International Scholarly Research Network
ISRN Pulmonology
Volume 2012, Article ID 452307, 10 pages
doi:10.5402/2012/452307

Review Article

Controversies Surrounding the Potential Use of Histone Deacetylase Inhibitors for the Treatment of Asthma

Simon G. Royce,[1,2] Katherine Ververis,[2,3] and Tom C. Karagiannis[2,3]

[1] *Allergy and Immune Disorders, Murdoch Children's Research Institute, Parkville, VIC, Australia*
[2] *Department of Pathology, The University of Melbourne, Parkville, VIC, Australia*
[3] *Epigenomic Medicine, Baker IDI Heart and Diabetes Institute, The Alfred Medical Research and Education Precinct, Melbourne, VIC, Australia*

Correspondence should be addressed to Tom C. Karagiannis, tom.karagiannis@bakeridi.edu.au

Received 18 October 2011; Accepted 5 December 2011

Academic Editors: A. Altraja, K. Ito, and C. C. Witt

Management of asthma with long-acting β_2-adrenergic receptor agonists and corticosteroids is exceptionally effective for the majority of asthma patients. However, corticosteroid insensitivity or resistance remains a significant clinical problem for a significant proportion of patients, requiring the investigation of new potential therapeutics for asthma. Histone deacetylase inhibitors represent a different class of compounds that have been evaluated for their potential antiasthmatic effects. Although accumulating evidence is indicating beneficial effects in rodent models of allergic airways disease, the potential use of histone deacetylase inhibitors in asthma remains controversial given their mechanisms of action. The aim of this paper is to provide an overview of histone deacetylases and pharmacological modifiers of these enzymes. The discussion represents a balanced account of the emerging evidence indicating the beneficial effects of histone deacetylase inhibitors in inflammatory lung diseases. The potential problems associated with the use of this class of compounds in asthma are also carefully considered.

1. Introduction

Asthma is a multifaceted, chronic inflammatory condition of the airways [1]. It is widely considered as a T-helper (Th)2 type inflammatory disorder typically associated with atopy [2, 3]. The disease is characterized by inflammation-mediated bronchoconstriction, airway hyperresponsiveness (AHR), and mucus hypersecretion by goblet cells [4–6]. The inflammatory response in asthma involves the activation and recruitment of numerous leukocytes (particularly infiltrating eosinophils) as reviewed extensively [7–9]. The molecular basis of the inflammatory response in asthma has also been reviewed recently and is thought to be mediated by a complex network of inflammatory mediators [10, 11]. Activation of inflammatory genes regulated by the proinflammatory transcription factors, nuclear factor (NF)-κb, and activator protein (AP)-1, are thought to be of particular importance [10–12].

Asthma is managed with use of long-acting β_2-adrenergic receptor agonists as bronchodilators and low-dose inhaled glucocorticosteroids (corticosteroids) are used to control the inflammatory response [13, 14]. This treatment regime is exceptionally effective for the majority of asthma patients which amount to approximately 300 million people worldwide (and is expected to continue increasing). However, corticosteroid insensitivity or resistance is a significant clinical problem with approximately 10% of asthma patients requiring the maximum inhaled dose [13]. Further, approximately 1% of patients require regular treatment with oral corticosteroids and a smaller proportion of patients are resistant to corticosteroids [15–17]. Corticosteroids, particularly at the higher doses, are associated with nontrivial side effects [18]. Although the proportion of patients with corticosteroid insensitivity or resistance is very low, it is an important clinical problem considering the total number of people with asthma.

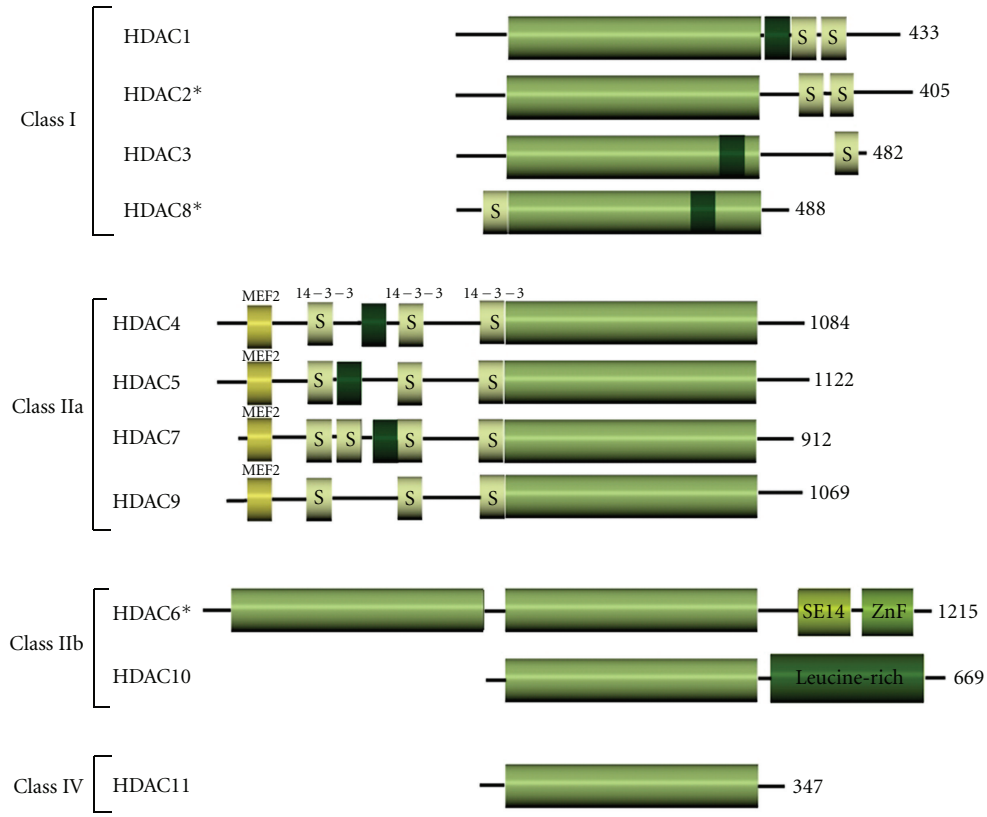


Figure 1: Histone acetylation is regulated by the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyze the addition of the acetyl moiety of acetyl-coA to the ε-amino group of lysine residues in the core histones resulting in a more open, transcriptionally permissive, chromatin conformation. HDAC enzymes remove acetyl groups from lysine residues resulting in a more condensed chromatin conformation and transcriptional repression. Numerous nonhistone proteins are also targets for deacetylation by HDACs. These include proteins involved in gene transcription (e.g., p53), DNA repair (e.g., Ku70), chaperones (e.g., HSP90) and cell motility (e.g., α-tubulin).

