Review Article

Application and Research Progress of Histone Deacetylase Inhibitors in Pulmonary Fibrosis

QIAN ZHANG* AND P. JIANG

Department of Respiratory and Critical Care Medicine, The First Central Hospital Affiliated to Nankai University, Nankai, Tianjin 300052, China

Idiopathic pulmonary fibrosis is a fatal and irreversible lung disease with limited therapeutic options. It has always been a difficult problem that we cannot overcome and there is a need for new therapies in clinical treatment. More and more experimental data suggests that the histone deacetylase family of transcriptional corepressors has emerged as crucial mediators of idiopathic pulmonary fibrosis pathogenesis. In order to clarify the role of histone deacetylase inhibitors in pulmonary fibrosis, we searched the database for relevant literatures on histone deacetylase inhibitors and pulmonary fibrosis, and summarized the latest literatures. Epigenetic regulation, such as histone modification and deoxyribonucleic acid methylation, plays an increasingly important role in idiopathic pulmonary fibrosis. Through the regulation of histone modification, we can affect the occurrence and development of idiopathic pulmonary fibrosis. Histone deacetylases not only participates in the development of tumor, but also they are proved to be related to the progress of organ fibrosis. Histone deacetylase inhibitors affect the development of protein function by changing the acetylation level of histone or non-histones. At present, histone deacetylase inhibitors and gene transcription are mostly used in the treatment of skin lymphoma. Many studies have shown that there is a common signal pathway in the occurrence of tumor and lung fiber. By summarizing the literature, upregulated histone deacetylase activities are observed in fibrotic diseases involving the heart, liver, kidneys and lungs. We suggest the significant imbalance of histone deacetylase activity in the onset and progression of idiopathic pulmonary fibrosis lungs. Therefore, the role of histone deacetylase inhibitors in pulmonary fibrosis needs a new understanding and we have also supported histone deacetylase inhibitors in targeting class I histone deacetylase activity in fibroblasts as a therapeutic option and a promising field for idiopathic pulmonary fibrosis patients.

Key words: Idiopathic pulmonary fibrosis, histone deacetylase inhibitors, fibroblasts, myofibroblasts

Idiopathic Pulmonary Fibrosis (IPF) is a progressive interstitial lung disease that is characterized with airway epithelial cell injury, fibroblast and myofibroblast aggregation, inflammatory cell infiltration, and extracellular matrix deposition[1]. The incidence rate of IPF is 50/10 000, with an average survival time of 3-5 y[2]. It also has a high mortality rate. At present, IPF is commonly managed with therapeutics like antioxidants (acetylcysteine), glucocorticoids (methylprednisolone), immunosuppressants (cyclophosphamide, azathioprine, methotrexate), new anti-pulmonary fibrosis drugs (pirfenidone, nintedanib) and so on. However, whether used alone or in combination, the outcome of these therapies is poor. In most cases, the pulmonary fibrosis progression does not cease and the patient ultimately dies. The potential multifactorial etiology of IPF is still under investigation[3]. In emerging studies, epigenetic regulation like histone modification (acetylation/deacetylation) and Deoxyribonucleic Acid (DNA) Methylation (DM) were reported to contribute to IPF development and progression. Hence, IPF occurrence and advancement may be modulated through histone modification. This study reviews the research progress of Histone Deacetylases (HDACs) and Histone Deacetylase inhibitors (HDACi) in general and in IPF conditions.

FUNCTIONAL CHARACTERISTICS AND CLASSIFICATION OF HDACs

HDACs are enzymes that work in consent with Histone Acetylase (HAT) to regulate gene transcription. Gene expression is often modulated by acetylation, phosphorylation and methylation,

***Address for correspondence**
E-mail: jenna9898@163.com

among which the activities of HATs and HDACs are the most prominent[4]. These enzymes function in a state of dynamic balance, by regulating the number of charged histones, *via* acetylation and deacetylation of histone lysine residues, in order to alter the histone structure, local state of protein octamer and DNA spatial conformation to affect the binding efficiency of transcription factors that regulate gene transcription[5,6].

