



Histone deacetylases and their inhibitors: new implications for asthma and chronic respiratory conditions

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Purpose of review

The importance of the role of histone deacetylase enzymes in the pathogenesis of asthma and chronic respiratory diseases is increasingly being recognized. Similarly, the potential clinical utility of histone deacetylase enzymes in the treatment of disease is emerging. In this review, the role of histone deacetylases (HDAC) and their inhibitors in asthma and chronic obstructive pulmonary disease is discussed.

Recent findings

HDAC are able to catalyze the hydrolysis of acetyl groups on lysine residues of histones, causing the condensation and coiling of chromosomal DNA around histones, and therefore regulating gene expression. Histone deacetylase inhibitors act specifically or broadly on HDAC and also on nonhistone targets. Some have been used in the oncology therapeutic field for some years, but it is only more recently that they have been suggested in the treatment of asthma and other inflammatory lung diseases.

Summary

Important developments have been made in the understanding of histone deacetylase expression in normal and diseased airways and pulmonary tissue as well as effects of histone deacetylase inhibitors on structural and inflammatory cells in the lung, including cell proliferation, differentiation and apoptosis and senescence. Many of these discoveries may have implications in addressing airway inflammation, airway remodeling and airway hyperresponsiveness in asthma.

Keywords

allergic airways disease, asthma, histone deacetylase inhibitor, inflammatory lung condition, trichostatin A

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the main airway stress diseases predicted to be the third leading cause of death by the year 2020 [1]. Asthma is a heterogeneous chronic inflammatory disease of the airways with some overlap in pathology with COPD. For instance, both diseases have a fibrotic component that is resistant to existing therapies, and in both diseases the epithelium plays one of the central roles in pathogenesis. Corticosteroids and β -agonists are the mainstays of existing asthma therapies but do not directly target airway remodeling (structural changes to the airway wall, including fibrosis) or airway epithelial susceptibility and damage. Predominantly due to steroid resistance, there is much interest in the development of antiinflammatory drugs that could complement these therapeutic modalities. One such group of compounds are the histone de-acetylase inhibitors (HDACi).

Enzymes known as histone deacetylases (HDAC) are able to catalyze the hydrolysis of N-acetyl lysine residues of histones, causing the condensation and coiling of chromosomal DNA around histones. There are 18 HDAC isoforms (HDAC1–18) in humans, and these are categorized into four main classes: class I, II (a and b), III and IV according to phylogeny. Class III HDACs are composed of seven mammalian sirtuins (SIRT1–7). Expression of

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KEY POINTS

- The expression of histone deacetylase enzymes is dysregulated in asthma and COPD with HDAC2 being of particular importance.
- Histone deacetylase inhibitors have been shown to have potent antiinflammatory and antifibrotic effects in animal models of asthma.
- Class or isoform-specific histone deacetylase inhibitors are currently being developed, and these may help increase our understanding of asthma pathogenesis, and may offer improved potential clinical utility for the treatment of disease.

HDACs is tissue specific and altered in disease states. Drugs shown to inhibit HDAC enzyme activity (HDACi) have been shown to act have many therapeutic effects including antiinflammation and potent anticancer activity. Although HDAC enzymes cause repression of transcription due to condensation of DNA around histones, HDACi may cause upregulation or downregulation of specific genes, and many have nonhistone targets [2,3]. The molecular effects of regulation of acetylation status by histone acetyltransferases (HAT) and HDAC enzymes, with a focus on chronic respiratory conditions have been reviewed recently [4].

FUNCTION OF HISTONE DEACETYLASES IN AIRWAY INFLAMMATION

HDAC may play an important role in inflammaging or chronic inflammation associated with the aging process, in the lung in COPD [5]. HDAC1 represses transcription of the C/EBP- δ gene, which amplifies inflammation. In the context of lipopolysaccharide-induced inflammation, the transcription factor Miz-1 is involved in the recruitment of HDAC-1 [6]. Loss of HDAC1 or HDAC2 leads to attenuation of proximal airway development. However, post-natal loss of these HDACs does not affect Sox2 or Bmp4 but can affect the regenerative properties of the airway epithelium [7]. This may have important implications because of the important role of the epithelium in asthma pathogenesis.