There has been an intense research effort aimed at further clarifying the pathobiology of asthma and at developing novel therapeutics to potentially improve the management of the disease. Despite this effort, only two different classes of compounds (four drugs in total) have been approved for the treatment of asthma in the past three decades [19]. Firstly, antileukotrienes including the leukotriene receptor antagonists, zafirlukast (Accolate) and montelukast (Singulair) and the 5-lipoxygenase inhibitor zileuton (Zyflo) have been approved for the treatment of asthma [20–25]. Another approach involves the investigation of anti-inflammatory antibodies, which have included clinical trials withanti-IL-5, IL-4, IL-13, TNFα, CCR3, CCR4, and OX40L [26, 27]. To date, the anti-IgE monoclonal antibody, omalizumab (Xolair), has been approved; for the treatment of moderate-to-severe adult and childhood asthma by the US Food and Drug Administration (FDA) in 2003 [28–30].

Although counter-intuitive, given that they are potent anticancer cytotoxics, histone deacetylase (HDAC) inhibitors, represent a different class of compounds that have been investigated for their potential clinical utility in asthma. The aim of this paper is provide an overview of HDAC enzymes and pharmacological inhibitors in the context of asthma. The potential therapeutic role for HDAC inhibitors in asthma remains controversial. In this paper we provide a balanced account of potential problems associated with the use of HDAC inhibitors in asthma, and the emerging evidence indicating the beneficial effects of this class of compounds.

2. Histone Acetylation

DNA metabolic processes including transcription, replication, and repair are facilitated by dynamic chromatin remodeling mediated by DNA methylation and various posttranslational histone modifications [31]. Histone acetylation is a relatively well-characterized posttranslational modification that is regulated by the opposing actions of histone acetyltransferases (HATs) and HDACs (Figure 1) [32–34]. HATs catalyze the addition of the acetyl moiety of acetyl-coA to the ε-amino group of lysine residues in the core histones [35]. This results in neutralization of the positive charge on the histone tails, weakening interactions with the negatively charged DNA [35, 36]. The effect is a more open, transcriptionally permissive chromatin conformation [35]. HDAC enzymes

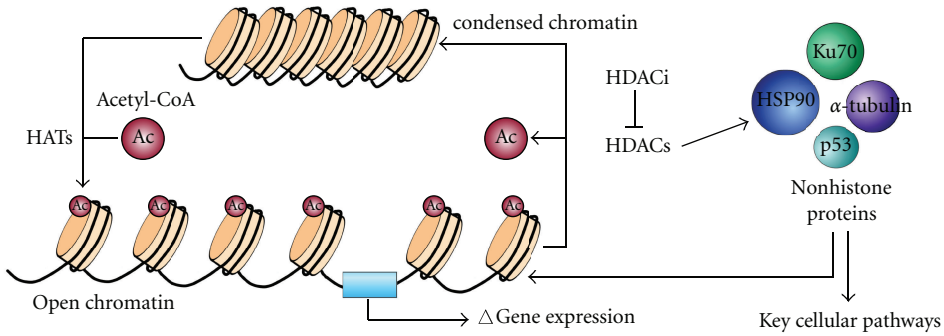


Figure 2: The putative SIRT1 activator, resveratrol, has been investigated as a potential therapeutic agent in airway disease. Using ovalbumin sensitization and challenge mouse models of allergic asthma, resveratrol has been shown to inhibit airway hyperresponsiveness and to decrease total and OVA-specific IgE. Further, resveratrol inhibits ovalbumin-mediated increases in IgG2a and Th2 cytokines IL-4 and IL-5 and decreases expression of TGFβ1. Eosinophilia and mucus hypersecretion is also attenuated by resveratrol in the mouse models of allergic airways disease.

remove acetyl groups from lysine residues resulting in a more condensed chromatin conformation and transcriptional repression [37–39]. Numerous nonhistone proteins are also targets for deacetylation by HDACs. These include proteins involved in gene transcription (e.g., p53, p73, c-Myc, BCL-2), DNA repair (e.g., Ku70, WRN), chaperones (e.g., HSP70), and cell motility (e.g., α-tubulin, cortactin) [32, 33].

3. Sirtuins and Resveratrol for the Treatment of Asthma

Eighteen, mammalian HDAC enzymes have been identified to date and these have been classified into two distinct families [40, 41]. Firstly, the class III HDACs is comprised of the sirtuins (SIRT) 1–7 which are homologous to the yeast enzyme silent information regulator 2 (Sir2) [42–44]. They are nicotinamide-adenine-dinucleotide-(NAD+)-dependent enzymes. SIRTs deacetylate proteins residues by utilizing NAD, releasing the metabolites nicotinamide and 1-O-acetyl-ADP-ribose [45]. SIRTs 4 and 6 also possess ADP-ribosyltransferase activity [46]. Following the identification that Sir2 proteins could expand the lifespan of lower-order model organisms (yeast, worms, and flies), the mammalian SIRTs have been given much attention [47–52]. Findings have indicated that mammalian SIRTs have numerous functions in aging and metabolism [43, 53, 54]. These are mediated through various molecular pathways, including repression of peroxisome proliferator-activated receptor-gamma (PPARγ), deacetylation of the transcriptional coactivator, PPARγ coactivator-1α (PGC-1α), and regulation via the forkhead box O (FOXO) transcription factors [55–58].

The putative SIRT1 activator, resveratrol, has been the subject of intense research for its potential metabolic and antiaging benefits [59–63]. Resveratrol (3,4′,5-trihydroxystilbene) is a natural phytoalexin that protects plants from fungal, viral, and bacterial pathogens and from ultraviolet radiation [64, 65]. The polyphenol is found in various fruits and vegetables and is abundant in grapes, berries, peanuts and the roots of the weed *Polygonum cuspidatum* [65–69]. Resveratrol is a potent antioxidant and anti-inflammatory agent and accumulating evidence indicates that is possesses anticarcinogenic and cardioprotective activities [64, 70–74].

The potent antioxidant and anti-inflammatory properties of resveratrol have prompted the investigation of this compound as a potential therapeutic agent in airway disease [64] (Figure 2). Studies have shown that resveratrol has anti-inflammatory effects in lung epithelial cells *in vitro* [75]. These effects were linked to inhibition of cytokine stimulated inducible nitric oxide synthase expression and nitrite production, inhibition of granulocyte-macrophage colony-stimulating factor release, IL-8 release, and cyclooxygenase-2 expression [75]. Using a mouse model of allergic asthma, resveratrol has been shown to have potential antiasthma effects *in vivo* [76]. Findings indicate that resveratrol inhibits increases in the Th2 cytokines IL-4 and IL-5, decreased eosinophilia and total and ovalbumin-specific IgE and IgG2a [76]. Further decreased mucus hypersecretion and airway hyperresponsiveness was observed in ovalbumin sensitization and challenge model of allergic airways disease [76]. Using a similar mouse model of allergic airways disease, findings from our laboratory, indicate that systemic administration of resveratrol, inhibits airway hyperresponsiveness, reduces subepithelial collagen deposition and has anti-inflammatory effects as assessed by TGFβ1 expression [77]. In paradoxical findings, the SIRT1 inhibitor, sirtinol has been recently shown to attenuate airway inflammation and hyperresponsiveness in an analogous ovalbumin-induced mouse model of asthma [78]. This indicates that the mechanisms accounting for the beneficial effects of resveratrol in models of asthma may be separate from modulation of SIRT1. Overall, these disparate findings highlight the need for further exploration of the functional role of SIRTs and relevant signaling networks models of asthma.

