Science
Search terms used	See Table S1
Timeframe	2020–2023
Inclusion and exclusion criteria	Inclusion criteria: intervention and treatment measures; HDAC6 inhibitors or HDAC6 knockout (gene). Exclusion criteria: reviews, case reports, duplicate publications, works without evaluation indices, conference abstracts, etc.; there existed no full-text literature to be found
Selection process	All authors participated, and final study inclusion was first selected by reading the abstract and then by reading the full text

epithelial cells. This damage triggers an inflammatory response, leading to the accumulation of monocytes, neutrophils, lymphocytes, and other inflammatory factors and chemokines, such as tumor necrosis factor α (TNF-α), IL-1, and IL-6, at the site of injury. These cells and factors contribute to the secretion of additional inflammatory factors and chemokines. The repair process during early acute inflammation is crucial for restoring organ integrity. However, as leukocytes infiltrate and accumulate in the damaged tissue, they not only activate fibroblasts but also produce collagen, promoting tissue fibrosis (13). While inflammation is necessary for tissue regeneration and healing, prolonged inflammation can impair cell function, leading to tissue damage, fibrosis, and even organ failure. Inhibiting of HDAC6 can block the activation of the *NF-κB* signaling pathway and suppress the release of multiple inflammatory cytokines and chemokines (14).

HDAC6 plays a role in the expression of various inflammatory cytokines (15-17). Its enzymatic activity, which regulates NADPH oxidase activity, is crucial for the optimal production of reactive oxygen species (ROS) and pro-inflammatory cytokines (14,18). This ultimately leads to the increased production of pro-inflammatory cytokines by macrophages, particularly when HDAC6 is overexpressed. In the absence of HDAC6, the recruitment of monocytes/macrophages in the inflammatory model is reduced. Conversely, overexpression of HDAC6 enhances ROS generation and the subsequent production of TNF-α, IL-1, and IL-6 (14). Additionally, T cells that produce IL-17 attract neutrophils to inflamed areas (19). Silencing HDAC6 affects the expression of the Toll-like receptors (TLR) adapter myeloid differentiation primary response gene 88 (*MyD88*), and acetylation of MyD88 regulates downstream signaling TLR involved in *NF-κB* transcription factor and pro-inflammatory cytokine-induced signaling (17). The loss of HDAC6's ubiquitin-binding function may contribute to lung fibrosis by impairing autophagy and/or activating NLRP3 inflammatory vesicles (16,20,21).

Therefore, when lung tissue undergoes abnormal repair after damage, the sustained inflammatory response can lead to lung tissue fibrosis. HDAC6 is potentially involved in the development of IPF through its active role in the inflammatory response. However, further *ex vivo* experimental studies in animal models and IPF patients are required to confirm the specific mechanism of action.

HDAC6 influences EMT involvement in IPF through α-tubulin deacetylation

In the context of pulmonary fibrosis in mice, recent research suggests that type II lung epithelial cells expressing the biomarker E-cadherin have the ability to undergo EMT and transform into myofibroblasts (22). Moimas and colleagues demonstrated that ATII cells from IPF patients express markers of senescence and EMT, and exhibit a diminished capacity to transdifferentiate into ATI cells (23). The acetylation status of α-tubulin might be used as a marker for EMT. In detail, a low acetylation status of α-tubulin in epithelial cells might be indicative of EMT. It has been reported that HDAC6, a deacetylase, reduces the stability of microtubules by deacetylating α-tubulin in epithelial cells. Conversely, HDAC6 inhibitors restore the levels of acetylated α-tubulin, thereby preventing EMT. Therefore, HDAC6 plays a crucial role in regulating of the EMT process (24). In A549 cells, TGF-β-induced EMT is mediated by HDAC6 activation of SMAD3,

resulting in α-tubulin deacetylation and the formation of mesenchymal stress fibers. Inhibition of HDAC6 reduces TGF-β-induced activation of the Notch signaling pathway and the expression of its target genes, *HEY-1* and *HES-1*, in A549 and H1299 cells. Importantly, siRNA knockdown of HDAC6 disrupts Notch1 signaling, decreases the production of EMT markers, and restores the expression of epithelial genes in TGF-β1-treated A549 cells, indicating that HDAC6 is essential for mediating the TGF-β-Notch1 signaling pathway during EMT (*Figure 1*) (25). Inhibition of HDAC6 activity reduces TGF-β1-induced expression of type 1 collagen, but silencing HDAC6 using siRNA does not have the same effect. Surprisingly, siRNA-mediated suppression of HDAC6 has no impact on TGF-β-induced production of α-SMA and collagen-I in fibrotic lung fibroblasts. Silencing HDAC10 alone or in combination with HDAC6 yields similar results (26).