Based on the structural and functional homology between HDACs and yeast, HDACs can be classified into four categories. Group I HDACs are similar to Reduced Potassium Dependency 3 (RPD3) and consist of HDAC1, HDAC2, HDAC3 and HDAC8, whereas group II HDACs are similar to Histone Deacetylase 1 (HDA1), and consist of HDAC4, HDAC5, HDAC6, HDAC7, HDAC9 and HDAC10. Among the group II HDACs, there exists further classification. Group IIA has an active catalytic domain similar to HDAC4, HDAC5, HDAC7 and HDAC9, whereas group IIB has two active catalytic domains, similar to HDAC6 and HDAC10. Group III HDACs include silent information regulator 2 related enzymes and Nicotinamide Adenine Dinucleotide (NAD^+) dependent HDAC. Lastly, group IV HDACs include HDAC11 and behave differently from group I and II HDACs[7,8]. Each HDAC member offers a unique regulation of gene transcription and is also involved in the modulation of inflammatory responses, cell proliferation, cell differentiation and cell apoptosis[9].

THE RELATIONSHIP BETWEEN HDACs AND TUMOR

The HDACs mediates to loose or compact chromatin structures and regulate multiple cellular functions. Humans possess four categories of HDACs. Type I is found in the nucleus. Type II can translocate from the nucleus to the cytoplasm and vice versa and is expressed in a cell-specific fashion. Type III can be found in small organelles like the mitochondria and exists in the form of Sirtuin (SIRT) 3, SIRT4 and SIRT5. The primary function of HDAC is to serve as a messenger connecting genome to the extracellular environment. Hence, it utilizes numerous downstream target proteins such as Suppressor of Mothers against Decapentaplegic (SMAD) protein family, tumor suppressor protein p53, Heat Shock Proteins (HSPs) and so on, to regulate inflammation, tumor and other diseases *via* activation of appropriate signaling pathways[10].

THE RELATIONSHIP BETWEEN HDACs AND FIBROSIS

Emerging reports suggest that HDACs not only contribute to tumor development and advancement, but are also related to certain fibrotic diseases[11,12] like IPF, myocardial fibrosis, chronic kidney disease, Systemic Sclerosis (SSc), and pulmonary cystic fibrosis. IPF is characterized by a significant imbalance of HDAC activities, with an abnormal increase of HDAC expression in fibroblasts/ myofibroblasts and bronchiolar basal cells, but lack of HDAC expression in type II Alveolar Epithelial Cells (AECII) is due to Endoplasmic Reticulum (ER stress), senescence and ptosis. This imbalance contributes and perpetuates the fibrotic process as shown in fig. 1[13]. Transforming Growth Factor-beta 1 (TGFβ1) is a powerful fibrogenic agent, which can mediate the transformation of fibroblasts into myofibroblasts. However, it is only partly responsible for the pathogenesis of fibrosis. In patients with IPF, the expression of HDAC1, HDAC2, HDAC3, HDAC8 and SIRT1 increase significantly, particularly in the fibrotic area, along with markedly upregulated nuclear localization of HDAC2 and HDAC3[14]. Moreover, it is reported that HDAC4 can regulate Protein Kinase B (AKT) phosphorylation, stimulate fibroblast differentiation and Epithelial-Mesenchymal Transition (EMT), and inhibit expression of alpha-Smooth Muscle Actin (α-SMA) and collagen[15,16]. Phosphorylation of HDAC4 and AKT is also essential in transforming healthy human lung fibroblasts into myofibroblasts[17]. Phosphorylation and dephosphorylation processes are generally maintained by protein kinase and Protein Phosphatase (PP) and are keys to numerous pathophysiological conditions. PP1 and PP2A are part of the serine/threonine phosphatase family. *In vitro*, PP2A can dephosphorylate AKT, while PP1 modulates HDAC1 and HDAC6. Moreover, PP activities can be inhibited by small interfering Ribonucleic Acid (siRNA), which increases the interaction between PP1 and AKT. In addition, the expression of TGF-β1-induced α-SMA requires AKT phosphorylation. Several reports also suggest that AKT activation is essential in the differentiation of TGF-β1-regulated lung fibroblasts. Furthermore, this effect can be blocked by HDACi or siRNA. Hence, PP1 and PP2A can reduce TGF-β1-modulated expression of α-SMA, thus inhibiting fibrosis.