4. Metal-Dependent Histone Deacetylases and Histone Deacetylase Inhibitors

The remaining 11 HDACs are the metal-dependent enzymes typically referred to as the classical HDACs (Figure 3). They

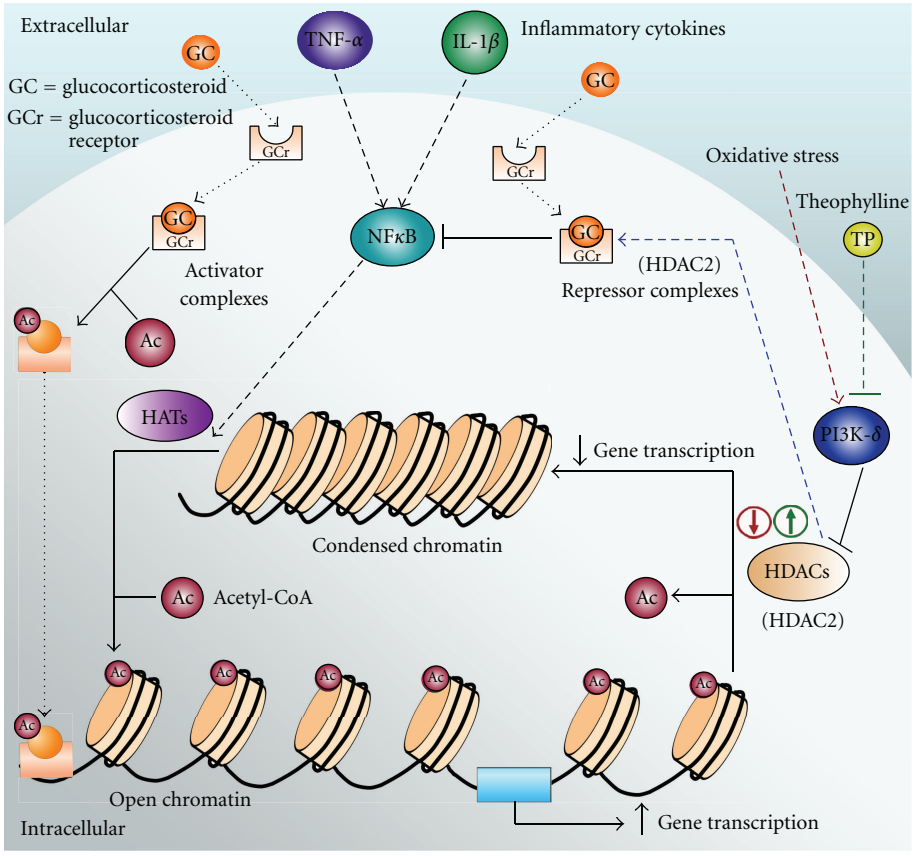


FIGURE 3: Metal-dependent histone deacetylase (HDAC) family. The classical HDACs are grouped into three classes based on their homology and sequence identity to yeast. Class I HDACs comprise of HDAC1, 2, 3, and 8 and these are primarily localized in the cell nucleus. Class II HDACs are divided into two subclasses. They consist of HDAC4, 5, 7, and 9 which make up Class IIa; these contain a myocyte enhancer factor-2 (MEF2)-binding motif, as shown. HDAC6 and 10 make up Class IIb and are primarily localized in the cell cytoplasm. HDAC11 shares homology with both the Class I and Class II HDACs and is the sole member of Class IV. The classical HDACs share a highly conserved deacetylase (DAC) domain shown as a long cylinder and nuclear localization signals are shown as short black cylinders. The 14-3-3 chaperone-binding motifs are shown as short grey cylinders labelled with "S" for serine phosphorylation sites. Black lines represent N- and C-terminal tails and the number of the amino acid of the longest isoform is shown. Other features shown are SE14, Ser-Glu-containing tetradecapeptide repeats; ZnF, ubiquitin-binding zinc finger; Leucine-rich domain. *HDAC2 expression is decreased in bronchial biopsies from patients with asthma; HDAC8 associates with α-actin and is essential for smooth muscle differentiation and contraction which may have implications in asthma; HDAC6 deacetylates α-tubulin and microtubules and this may have important implications in cellular activation and motility in asthma.

are grouped into three classes based on their homology to yeast proteins [32, 33, 37, 40]. Class I includes HDACs1, 2, 3, and 8 which are homologous with the *Saccharomyces cerevisiae* transcriptional regulator RDP3 [79, 80]. They are predominantly localized in the nucleus and have a ubiquitous tissue distribution [40, 81]. HDAC8 is phylogenetically associated with class I however it has overlapping features of both class I and class II enzymes, and has not been associated with any nuclear complexes [82]. In contrast, HDACs1–3 are part of nuclear repressor complexes including CoREST, NURD, SIN3, N-COR, and SMRT and have important roles in regulating gene transcription, cell survival, and proliferation [83–85].

Class II enzymes are structurally related to yeast HDA1 [86, 87]. They are further subdivided into class IIa (HDAC4, 5, 7 and 9) and class IIb (HDAC6 and 10). Class IIa HDAC shuttle between the nucleus and cytoplasm and have a more restricted tissue distribution and tissue-specific roles [32–34, 37, 40, 79, 88, 89]. The function of HDAC10 remains largely unknown, whereas the class IIb enzyme HDAC6 is a key cytoplasmic protein with numerous substrates including α-tubulin and HSP90 [90, 91]. Little is known about the function of HDAC11, the only member of class IV enzymes which shares conserved residues in the catalytic domain with both classes I and II enzymes proteins [37, 40]. With respect to inflammatory lung conditions the class I HDAC2 is considered to be critical, given that it has been implicated with the mechanism of action of corticosteroids and has been show to be downregulated in airway diseases [92–97]. The class I HDAC8 which has been shown to be associated α-actin in smooth muscle cells, and the class IIb HDAC6 which acetylates α-tubulin, HSP90, and microtubules may also have important functions in cellular activation and motility in inflammatory lung diseases [98, 99].