EXPRESSION OF HISTONE DEACETYLASES ENZYMES CHRONIC RESPIRATORY CONDITIONS

Pharmacologically, increasing the expression of HDAC2 activity may be useful in the treatment of COPD [8]. A number of studies have shown HDAC2 to have reduced expression in COPD and severe

asthma, and therefore is a novel approach to overcome steroid resistance is to increase HDAC2 expression using theophylline or phosphoinositide 3-kinase δ inhibitors [9]. This has proved successful in a small study [10], but longer-term studies and further investigations are required to determine the clinical efficacy of HDAC2 activators. Other studies have added to the debate on the role of HDACs in steroid insensitivity in asthma and COPD. Butler *et al.* [11[■]] examined HDAC1 and HDAC2 expression in endobronchial biopsies from a large series of patients with severe asthma and found no difference in protein or mRNA expression in severe asthma compared with normal controls. HDAC1 expression was increased in severe asthma versus normal controls. Butler found higher mRNA ($P < 0.05$) but not higher protein. Further, HDAC9 mRNA has been shown to be significantly upregulated in the peripheral blood of asthma sufferers and was associated with severity of disease. HDAC9 was negatively associated with forced expiratory volume 1%. In addition, it was associated with GATA-binding factor 3, interleukin 4, Th17 and Treg-related cytokines [12].

Another study [13] showed that cigarette smoke inhibited HDAC activity in human pulmonary artery endothelial cells. In a study of 49 COPD patients and 42 healthy controls, HDAC2 mRNA and protein expression was found to correlate with development and prognosis of COPD, suggesting it could be used as a biomarker. There was no correlation between HDAC3 or HDAC5 with disease parameters [14]. In a separate in-vitro human macrophage study, smoke exposure led to reduced HDAC3 activity but did not reduce the activity of other HDAC enzymes. Interesting knockdown of HDAC3 resulted in inflammatory cytokine expression, but knockdown of HDAC2 had no effect [15]. The activity of HDAC2 was characterized in a comparative study [16] of three rat models of COPD and was found to be reduced only in a cigarette-smoking model of COPD.

In a recent study [17] using a bleomycin model of pulmonary fibrosis, HDAC2 and 4 expression was increased in primary cultures of lung fibroblasts from mice. Treatment with HDACi was able to increase Fas expression, restoring susceptibility to Fas-mediated apoptosis. Similar effects were seen with lung fibroblasts from human individuals with interstitial pulmonary fibrosis (IPF) [17]. Therefore, HDAC may represent an important aspect of the therapeutic targeting of resistance to apoptosis in fibrotic lung diseases, and exploiting the profibrotic effects of HDACi may hold promise in this area. There is also a report examining the expression of HDAC in idiopathic pulmonary fibrosis ($n = 10$

disease, seven normal), which shows increased protein expression of HDAC1, 2, 3, 8 and sirtuin 1, including strong nuclear localization of HDAC2 and 3 and sirtuin 1 to myofibroblast and p63 basal epithelial cells in fibrotic foci. However, there was little expression of HDACs in type II pneumocytes apart from HDAC6 [18].

POTENTIAL THERAPEUTIC EFFICACY OF HISTONE DE-ACETYLASE INHIBITORS IN ASTHMA AND CHRONIC RESPIRATORY CONDITIONS

HDACi targeting HDAC1 have been shown to regulate levels of expression of defensin, beta 1, the gene for human β defensin 1. This peptide is expressed in the lung and has an important antimicrobial function pertinent to asthma and COPD [19]. Similarly, Trichostatin A (TSA) and sodium butyrate (NaB) have been shown to increase the expression of cathelicidin LL37 (a bacteriocidal protein) *in vitro* in human airway and nasal epithelial cells [20]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is also involved in host defense and represents an attractive target in COPD [21]. The HDACi L-sulforaphane has been shown to activate Nrf2 adding to its beneficial effects in treating pathological processes relevant to lung diseases.