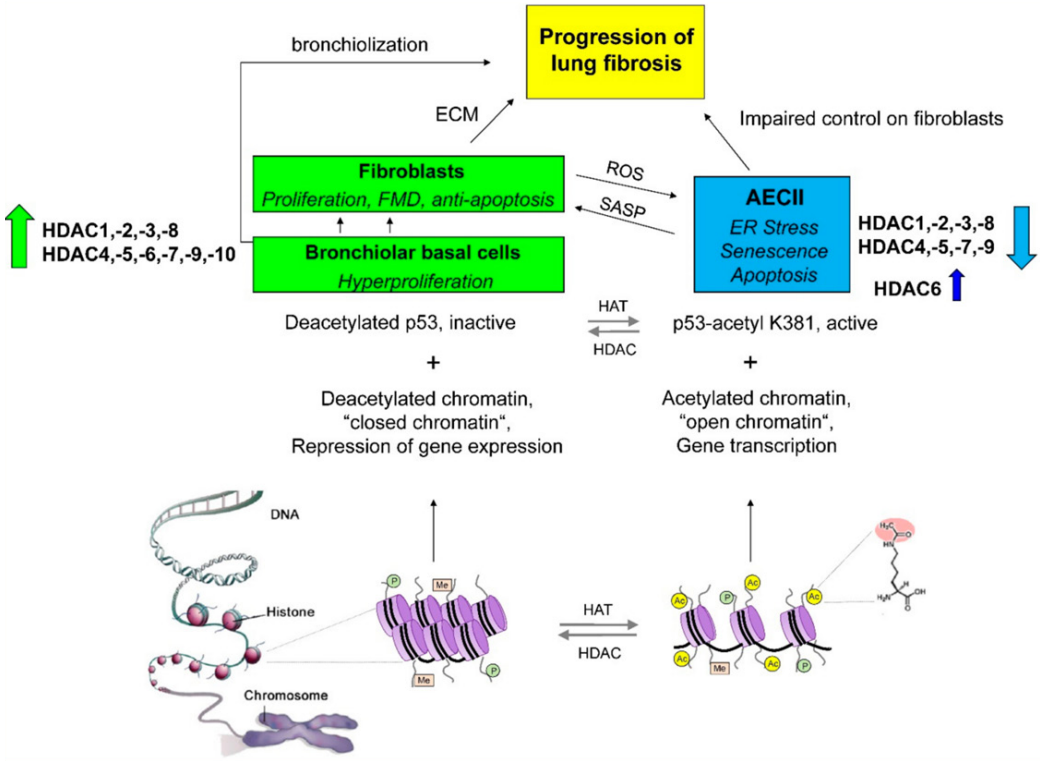

Fig. 1: Imbalance of HDAC activities in IPF
Note: ECM: Extracellular Matrix; FMD: Fibroblast-to-Myofibroblast Differentiation; AECII: Type II Alveolar Epithelial Cells; ROS: Reactive Oxygen Species; SASP: Senescence-Associated Secretory Phenotype; HAT: Histone Acetyltransferase; p: phosphorylation; Me: Methylation and Ac: Acetylation

FUNCTIONS AND CLINICAL APPLICATIONS OF HDACi

HDACi suppresses HDACs function by concealing the catalytically active fragment of HDACs. Furthermore, it alters histone and non-histone acetylation status to further prevent gene transcription and bring about cell cycle arrest, apoptosis, cell differentiation, autophagy, anti-angiogenesis, and so on. Several studies have established that HDACs can severely reduce levels of Tumor Suppressor Genes (TSGs). Alternately, HDACi can upregulate TSGs levels, delay tumor growth and induce tumor cell death *in vitro*. Similar to non-pathological conditions, HDACi can inhibit the growth and cytotoxicity of tumor cells *via* acetylation and modification of target proteins. In fact, scarcely acetylated histone proteins are correlated with development of numerous hematological tumors and malignant solid tumors[18]. At present, HDACi has entered the clinical trial stage as a new class of anti-tumor drugs. It exerts significant inhibitory action on tumor proliferation and angiogenesis, and induces programmed cell death and cell differentiation of a variety of tumor cells, while having almost no effect on healthy cells. Its anti-tumor activity is especially promising due to its high efficiency and low toxicity[19].