A structurally diverse group of compounds have been shown to inhibit the activity of the metal-dependent HDAC enzymes. HDAC inhibitors hyperacetylate the core histones and they also have numerous nonhistone substrates with critical roles in various cellular functions including cell signaling, motility, chromatin structure, and DNA repair [32, 33, 100]. The have been shown to alter the expression of approximately 2–20% of genes in malignant cells [37, 38, 79, 101]. In general, HDAC inhibitors have been shown to decrease proliferation, induce cell-death, apoptosis, and differentiation, alter the cell cycle distribution (with G1 arrest and G2/M arrest at relatively high doses), and decrease migration, invasion, and angiogenesis in cancer cells [32, 33, 37, 38]. This provides the basis of their clinical utility in cancer. Indeed, suberoylanilide hydroxamic acid (SAHA, Vorinostat, Zolinza) and the cyclic peptide, depsipeptide (Romidepsin, Istodax), have been approved by the US FDA, for the treatment of cutaneous T-cell lymphoma [102–105].

The prototypical hydroxamic acid, Trichostatin A, is a potent antifungal antibiotic that was isolated from a metabolite of *Streptomyces hygroscopicus* [106]. The hydroxamic acids have broad-spectrum HDAC inhibition activity in the nanomolar to low-micromolar range [33, 107]. The cyclic peptides which include trapoxin and depsipeptide are also potent HDAC inhibitors, as are the benzamides which include entinostat (MS-275, SNDX 275) and MGCD0103 [32, 102, 103, 107]. The aliphatic acids which include sodium butyrate and widely used antiepileptic valproic acid, represent the least potent group of HDAC inhibitors possessing activity in the millimolar range [108–110].

5. Activation of Histone Deacetylase 2 as a Potential Therapeutic Target for Asthma

Evidence indicates that HDAC2 is an important enzyme in asthma and has been linked with corticosteroid resistance [13, 93, 95]. HDAC2 activity and expression has been shown to be decreased in bronchial biopsies and peripheral blood in patients with severe asthma; a correlation has been observed between HDAC2 expression levels and disease severity [111, 112]. Furthermore, HDAC expression levels are concordant with impaired corticosteroid sensitivity [113]. This is related to the molecular mechanisms of action of corticosteroids (Figure 4). Corticosteroids diffuse into the cell where they bind to the glucocorticoid receptor. Activated glucocorticoid receptors are released from chaperone proteins, including the HDAC6 substrate heat shock protein 90 and translocate to the nucleus [18, 93, 114]. Homodimerized receptors bind to glucocorticoid response elements in promoters and alter the transcription of a myriad of glucocorticoid-responsive genes [18, 114]. The major action of corticosteroids in asthma is the attenuation of inflammatory gene transcription which is mediated by proinflammatory transcription factors particularly, NF-κB [9, 18, 114]. Corticosteroids have been shown to inhibit NF-κB-induced expression of inflammatory genes by (1) direct inhibition of HAT (CREB-binding protein) activity and (2) by the recruitment of HDAC2 which suppresses inflammatory gene transcription [9, 17, 18, 93, 96, 97, 114].

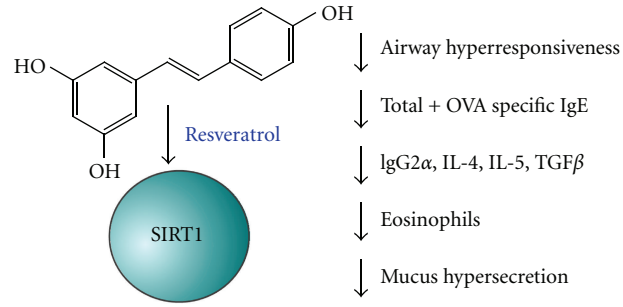
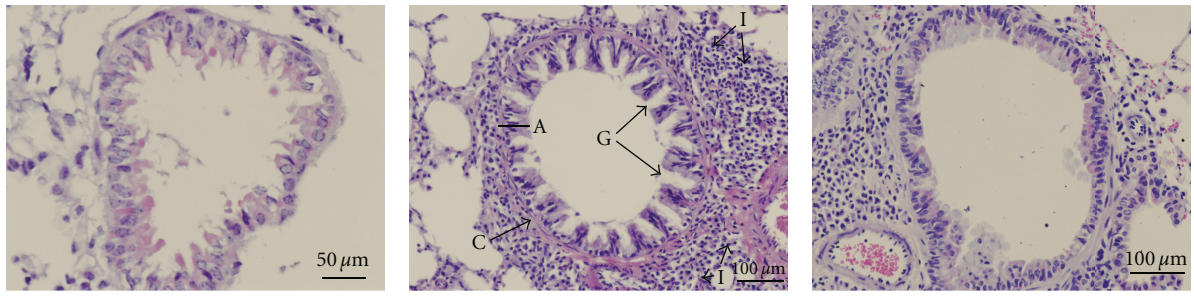


Figure 4: Corticosteroids diffuse into the cell where they bind to the glucocorticoid receptor. Activated receptors bind to glucocorticoid response elements in promoters and alter the transcription of glucocorticoid-responsive genes. Corticosteroids attenuate inflammatory gene transcription which, is mediated by the proinflammatory transcription factor NF-κB, by inhibiting HAT activity and by recruiting HDAC2 repressor complexes. Theophylline reverses oxidative stress-induced decreases in the expression of HDACs which are mediated by activation of PI3K-δ. This mechanism may account, at least in part, for the therapeutic benefits seen by combinations of low-dose theophylline and corticosteroids.

In accordance with this mechanism, downregulation of HDAC2 in bronchoalveolar lavage macrophages results in impaired corticosteroid sensitivity and overexpression of HDAC2 enhances the function of corticosteroids [115].

Another observation is that theophylline, which has a more than 70-year clinical history as a bronchodilator in asthma, interacts with corticosteroid therapy (Figure 4) [116]. There is evidence that theophylline has anti-inflammatory or immunomodulatory effects in asthma [117–121]. A number of studies have indicated that low-dose theophylline used in combination with corticosteroids provides an enhanced therapeutic benefit in asthma [122–124]. Findings indicate that the molecular mechanism accounting for the beneficial effects of combinations of theophylline and corticosteroids may involve enhancing HDAC activity [116]. For example, it has been shown that low-dose theophylline enhances HDAC activity in epithelial cells and macrophages both *in vitro* and *in vivo* [116]. Evidence indicates that theophylline reverses oxidative stress-induced decreases in the expression of HDACs which are mediated by activation of phosphoinositide-3-kinase-δ (PI3K-δ) [111, 125]. This is in line with findings indicating that PI3K-δ inhibitors reverse corticosteroid sensitivity in relevant model systems [125, 126]. Overall, it has been suggested that theophylline reverses corticosteroid sensitivity in asthma by increasing HDAC2 activity which is required for recruitment by the activated glucocorticoid receptor to repress the expression of inflammatory genes [13].