Mucin 5AC (MUC5AC) is the predominant mucin gene product associated with respiratory goblet cell metaplasia and mucus hypersecretion in the airway. The gene has also been flagged in genome wide association studies of inflammatory lung diseases. Glucocorticoid response elements are present in the MUC5AC promoter. In a recent article, the glucocorticoid dexamethasone was shown to reduce MUC5AC in cancer and normal cell lines [22]. Mucin hypersecretion in asthma is upregulated by Th2 cytokines and may contribute to airway occlusion, but it is unclear whether corticosteroids are able to suppress mucin hypersecretion clinically. In the cancer and noncancer cell lines, HDAC2 was found to colocalize to the nucleus with glucocorticoid receptor. Furthermore, short interfering RNA knockdown of abrogated dexamethasone-induced MUC5AC repression [22].

HDAC1 and HDAC5 proteins have been shown to be elevated in remodeled blood vessels in human idiopathic pulmonary hypertension. In a rat hypoxia model with similar HDAC expression, treatment with the HDACi valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA, Vorinostat) reduced platelet derived growth factor (PDGF) β and stromal-derived factor-1 expression and vascular remodeling and fibrosis [23]. NaB is a dietary molecule with HDACi activity. It was shown to

decrease migration and proliferation of pulmonary artery smooth muscle cells and also to decrease PDGF-receptor β . This has important implications for pulmonary arterial hypertension and may be of relevance to asthma [24].

Similarly, the prototypical HDACi, TSA has been shown to exhibit a range of effects that may be relevant to allergy. TSA has been shown to ameliorate 2,4-dinitrofluorobenzene-induced allergic contact dermatitis in mice. Skin lesion severity was reduced in TSA-treated mice, with reduction in epidermal Langerhans cell and splenic dendritic cell numbers. However, effect on regulatory T cells (increased FoxP3 expression) previously observed in some HDACi treatment experiments was not replicated in this model [25]. In a separate model of skin anaphylaxis, TSA was shown to decrease HDAC3. This resulted in decreased monocyte chemoattractant protein 1 secretion [26]. HDACi specific for HDAC3 may represent an important avenue for further investigations for skin allergy therapeutics. Further evidence of broad antiinflammatory effects of HDACi comes from a study of VPA, which was shown to play a role in B-cell development. In the study [27], VPA was shown to inhibit the differentiation of naive B cells into plasmablasts via interference with B-cell proliferation.

Encouragingly, since the time of submission of our article, the others have demonstrated a therapeutic effect of the HDACi TSA on bronchoconstriction on airway smooth muscle cells and in a short-term allergic airways disease (AAD) model. This supports our published findings with TSA in the chronic AAD model. TSA was shown to inhibit the agonist-induced contraction of lung slices and mobilization of Ca^{2+} in airway smooth muscle cells [28²²].

α -1 antitrypsin deficiency is the genetic cause of panacinar emphysema, and is an example of a disease of proteostasis or proteome homeostasis. α -1 antitrypsin deficiency may contribute to extracellular protein folding stress, dysregulation of Nrf2 and also misprocessing of HAT and HDAC pathways [1]. One of the most important articles in the period of the current review concerns correction of α 1 antitrypsin deficiency by the HDACi SAHA or Vorinostat. Levels of α 1 antitrypsin secretion were restored to 50% of those observed in wild-type individuals. The major mechanisms appeared to be calnexin sensitive and via HDAC7 silencing by SAHA. This may represent an important way to address an unmet clinical need in COPD treatment and points to other applications for HDACi in diseases involving proteostasis and protein misfolding [29].