HDAC6 ameliorates pulmonary fibrosis by targeting the TGFβ-PI3K-AKT pathway

The PI3K/AKT signaling pathway plays a significant role in fibroblast proliferation and differentiation into myofibroblasts. It has been observed that fibroblasts isolated from IPF patients exhibit abnormal AKT activation (27). Tubastatin, an HDAC6 inhibitor, suppresses AKT phosphorylation induced by TGF-β1. This inhibition subsequently leads to the suppression of the HIF-1-VEGF axis and the induction of autophagy. Consequently, TGF-β1-induced collagen expression is reduced, resulting in the amelioration of pulmonary fibrosis (*Figure 1*) (26). The PI3K-AKT pathway has been associated with pulmonary fibrosis through multiple mechanisms. For instance, the pathway enhances lung fibrosis by increasing the production of HIF-1 and VEGF. HIF-1 levels are elevated in lung fibrosis (28) and may contribute to the progression of the disease by promoting VEGF production and subsequent collagen expression (29).

Potential anti-fibrotic effects of HDAC6 inhibitor

By modulating macrophage polarization

Injured alveolar and airway epithelial cells have the ability to attract various inflammatory cells, with macrophages being the most important among them. Macrophages are highly adaptable and functionally diverse. During the intrinsic immune response, they can transform into different cell subtypes in response to various external stimuli. These different subtypes of macrophages secrete different cytokines to regulate the external environment (30). This suggests a mutual regulation between macrophages and the surrounding milieu.

Tubastatin has been found to inhibit PI3K/AKT, STAT3, and STAT6 signaling *in vivo*, effectively preventing M2 macrophage polarization (31). In the context of IPF, fibrogenesis is primarily regulated by the infiltration of M2 macrophages into the lungs (32). M2 macrophages present at the site of lung tissue injury release CCL18, which in turn stimulates fibroblasts to produce collagen. This process is further amplified by the activation of nearby macrophages, leading to increased synthesis of CCL18 and excessive collagen production by activated fibroblasts (33). Additionally, activated M2 macrophages can generate pro-fibrotic mediators like TGF-β1 and platelet-derived growth factor (34), which contribute to the maintenance of fibroblast activation and the growth of myofibroblast (32).

TGF-β-Smad signaling pathway

There is existing research indicating the potential role of HDAC6 inhibitor in treating other types of fibrosis. The involvement of HDAC6 in renal fibrosis may be linked to the activation of TGF-β1/Smad3 signaling pathway. In a study conducted on UUO-injured kidneys, the administration of HDAC6 inhibitor resulted in a decrease in TGF-β1 expression and Smad3 phosphorylation levels, indicating the necessity of HDAC6 for the activation of TGF-β1-Smad3 signaling (35). The HDAC6 selective inhibitor Tubastatin did not reduce the ANG-induced blood pressure increase in mice, it prevented kidney fibrosis both *in vitro* and *in vivo* (36). HDAC6 is required for activation of the TGF-β1-Smad3 signaling pathway in peritoneal mesothelial cells (37).

In animal models, the overexpression of TGF-β1 induces pulmonary fibrosis, whereas the inhibition of the TGF-β-Smad signaling suppresses the development of pulmonary fibrosis (38). It is reasonable to anticipate that HDAC6 inhibitor will have an effect on IPF via the TGF-β-Smad signaling.

Therapeutic potential of HDAC6 inhibitors in pulmonary fibrosis

Due to HDAC6 is involvement in the inflammatory response and pro-fibrosis, there has been an increasing interest in investigating the inhibition of HDAC in fibrotic diseases. In recent studies, researchers have successfully designed and