It follows from the preceding discussion that HDAC activation, particularly HDAC2, may represent a molecular target for the development of new therapeutics for asthma. Further, it would appear that classical broad-sprectrum HDAC inhibitors would be inappropriate as candidate potential therapeutics for asthma. However, as discussed below, emerging evidence is suggesting beneficial effects of HDAC



(a) (b) (c)

Figure 5: The therapeutic potential of histone deacetylase inhibitors (HDAC) in the treatment of asthma is emerging. Findings have indicated that Trichostatin A attenuates airway constriction but not inflammation in murine models of allergic airways disease. In our chronic model of allergic airways disease, apart from airway hyperresponsiveness, goblet cell hyperplasia and metaplasia (G), inflammation (I), airway wall thickening (A), and subepithelial collagen deposition (C) are evident in ovalbumin-sensitized (OVA-VEH) mice (b) compared to controls (saline) (a). Treatment with valproic acid (c) attenuates airway hyperresponsiveness and results in a reduction in airway epithelial thickness, subepithelial collagen deposition, and goblet cell hyperplasia. (a) = ×40 magnification, (b and c) = ×20 magnification.

inhibitors in relevant animal models of allergic airways disease and in a preliminary clinical trial.

6. Histone Deacetylase Inhibitors in Experimental Models of Asthma

Trichostatin A has been shown to reduce airway inflammation in an established mouse model of allergic airways disease involving sensitization and challenge with ovalbumin [127]. Findings indicated that Trichostatin A attenuated methacholine-induced AHR and decreased numbers of eosinophils and lymphocytes in bronchial alveolar lavage fluid (BALF) in mice [127]. Further, the results indicated that Trichostatin A decreased expression of the Th2 cytokines IL-4 and IL-5 and reduced OVA-specific IgE [127]. Further studies have indicated that the hydroxamic acid, SAHA, is a potent inhibitor of antigen-induced contraction using isolated sensitized guinea pig tracheal rings as a model system [128]. The HDAC inhibitor MGCD0103 also inhibited agonist-induced contraction in the same model and also reduced antigen- and agonist-induced histamine release from rat peritoneal mast cells [128]. In other *ex vivo* studies using isolated rodent lungs, Trichostatin A was shown to exhibit anti-inflammatory effects reducing the stimulated release of TNF, MIP-2α, and IL-6 [129]. However, the findings from a recent *in vivo* study have indicated that Trichostatin A reduces airway constriction but does not have anti-inflammatory effects in mouse and human models of asthma [130]. Using the mouse model of *Aspergillus fumigatus* antigen-induced airways disease, Trichostatin A has been shown to reduce methacholine-induced AHR but did not have an effect on leukocytes in BALF or on the levels of the proinflammatory cytokines IL-4 and IL-6 [130].

A preliminary clinical trial has indicated that the broad-spectrum HDAC inhibitor valproic acid has potent antiasthmatic activity [131]. Valproic acid was used in this trial on the basis of its well-known antiepileptic effects given that an old hypothesis considers allergy and bronchial asthma as neuropathic conditions [132, 133]. Indeed, findings from another preliminary clinical trial published in 1968, indicate that anti-epileptics were used successfully to treat asthma [132]. Similarly, in the more recent clinical trial treatment with valproic acid was found that result in stable and complete remission in 11/14 patients; an effect which persisted, at least until the three-year followup [131]. Recent findings from our laboratory using the conventional mouse model of chronic allergic airways disease, involving ovalbumin sensitization and challenge, indicate the beneficial antiasthmatic effects of valproic acid (Figure 5) [134]. Our findings indicate that valproic acid attenuated structural airway remodeling changes (epithelial thickness and subepithelial collagen deposition) and methacholine-induced AHR [134]. The findings from our study did not indicate an anti-inflammatory response with increases in leukocytes BALF and IgE not affected by treatment with valproic acid [134].

7. Conclusions

Collectively, the findings using *in vivo* and *ex vivo* models of allergic airways disease indicate that HDAC inhibitors may have potential as therapeutics in asthma. Similarly, the preliminary clinical trial with valproic acid is indicative of the promise of this class of compounds. However, the findings to date are inconsistent with respect to mechanism. It appears that inhibition of methacholine-induced AHR and attenuation of structural remodeling are consistently observed, whereas anti-inflammatory responses require further clarification. Additionally, findings with HDAC activators such as theophylline, which may improve responses to corticosteroids via HDAC2, highlight the paradox. In this context it would be important to evaluate class- or isoform-specific HDAC inhibitors, which are increasingly becoming available, in relevant model systems. To date, studies have focused on classical broad-spectrum HDAC inhibitors which, apart from inhibiting HDAC2, may have significant off-targets effects given that they are potent antineoplastic agents. More specific compounds do not only have the potential to ameliorate unwanted side effects, but will also

assist in clarifying the mechanisms of action of HDAC inhibitors in asthma.

Acknowledgments

The support of the Australian Institute of Nuclear Science and Engineering is acknowledged. T. C. Karagiannis was the recipient of AINSE awards. Epigenomic Medicine Laboratory is supported by the National Health and Medical Research Council of Australia. K. Ververis is supported by a Baker IDI postgraduate scholarship, supported in part by the Victorian Government's Operational Infrastructure Support Program. The authors would like to acknowledge the use of the facilities provided by Monash Micro Imaging @ AMREP and particularly, the expert assistance from Drs Stephen Cody and Iśka Carmichael. All of the authors (S. G. Royce, K. Ververis and T. C. Karagiannis) declare that they have no direct financial relation with the commercial identities mentioned in this paper that might lead to a conflict of interests.

References

[1] T. R. Myers and L. Tomasio, "Asthma: 2015 and beyond," *Respiratory Care*, vol. 56, no. 9, pp. 1389–1410, 2011.

[2] N. R. Bhakta and P. G. Woodruff, "Human asthma phenotypes: from the clinic, to cytokines, and back again," *Immunological Reviews*, vol. 242, no. 1, pp. 220–232, 2011.

[3] J. A. Elias, C. G. Lee, T. Zheng, B. Ma, R. J. Homer, and Z. Zhu, "New insights into the pathogenesis of asthma," *The Journal of Clinical Investigation*, vol. 111, no. 3, pp. 291–297, 2003.

[4] C. M. Evans, K. Kim, M. J. Tuvim, and B. F. Dickey, "Mucus hypersecretion in asthma: causes and effects," *Current Opinion in Pulmonary Medicine*, vol. 15, no. 1, pp. 4–11, 2009.

[5] R. Djukanovic, W. R. Roche, J. W. Wilson et al., "Mucosal inflammation in asthma," *American Review of Respiratory Disease*, vol. 142, no. 2, pp. 434–457, 1990.

[6] D. R. Curran and L. Cohn, "Advances in mucous cell metaplasia: a plug for mucus as a therapeutic focus in chronic airway disease," *American Journal of Respiratory Cell and Molecular Biology*, vol. 42, no. 3, pp. 268–275, 2010.

[7] S. T. Holgate, "Pathogenesis of asthma," *Clinical and Experimental Allergy*, vol. 38, no. 6, pp. 872–897, 2008.