CLINICAL APPLICATIONS OF HDACs

HDACs can be classified into four categories, based on their chemical structures. The first category includes short chain fatty acids like benzoic and isovaleric acid. The second category includes hydroxamic acids like Trichostatin A (TSA), vorinostat (Suberoylanilide Hydroxamic Acid (SAHA)) and Belinostat (PXD101). Interestingly, vorinostat is the first HDACi to be approved by the United States Food and Drug Administration (US FDA) and it treats cutaneous T-cell lymphoma[20]. PXD101, on the other hand, was FDA-approved in 2014 for the management of peripheral T-cell lymphoma[21]. The third category includes cyclic tetrapeptide compounds like Trapoxin (TPX) and Romidepsin (FK228), which can effectively inhibit HDAC1 and HDAC4. Among the third category of HDACi, FK228 was FDA-approved in 2009 and 2011 to treat cutaneous T-cell lymphoma and peripheral T-cell lymphoma, respectively[22,23]. Lastly, the fourth category includes benzamide compounds like Entinostat (MS-275).

NEW DRUG DEVELOPMENT OF HDACs

Most HDACi can inhibit a variety of HDACs. Unfortunately, due to its lack of specificity, therapies

with HDACi may produce rampant toxic side effects. Therefore, it is crucial for doctors to choose selective HDACs for treatment, which can maximize therapeutic effect while minimizing side effects. Recently, a group of specific HDACs have gained much attention. MS-275, for instance, is a specific inhibitor of HDAC1, HDAC2 and HDAC3, and can effectively inhibit renal interstitial fibrosis and vascular remodeling in hypertensive nephropathy. Similarly, tasquinimod is a HDAC4-specific inhibitor, which has been shown to inhibit Vascular Endothelial Growth Factor (VEGF) expression and angiogenesis. Likewise, Tubulin acetylation inducer (Tubacin), a HDAC6-specific inhibitor, regulates the acetylation status of various substrate proteins involved in multiple pathological processes and it further suppress angiogenesis, remodeling, organ fibrosis and extracellular collagen deposition[24-27]. In addition, PCI-34051 is a specific inhibitor of HDAC8, which can regulate the acetylation status of H3K9 and H3K27 sites on histones and contributes to the modulation of T cell differentiation, autoimmune response and smooth muscle cell differentiation[28-31]. Korfei *et al*.[13] summarizes the broad therapeutic effects of various pan-HDACi on preclinical models of lung fibrosis or IPF in recent years. HDACi for treatment of pulmonary fibrosis/IPF are shown in Table 1[32-47].