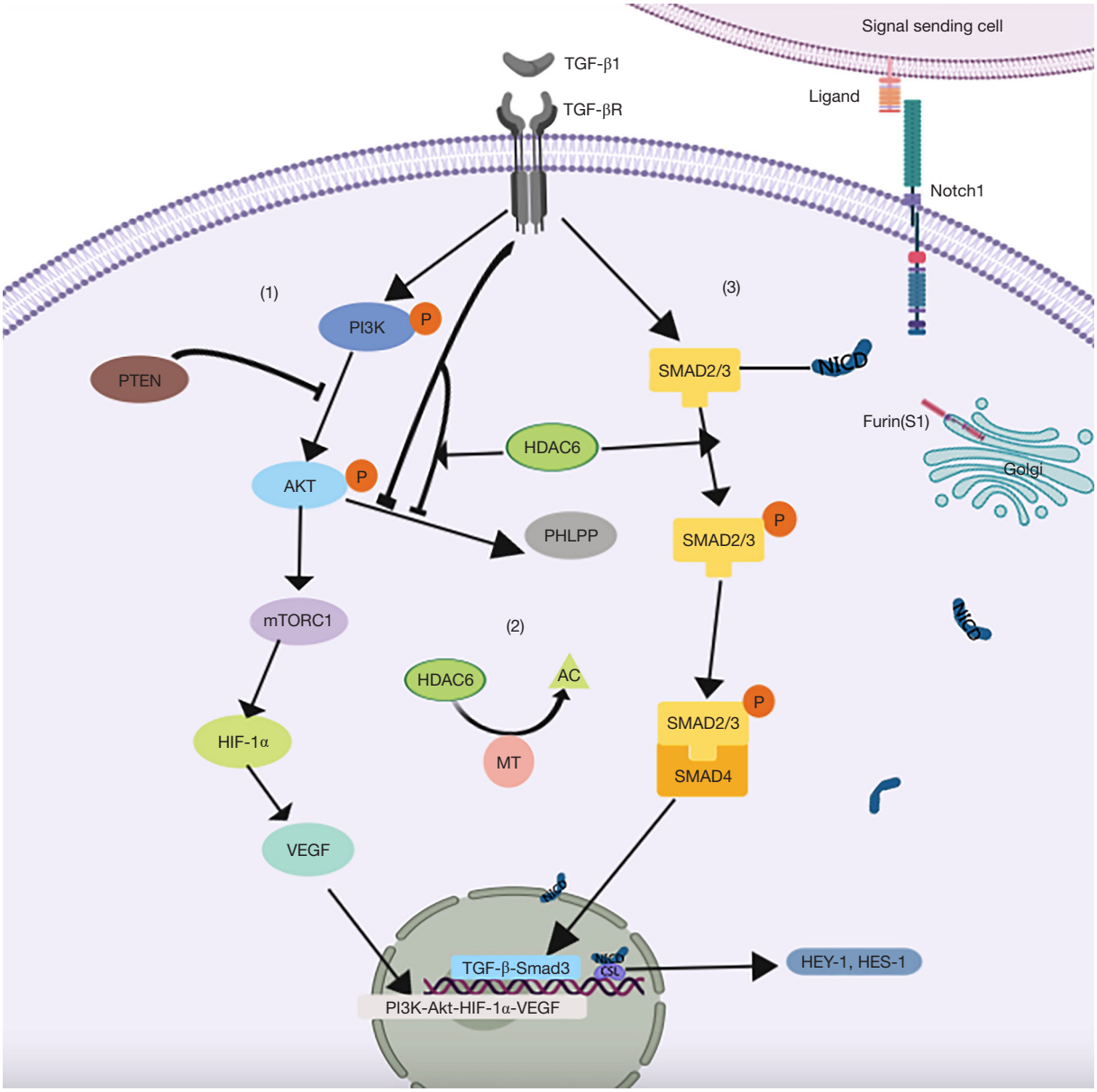

Figure 1 Multiple pathways of HDAC6 involvement in IPF. 1, HDAC6 reduces lung fibrosis by inhibiting the TGF-PI3K-Akt signaling pathway. TGF-β1 inhibits the interaction of Akt and PHLPP, while HDAC6 inhibition partially restores the Akt-PHLPP relationship. 2, in epithelial cells, HDAC6 deacetylates -tubulin, resulting in reduced MT stability. 3, TGF-β-induced stimulation of Notch signaling and expression of its target genes *HEY-1* and *HES-1* in cells were reduced by inhibiting HDAC6. SMAD2, drosophila mothers against decapentaplegic protein 2; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome ten; AKT, protein kinase B; HDAC6, histone deacetylase 6; PHLPP, PH domain and leucine rich repeat protein phosphatase; mTORC1, mammalian target of rapamycin C1; AC, acetylation; MT, microtubule; HIF-1α, hypoxia inducible factor-1 alpha; VEGF, vascular endothelial growth factor; NICD, Notch Intracellular Domain; Furin(S1), paired basic amino acid cleaving enzyme S1 subunit; Golgi, Golgi apparatus; HEY-1, hairy/enhancer of-split related with YRPW motif 1; HES-1, hairy and enhancer of split 1; IPF, idiopathic pulmonary fibrosis.

synthesized 24 new inhibitors targeting HDAC6, HDAC8, or both. These inhibitors have shown promising results in alleviating TGF-β-induced pulmonary fibrosis *in vitro* trials (39). HDAC6 inhibitors has shown effectiveness in a bleomycin animal model of lung fibrosis (26). A new clinical-stage HDAC inhibitor called CG-745, which specifically targets class I HDACs and class IIB HDAC6, has recently demonstrated promising therapeutic efficacy in mice treated with bleomycin. This inhibitor significantly reduced the number of inflammatory cells in the BALF and decreased collagen levels to a similar extent as the saline-treated controls. As a result, it led to significant improvements in fibrosis and EMT (40).