[8] L. R. Bisset and P. Schmid-Grendelmeier, "Chemokines and their receptors in the pathogenesis of allergic asthma: progress and perspective," *Current Opinion in Pulmonary Medicine*, vol. 11, no. 1, pp. 35–42, 2005.

[9] P. J. Barnes, "The role of inflammation and anti-inflammatory medication in asthma," *Respiratory Medicine*, vol. 96, no. 1, supplement A, pp. S9–S15, 2002.

[10] P. J. Barnes, "Immunology of asthma and chronic obstructive pulmonary disease," *Nature Reviews Immunology*, vol. 8, no. 3, pp. 183–192, 2008.

[11] P. J. Barnes, "Pathophysiology of allergic inflammation," *Immunological Reviews*, vol. 242, no. 1, pp. 31–50, 2011.

[12] I. M. Adcock, P. C. Chou, A. Durham, and P. Ford, "Overcoming steroid unresponsiveness in airways disease," *Biochemical Society Transactions*, vol. 37, no. 4, pp. 824–829, 2009.

[13] P. J. Barnes and I. M. Adcock, "Glucocorticoid resistance in inflammatory diseases," *The Lancet*, vol. 373, no. 9678, pp. 1905–1917, 2009.

[14] K. F. Chung, G. Caramori, and I. M. Adcock, "Inhaled corticosteroids as combination therapy with β-adrenergic agonists in airways disease: present and future," *European Journal of Clinical Pharmacology*, vol. 65, no. 9, pp. 853–871, 2009.

[15] I. M. Adcock and P. J. Barnes, "Molecular mechanisms of corticosteroid resistance," *Chest*, vol. 134, no. 2, pp. 394–401, 2008.

[16] P. J. Barnes, "Mechanisms and resistance in glucocorticoid control of inflammation," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 120, no. 2-3, pp. 76–85, 2010.

[17] I. M. Adcock, P. A. Ford, P. Bhavsar, T. Ahmad, and K. F. Chung, "Steroid resistance in asthma: mechanisms and treatment options," *Current Allergy and Asthma Reports*, vol. 8, no. 2, pp. 171–178, 2008.

[18] P. J. Barnes, "Glucocorticosteroids: current and future directions," *British Journal of Pharmacology*, vol. 163, no. 1, pp. 29–43, 2011.

[19] K. Mullane, "The increasing challenge of discovering asthma drugs," *Biochemical Pharmacology*, vol. 82, no. 6, pp. 586–599, 2011.

[20] R. A. Nathan, "Anti-leukotriene agents: a new direction in asthma therapy," *Journal of Asthma*, vol. 33, no. 6, pp. 353–366, 1996.

[21] P. J. Barnes, "Anti-leukotrienes: a new treatment for asthma," *Practitioner*, vol. 242, no. 1586, pp. 395–399, 1998.

[22] A. R. Leff, "Regulation of leukotrienes in the management of asthma: biology and clinical therapy," *Annual Review of Medicine*, vol. 52, pp. 1–14, 2001.

[23] "FDA approves zafirlukast, first of new type of asthma drug," *American Journal of Health-System Pharmacy*, vol. 53, article 2778, 1996.

[24] "Montelukast approved for asthma management," *American Journal of Health-System Pharmacy*, vol. 55, article 759, 1998.

[25] A. M. Stevenson, "Leukotriene receptor antagonists: the newest in asthma drugs," *The American Journal of Maternal Child Nursing*, vol. 22, no. 3, pp. 170–169, 1997.

[26] F. Tarantini, I. Baiardini, G. Passalacqua, F. Braido, and G. W. Canonica, "Asthma treatment: 'Magic bullets which seek their own targets'," *Allergy*, vol. 62, no. 6, pp. 605–610, 2007.

[27] M. C. Catley, J. Coote, M. Bari, and K. L. Tomlinson, "Monoclonal antibodies for treatment of asthma," *Pharmacology & Therapeutics*, vol. 132, no. 3, pp. 333–351, 2011.

[28] "Omalizumab: anti-IgE monoclonal antibody E25, E25, humanised anti-IgE MAb, IGE 025, monoclonal antibody E25, Olizumab, Xolair, rhuMAb-E25," *BioDrugs*, vol. 16, pp. 380–386, 2002.

[29] R. E. Jonkers and J. S. van der Zee, "Anti-IgE and other new immunomodulation-based therapies for allergic asthma," *Netherlands Journal of Medicine*, vol. 63, no. 4, pp. 121–128, 2005.

[30] A. H. Liu, "Treatment of asthma with anti-immunoglobulin E monoclonal antibody," *Allergy and Asthma Proceedings*, vol. 27, no. 2, pp. S24–S28, 2006.

[31] T. Kouzarides, "Chromatin modifications and their function," *Cell*, vol. 128, no. 4, pp. 693–705, 2007.

[32] P. A. Marks, "Histone deacetylase inhibitors: a chemical genetics approach to understanding cellular functions," *Biochimica et Biophysica Acta*, vol. 1799, no. 10–12, pp. 717–725, 2010.

[33] P. A. Marks and W. S. Xu, "Histone deacetylase inhibitors: potential in cancer therapy," *Journal of Cellular Biochemistry*, vol. 107, no. 4, pp. 600–608, 2009.

[34] S. Minucci and P. G. Pelicci, "Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer," *Nature Reviews Cancer*, vol. 6, no. 1, pp. 38–51, 2006.

[35] S. Y. Roth, J. M. Denu, and C. D. Allis, "Histone acetyltransferases," *Annual Review of Biochemistry*, vol. 70, pp. 81–120, 2001.

[36] B. C. Smith and J. M. Denu, "Chemical mechanisms of histone lysine and arginine modifications," *Biochimica et Biophysica Acta*, vol. 1789, no. 1, pp. 45–57, 2009.

[37] M. Dokmanovic, C. Clarke, and P. A. Marks, "Histone deacetylase inhibitors: overview and perspectives," *Molecular Cancer Research*, vol. 5, no. 10, pp. 981–989, 2007.

[38] M. Dokmanovic and P. A. Marks, "Prospects: histone deacetylase inhibitors," *Journal of Cellular Biochemistry*, vol. 96, no. 2, pp. 293–304, 2005.

[39] T. A. McKinsey, E. N. Olson, and Berger, "Dual roles of histone deacetylases in the control of cardiac growth," *Novartis Foundation Symposium*, vol. 259, pp. 132–141, 2004.

[40] A. J. M. de Ruijter, A. H. van Gennip, H. N. Caron, S. Kemp, and A. B. P. van Kuilenburg, "Histone deacetylases (HDACs): characterization of the classical HDAC family," *Biochemical Journal*, vol. 370, no. 3, pp. 737–749, 2003.