TABLE 1: HDACi FOR TREATMENT OF PULMONARY FIBROSIS/IPF

Study	Lung fibrosis model	HDAC inhibition	Effect/Involved molecules
Coward *et al*.[32]	TGF-ß-treated IPF fibroblasts	Panobinostat (LBH589), pan-HDAC	H3 and H4 acetylation at COX-2 promoter, derepression of COX-2 expression
Huang *et al*.[33]	Lung fibroblasts of bleomycin mice, primary IPF fibroblasts	TSA, vorinostat (SAHA), pan-HDAC	H3 acetylation at the Fas/Fas promoter, derepression of Fas/Fas expression
Sanders *et al*.[34]	Primary IPF fibroblasts, bleomycin mouse model	Vorinostat (SAHA), pan-HDAC	*In vitro*: Proliferation, H3 and H4 acetylation, H3K9Ac↑, BAK↑, BID↑, BCL2L1↓. *In vivo*: Ameliorated lung fibrosis H3K9Ac↓ and BAK+BCL2L1↓
Korfei *et al*.[14]	Primary IPF fibroblasts	Panobinostat (LBH589), pan-HDAC	Tubulin acetylation↑, H3K27 acetylation, CIP1/p21↑, CHOP↑, proliferation (CCND1)↓, FMD (ACTA2, COL1A1, COL1A3, FN)↓, surviving↓, BCL-XL↓
Zhang *et al*.[35]	Primary IPF fibroblasts, bleomycin mouse model	Vorinostat (SAHA), pan-HDAC	*In vitro*: H3 and H4 acetylation, COL3A1 (mRNA and protein)↓, *In vivo*: Ameliorated lung fibrosis, collagen-Ⅲ↓
Ota *et al*.[36]	TGF-ß-stimulated A549 cells, bleomycin mouse model	TSA	*In vitro*: EMT↓ restoration of CDH1 expression. *In vivo*: Partial attenuation of fibrosis, restoration of AECII-Sftpc expression
Kim *et al*.[37]	Bleomycin mouse model, PHMG induced lung fibrosis	CG-745, Class I-HDAC+HDAC6	Abrogation of bleomycin-fibrosis, H3 acetylation, Pai-1↓, α-SMA↓, collagen-I↓, BALF:TNF-α↓, Il-6↓ and attenuation of PHMG-fibrosis
Jones *et al*.[38]	TGF-ß-treated primary IPF fibroblasts	Pracinostat, pan-HDAC except HDAC6	H3 acetylation at PGC1A promoter, derepression of PGC1A expression, HDAC7 signalling↓, ACTA2↓, TNC↓, IL6↓, PDGFA↓ and inhibition of FMD
Coward *et al*.[39]	TGF-ß-treated primary IPF fibroblasts	Panobinostat (LBH589), pan-HDAC	H3 and H4 acetylation at CXCL10 promoter, reduction of repressive H3K9Me3 at CXCL10 promoter, derepression of CXCL10 expression
Sanders *et al*.[40]	Fibrotic rat Thy1 (-) lung fibroblasts	TSA	H3 and H4 acetylation, derepression of Thy1 (CD90) expression
Korfei *et al*.[41]	Primary IPF fibroblasts	Panobinostat (LBH589), pan-HDAC	Tubulin acetylation↑, H3K27Ac↑, STAT3-pTyr705↓, proliferation, FMD↓, ECM (pro-collagen-I)↓, HDAC1↓, HDAC2↓, HDAC7 (mRNA and protein)↓

Guo *et al*.[15]	TGF-ß-treated human normal lung fibroblasts	TSA, pan-HDAC	HDAC4 signalling↓, ACTA2↓, COL1A1↓, CTGF↑, inhibition of FMD, α-SMA, AKT phosphorylation↓
Ye *et al*.[42]	Bleomycin rat model	TSA, pan-HDAC	Reduction of lung fibrosis, HDAC2 (mRNA and protein)↓
Rao *et al*.[43]	TGF-ß-treated normal Human, Lung Fibroblasts (HFL1), paraquat-induced lung fibrosis in rats	Vorinostat (SAHA), pan-HDAC	*In vitro* and *in vivo*: SMAD7 acetylation and stabilization, SMAD3 dephosphorylation, FMD↓, attenuation of lung fibrosis
Glenisson *et al*.[44]	TGF-ß-treated primary normal skin fibroblasts (human)	TSA, pan-HDAC	HDAC4 signalling↓, ACTA2/α-SMA↓, inhibition of FMD
Kabel *et al*.[45]	Bleomycin rat model	4-Phenylbutyric Acid (4-PBA), class I and class IIA-HDAC	Attenuation of lung fibrosis, oxidative stress↓, BALF: IL6↓,TGF-ß↓,TNF-α↓
Jiang *et al*.[46]	A549 cells overexpressing mutant SP-AG231V, or SP-A F198S	4-PBA, class I and class II A-HDAC	GRP78↑, suppressed protein aggregation, improved secretion
Zhao *et al*.[47]	Bleomycin mouse model	4-PBA, class I and class II A-HDAC	ER stress↓, EMT↓, NF-κB (p65)↓, cytokines↓, α-SMA↓, COL1A1↓, COL1A2↓, alleviation of lung fibrosis