Discussion

There is no effective treatment for IPF. However, medication and rehabilitation training can help delay the progression of the disease and improve patients' quality of life and survival time. In cases of acute IPF, lung transplantation has shown to be the most successful treatment option. Pirfenidone, an antifibrotic drug, has been licensed as the first medication for IPF treatment due to its ability to slow down disease progression. Although pirfenidone and nintedanib have been recently approved as IPF treatments with reasonable side effects, they only serve to halt the progression of the disease. Apart from lung transplantation, there are no other treatment options available. Therefore, it is crucial to develop effective novel therapeutic techniques for IPF.

In this study, it has been observed that HDAC6 promotes lung tissue fibrosis by influencing collagen deposition and targeting the TGF-β-PI3K-AKT pathway. Both of these factors contribute to the initiation and progression of IPF. Given the connection between epigenetic changes and IPF, researchers have recently discovered that HDAC6 inhibitors can effectively reduce fibrotic remodeling in both laboratory and animal models. Furthermore, the HDAC6 inhibitor Tubastatin has been found to inhibit TGF-β1-induced collagen expression by blocking the PI3K-AKT-HIF-1-VEGF pathway (27). This mechanism of action is similar to that of nintedanib, a new tyrosine kinase inhibitor, which suppresses VEGF and FGF activity, reduces collagen deposition, and inhibits pro-collagen synthesis (41). Reduced collagen deposition and inhibition of pro-fibrotic gene expression reduce pulmonary fibrosis, although the specific therapeutic targets of Tubastatin must be studied further.

At the same time, we propose three possible mechanisms that may inspire researchers in the field. Firstly, it is known that there is an inflammatory response in IPF, and HDAC6 has the ability to regulate the expression of various inflammatory cytokines (14). However, there is limited literature on the effect of HDAC6 on IPF through its influence on the inflammatory pathway, and further research is required. HDAC6 plays a crucial role in the inflammatory response by interacting with pro-fibrotic mediators (14). Secondly, this interaction involves macrophages, which are the most abundant immune cells in the lungs. Macrophages can differentiate into different subtypes in response to various stimuli and microenvironment polarization, and they play important roles in anti-infection, inflammation, and the elimination of cell debris. M2 macrophages, when activated by IL-4 or IL-13, can reduce inflammation and promote wound repair (42,43), but they also produce pro-fibrotic mediators. However, there is a lack of understanding regarding the mechanisms that regulate M2 macrophage polarization, as well as the role and mechanism of HDAC6 in this process. Therefore, further research and experiments are needed to clarify the underlying mechanisms. Finally, TGF-β-Smad signaling is a crucial pathway in fibrogenesis, particularly in IPF (35). This pathway's activation results in the activation of myofibroblasts, excessive production of ECM, and inhibition of ECM degradation (38). HDAC6 has been identified as a potential therapeutic target in renal fibrosis and peritoneal fibrosis (35-37). We aim to uncover a similar finding in IPF.

Conclusions

The origin and pathogenesis of IPF are currently unknown, leading to a poor prognosis for patients and limited therapeutic options. In the future, HDAC6 inhibitors are expected to play a crucial role in the treatment of fibrotic disorders. HDAC6 has been found to enhance the inflammatory response and fibrosis of lung tissues, contributing to the development of IPF. However, further investigation is needed to understand the precise mechanism of action through animal models of pulmonary fibrosis as well as *in vitro* and *ex vivo* research in IPF patients. Targeting HDAC6 may offer a unique treatment approach for pulmonary fibrosis, and combining HDAC6 inhibitors with pirfenidone or nintedanib could potentially provide greater therapeutic benefits for IPF patients. Future trials should explore this further. To summarize, research on the application of HDAC6 inhibitors in pulmonary fibrosis is still in its early stages, with most studies being basic, such

as animal models. While current investigations suggest that HDAC6 inhibitors improve pulmonary fibrosis, extensive scientific and clinical studies are necessary before their clinical use can be considered.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1183/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1183/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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