[41] I. V. Gregoretti, Y. M. Lee, and H. V. Goodson, "Molecular evolution of the histone deacetylase family: Ffunctional implications of phylogenetic analysis," *Journal of Molecular Biology*, vol. 338, no. 1, pp. 17–31, 2004.

[42] J. Landry, A. Sutton, S. T. Tafrov et al., "The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 11, pp. 5807–5811, 2000.

[43] M. C. Haigis and L. P. Guarente, "Mammalian sirtuins—emerging roles in physiology, aging, and calorie restriction," *Genes and Development*, vol. 20, no. 21, pp. 2913–2921, 2006.

[44] J. Landry, J. T. Slama, and R. Sternglanz, "Role of NAD^+ in the deacetylase activity of the SIR2-like proteins," *Biochemical and Biophysical Research Communications*, vol. 278, no. 3, pp. 685–690, 2000.

[45] K. G. Tanner, J. Landry, R. Sternglanz, and J. M. Denu, "Silent information regulator 2 family of NAD-dependent histone/protein deacetylases generates a unique product, 1-O-acetyl-ADP-ribose," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 26, pp. 14178–14182, 2000.

[46] B. C. Smith, W. C. Hallows, and J. M. Denu, "Mechanisms and molecular probes of sirtuins," *Chemistry and Biology*, vol. 15, no. 10, pp. 1002–1013, 2008.

[47] R. A. Frye, "Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins," *Biochemical and Biophysical Research Communications*, vol. 273, no. 2, pp. 793–798, 2000.

[48] L. Guarente and C. Kenyon, "Genetic pathways that regulate ageing in model organisms," *Nature*, vol. 408, no. 6809, pp. 255–262, 2000.

[49] D. Gems, "Yeast longevity gene goes public," *Nature*, vol. 410, no. 6825, pp. 154–155, 2001.

[50] A. L. Barlow, C. M. van Drunen, C. A. Johnson, S. Tweedie, A. Bird, and B. M. Turner, "dSIR2 and dHDAC6: Ttwo novel, inhibitor-resistant deacetylases in *Drosophila melanogaster*," *Experimental Cell Research*, vol. 265, no. 1, pp. 90–103, 2001.

[51] J. G. Wood, B. Rogina, S. Lavu et al., "Sirtuin activators mimic caloric restriction and delay ageing in metazoans," *Nature*, vol. 430, pp. 686–689, 2004.

[52] L. Guarente and F. Picard, "Calorie restriction—the SIR2 connection," *Cell*, vol. 120, no. 4, pp. 473–482, 2005.

[53] L. Bordone and L. Guarente, "Calorie restriction, SIRT1 and metabolism: understanding longevity," *Nature Reviews Molecular Cell Biology*, vol. 6, no. 4, pp. 298–305, 2005.

[54] S. Michan and D. Sinclair, "Sirtuins in mammals: insights into their biological function," *Biochemical Journal*, vol. 404, no. 1, pp. 1–13, 2007.

[55] P. J. Elliott and M. Jirousek, "Sirtuins: novel targets for metabolic disease," *Current Opinion in Investigational Drugs*, vol. 9, no. 4, pp. 371–378, 2008.

[56] M. E. Giannakou and L. Partridge, "The interaction between FOXO and SIRT1: tipping the balance towards survival," *Trends in Cell Biology*, vol. 14, no. 8, pp. 408–412, 2004.

[57] N. Chaudhary and P. T. Pfluger, "Metabolic benefits from Sirt1 and Sirt1 activators," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 12, no. 4, pp. 431–437, 2009.

[58] M. C. Sugden, P. W. Caton, and M. J. Holness, "PPAR control: it's SIRTainly as easy as PGC," *Journal of Endocrinology*, vol. 204, no. 2, pp. 93–104, 2010.

[59] A. Camins, F. X. Sureda, F. Junyent et al., "Sirtuin activators: designing molecules to extend life span," *Biochimica et Biophysica Acta*, vol. 1799, no. 10–12, pp. 740–749, 2010.

[60] S. Chung, H. Yao, S. Caito, J. W. Hwang, G. Arunachalam, and I. Rahman, "Regulation of SIRT1 in cellular functions: role of polyphenols," *Archives of Biochemistry and Biophysics*, vol. 501, no. 1, pp. 79–90, 2010.

[61] S. Fröjdö, C. Durand, and L. Pirola, "Metabolic effects of resveratrol in mammals—a link between improved insulin action and aging," *Current Aging Science*, vol. 1, no. 3, pp. 145–151, 2008.

[62] S. Sadruddin and R. Arora, "Resveratrol: biologic and therapeutic implications," *Journal of the CardioMetabolic Syndrome*, vol. 4, no. 2, pp. 102–106, 2009.

[63] M. D. Knutson and C. Leeuwenburgh, "Resveratrol and novel potent activators of SIRT1: effects on aging and age-related diseases," *Nutrition Reviews*, vol. 66, no. 10, pp. 591–596, 2008.

[64] L. G. Wood, P. A. B. Wark, and M. L. Garg, "Antioxidant and anti-inflammatory effects of resveratrol in airway disease," *Antioxidants and Redox Signaling*, vol. 13, no. 10, pp. 1535–1548, 2010.

[65] S. Pervaiz and A. L. Holme, "Resveratrol: its biologic targets and functional activity," *Antioxidants and Redox Signaling*, vol. 11, no. 11, pp. 2851–2897, 2009.

[66] F. Yang, T. Zhang, and Y. Ito, "Large-scale separation of resveratrol, anthraglycoside A and anthraglycoside B from Polygonum cuspidatum Sieb. et Zucc by high-speed counter-current chromatography," *Journal of Chromatography A*, vol. 919, no. 2, pp. 443–448, 2001.

[67] M. Yadav, S. Jain, A. Bhardwaj et al., "Biological and medicinal properties of grapes and their bioactive constituents: an update," *Journal of Medicinal Food*, vol. 12, no. 3, pp. 473–484, 2009.

[68] W. R. Leifert and M. Y. Abeywardena, "Cardioprotective actions of grape polyphenols," *Nutrition Research*, vol. 28, no. 11, pp. 729–737, 2008.

[69] G. J. Soleas, E. P. Diamandis, and D. M. Goldberg, "Resveratrol: a molecule whose time has come? And gone?" *Clinical Biochemistry*, vol. 30, no. 2, pp. 91–113, 1997.

[70] P. Signorelli and R. Ghidoni, "Resveratrol as an anticancer nutrient: molecular basis, open questions and promises," *Journal of Nutritional Biochemistry*, vol. 16, no. 8, pp. 449–466, 2005.

[71] N. R. Sundaresan, V. B. Pillai, and M. P. Gupta, "Emerging roles of SIRT1 deacetylase in regulating cardiomyocyte survival and hypertrophy," *Journal of Molecular and Cellular Cardiology*, vol. 51, no. 4, pp. 614–618, 2011.