Note: IPF: Idiopathic Pulmonary Fibrosis; EMT: Epithelial-Mesenchymal Transition; ECM: Extracellular Matrix; FMD: Fibroblast-To-Myofibroblast Differentiation; H3/H4: Histone H3/H4; Ac: Acetylation; BALF: Bronchoalveolar Lavage Fluid; PHMG: Polyhexamethylene Guanidine; ↑: Upregulation; ↓: Downregulation; BAK: Bcl-2 Homologous Antagonist/Killer; BID: BH3 Interacting Domain Death Agonist; BCL2L1: Bcl-2-Like Protein 1; CIP1/p21: Cyclin-Dependent Kinase Inhibitor p21; CHOP: C/EBP Homologous Protein; CCND1: Cyclin D1; ACTA2: Actin Alpha 2; COL1A1: Collagen type I Alpha 1; COL1A3: Collagen type I Alpha 1; BCL-XL: B-Cell Lymphoma-Extra Large; mRNA: messenger RNA; CDH1: Cadherin 1; TNF-α: Tumor Necrosis Factor alpha; PGC1A; Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1 Alpha; TNC: Tenascin-C; IL6: Interleukin 6; PDGFA: Platelet-Derived Growth Factor Alpha; H3K9me3: Histone 3 lysine 9 trimethylation; CXCL10: C-X-C motif Chemokine Ligand 10; Thy-1: Thymocyte differentiation antigen 1; CD90: Cluster of Differentiation 90; H3K27Ac: H3 lysine 27 Acetylation; STAT3-pTyr705: Signal transducer and activator of transcription 3-phosphorylated Tyr705; CTGF: Connective Tissue Growth Factor; GRP78: Glucose-Regulated Protein 78 and NF-κB: Nuclear Factor kappa B

TSA AND PULMONARY FIBROSIS

TSA is the most common HDACi used in clinical settings and it inhibits group I and II HDACs. It works by suppressing TGF-β1-stimulated collagen I *via* reducing the levels of conversion factors. In mice, HDACi can prevent cardiac interstitial fibrosis induced by abnormal expression of HDAC2 related nucleoprotein. Other studies have discovered that deacetylation of the Fas cell surface death receptor (Fas) protein gene promoter leads to the down-regulation of Fas proteins in the fibroblasts of IPF patients, whereas TSA up-regulates Fas gene expression and promotes cell apoptosis, induced by the Fas signaling pathway. Other reports have suggested that TSA enhances Thymocyte differentiation antigen 1 (Thy-1) expression in pulmonary myofibroblasts and suppresses fibroblasts proliferation, thereby serving an anti-fibrotic role[33,40]. Recent studies[32] discovered that excessive deacetylation of the Cyclooxygenase (COX) gene promoter can reduce the expression of COX gene and aggravate pulmonary fibrosis, while vorinostat, an inhibitor of HDAC, can reduce the deacetylation state of COX, thus increasing expression of COX and producing prostaglandin E2 that serve as an anti-fibrotic role.

CONCLUSION

IPF is associated with a progressive deterioration of lung function and poor prognosis. Approved antifibrotic drugs, nintedanib and pirfenidone, only can delay the progression of the disease, but IPF remains incurable and there is an urgent need for new therapies. The majority of the evidence generated to date indicates that the overexpression of Class I and Class II HDACs is associated with fibroblast proliferation and Fibroblast-to-Myofibroblast Differentiation (FMD), as well as accounts for the apoptosis resistant, invasive phenotype of fibroblast/myofibroblast and bronchiolar basal cells in IPF. Therefore, they hold great potential as therapeutics for pulmonary fibrosis. However, its mechanism remains elusive. Hence, future investigations on the different types of HDACs and the mechanisms of HDACi in IPF have not yet been addressed and should be elucidated in future studies.

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Qian Zhang is the major contributor in writing the manuscript and Ping Jiang is mainly responsible for the editing the manuscript.

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Conflict of interests:

The authors declared no conflict of interest.

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