TSA has been shown to be useful in treating long-term high altitude hypoxia in a fetal lamb model. Pulmonary arterial smooth muscle remodeling was

decreased via reduction of p21 regulated cell proliferation and PDGF-induced cell migration [30]. Our own study illustrated the pleiotropic effects of TSA in a chronic mouse model of ovalbumin-induced allergic airways disease. Mice treated with TSA intraperitoneally during the ovalbumin challenge period had reduced inflammation and total and eosinophil cell counts in bronchoalveolar lavage fluid compared with vehicle-treated mice. TSA treatment was also able to partially prevent the development of goblet cell metaplasia in airways, subepithelial fibrosis. Furthermore the TSA-treated mice had attenuated methacholine-induced airway hyperresponsiveness [31].

The future of HDACi treatment perhaps lies with the development and application of more specific HDACi compounds. Spiruchostatin A is one such compound that is naturally derived and targets class I HDACs. This compound has been shown to have strong antiproliferative and antifibrotic effects on TGF β 1-stimulated lung fibroblasts from patients with IPF including reduced α smooth muscle actin and collagen I and III synthesis [32]. It is also emerging that romidepsin (also known as depsipeptide or FK228), a class I-specific HDACi isolated from *Chromobacterium violaceum* has potent antifibrotic effects in IPF. In the context of idiopathic pulmonary fibrosis, telomere transcriptase expression has been shown to be upregulated in fibroblast samples by an HDACi [33].

SIRTUINS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The sirtuins are an evolutionarily conserved family of proteins that function mainly as nicotinamide adenine dinucleotide-dependent deacetylases. Sirtuins may play an important role in inflammaging in the lung in COPD [34]. Smad3 deficiency leads to downregulation of SIRT1; this results in increased acetylation of H3 histone and nuclear factor kappa-beta (NF- κ B) and subsequent upregulation of matrix metalloprotease 9 important in egress of inflammatory cells in COPD [35]. Therefore, SIRT1 activation may represent a novel antiinflammatory approach in COPD treatment. Ablation of SIRT1 in airway epithelial cells in mice leads to airspace enlargement, reduced lung function and tolerance to exercise [36]. SIRT1 may also suppress lung coagulation after particulate matter exposure in mice [37].

Using immunohistochemistry and western blotting, sirtuins were shown to be highly suppressed in large and small airways in human COPD, in which smoking led to suppression mainly in the large airways [38]. Epigenetic factors play a role in development of fibrosis [39]. In an ovalbumin mouse model

of allergic airways disease, the SIRT1 activator SRT1720 and resveratrol suppressed splenocyte tumor necrosis factor- α (TNF α) and IL6 cytokine production as well as splenocyte proliferation. In addition, SRT1720 suppressed lung inflammatory infiltration and cytokine production [40]. Resveratrol has been shown to have numerous antiinflammatory effects in multiple disease systems, including the lung. In one recent study [41], it was able to ameliorate staphylococcal enterotoxin B-induced lung injury in part by inhibition of T-cell activation, upregulation of SIRT1 and downregulation of NF- κ B in lung inflammatory cells. Our own studies have demonstrated protective effects of resveratrol against airway remodeling and hyperresponsiveness in an animal model of allergic airways disease [42].

CONCLUSION

It is emerging that HDAC inhibitors may have clinical application for the treatment of inflammatory and fibrotic diseases. HDAC enzymes are widely expressed in the lung and may be of altered expression in disease. Therefore, delivery of HDACi inhibitors to the lung is a possibility in the treatment of lung disease. However, the role of HDACs in asthma remains controversial, and the nonHDAC targets of HDAC inhibitors are not clearly defined. Certainly, it is becoming clear that HDACi have a number of effects that may be of benefit in addressing airway remodeling and fibrosis, as well as epithelial defence and tissue homeostasis. The development and evaluation of class-selective and/or isoform-specific HDACi will assist in our understanding the role of HDAC enzymes in asthma.

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Conflicts of interest

S.G.R. and T.C.K. declare that there are no conflicts of interest.

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