[72] T. Hsieh and J. M. Wu, "Resveratrol: biological and pharmaceutical properties as anticancer molecule," *BioFactors*, vol. 36, no. 5, pp. 360–369, 2010.

[73] C. C. Udenigwe, V. R. Ramprasath, R. E. Aluko, and P. J. H. Jones, "Potential of resveratrol in anticancer and anti-inflammatory therapy," *Nutrition Reviews*, vol. 66, no. 8, pp. 445–454, 2008.

[74] B. L. Liu, X. Zhang, W. Zhang, and H. N. Zhen, "New enlightenment of French paradox: resveratrol's potential for cancer chemoprevention and anti-cancer therapy," *Cancer Biology and Therapy*, vol. 6, no. 12, pp. 1833–1836, 2007.

[75] L. E. Donnelly, R. Newton, G. E. Kennedy et al., "Anti-inflammatory effects of resveratrol in lung epithelial cells: molecular mechanisms," *American Journal of Physiology*, vol. 287, no. 4, pp. L774–L783, 2004.

[76] M. Lee, S. Kim, O. K. Kwon, S. R. Oh, H. K. Lee, and K. Ahn, "Anti-inflammatory and anti-asthmatic effects of resveratrol, a polyphenolic stilbene, in a mouse model of allergic asthma," *International Immunopharmacology*, vol. 9, no. 4, pp. 418–424, 2009.

[77] S. G. Royce, W. Dang, Y. Gao et al., "Resveratrol has protective effects against airway remodeling and airway inflammation in a murine model of allergic airways disease," *Pathobiology of Aging & Age-Related Diseases*, vol. 1, article 7134, 2011.

[78] S. R. Kim, K. S. Lee, S. J. Park et al., "Involvement of sirtuin 1 in airway inflammation and hyperresponsiveness of allergic airway disease," *Journal of Allergy and Clinical Immunology*, vol. 125, no. 2, pp. 449–460, 2010.

[79] J. E. Bolden, M. J. Peart, and R. W. Johnstone, "Anticancer activities of histone deacetylase inhibitors," *Nature Reviews Drug Discovery*, vol. 5, no. 9, pp. 769–784, 2006.

[80] P. A. Marks, R. A. Rifkind, V. M. Richon, R. Breslow, T. Miller, and W. K. Kelly, "Histone deacetylases and cancer: causes and therapies," *Nature Reviews Cancer*, vol. 1, no. 3, pp. 194–202, 2001.

[81] R. W. Johnstone, "Histone-deacetylase inhibitors: novel drugs for the treatment of cancer," *Nature Reviews Drug Discovery*, vol. 1, no. 4, pp. 287–299, 2002.

[82] G. Estiu, N. West, R. Mazitschek, E. Greenberg, J. E. Bradner, and O. Wiest, "On the inhibition of histone deacetylase 8," *Bioorganic and Medicinal Chemistry*, vol. 18, no. 11, pp. 4103–4110, 2010.

[83] J. Ahringer, "NuRD and SIN3: histone deacetylase complexes in development," *Trends in Genetics*, vol. 16, no. 8, pp. 351–356, 2000.

[84] Y. Huang, S. J. Myers, and R. Dingledine, "Transcriptional repression by REST: recruitment of Sin3A and histone deacetylase to neuronal genes," *Nature Neuroscience*, vol. 2, no. 10, pp. 867–872, 1999.

[85] Y. D. Wen, V. Perissi, L. M. Staszewski et al., "The histone deacetylase-3 complex contains nuclear receptor corepressors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 13, pp. 7202–7207, 2000.

[86] M. Martin, R. Kettmann, and F. Dequiedt, "Class IIa histone deacetylases: regulating the regulators," *Oncogene*, vol. 26, no. 37, pp. 5450–5467, 2007.

[87] O. Witt, H. E. Deubzer, T. Milde, and I. Oehme, "HDAC family: what are the cancer relevant targets?" *Cancer Letters*, vol. 277, no. 1, pp. 8–21, 2009.

[88] A. Mai, D. Rotili, S. Valente, and A. G. Kazantsev, "Histone deacetylase inhibitors and neurodegenerative disorders: holding the promise," *Current Pharmaceutical Design*, vol. 15, no. 34, pp. 3940–3957, 2009.

[89] W. S. Xu, R. B. Parmigiani, and P. A. Marks, "Histone deacetylase inhibitors: molecular mechanisms of action," *Oncogene*, vol. 26, no. 37, pp. 5541–5552, 2007.

[90] J. J. Kovacs, P. J. M. Murphy, S. Gaillard et al., "HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor," *Molecular Cell*, vol. 18, no. 5, pp. 601–607, 2005.

[91] M. Haberland, R. L. Montgomery, and E. N. Olson, "The many roles of histone deacetylases in development and physiology: implications for disease and therapy," *Nature Reviews Genetics*, vol. 10, no. 1, pp. 32–42, 2009.

[92] I. M. Adcock, L. Tsaprouni, P. Bhavsar, and K. Ito, "Epigenetic regulation of airway inflammation," *Current Opinion in Immunology*, vol. 19, no. 6, pp. 694–700, 2007.

[93] P. J. Barnes, "Histone deacetylase-2 and airway disease," *Therapeutic Advances in Respiratory Disease*, vol. 3, no. 5, pp. 235–243, 2009.

[94] P. Bhavsar, T. Ahmad, and I. M. Adcock, "The role of histone deacetylases in asthma and allergic diseases," *Journal of Allergy and Clinical Immunology*, vol. 121, no. 3, pp. 580–584, 2008.

[95] P. J. Barnes, I. M. Adcock, and K. Ito, "Histone acetylation and deacetylation: importance in inflammatory lung diseases," *European Respiratory Journal*, vol. 25, no. 3, pp. 552–563, 2005.

[96] K. Ito, C. E. Charron, and I. M. Adcock, "Impact of protein acetylation in inflammatory lung diseases," *Pharmacology and Therapeutics*, vol. 116, no. 2, pp. 249–265, 2007.

[97] I. M. Adcock, K. Ito, and P. J. Barnes, "Histone deacetylation: an important mechanism in inflammatory lung diseases," *COPD*, vol. 2, no. 4, pp. 445–455, 2005.

[98] D. Waltregny, W. Glénisson, S. L. Tran et al., "Histone deacetylase HDAC8 associates with smooth muscle α-actin and is essential for smooth muscle cell contractility," *The FASEB Journal*, vol. 19, no. 8, pp. 966–968, 2005.

[99] Y. Zhang, N. Li, C. Caron et al., "HDAC-6 interacts with and deacetylates tubulin and microtubules *in vivo*," *The EMBO Journal*, vol. 22, no. 5, pp. 1168–1179, 2003.

[100] F. A. A. Kwa, A. Balcerczyk, P. Licciardi, A. El-Osta, and T. C. Karagiannis, "Chromatin modifying agents—the cutting edge of anticancer therapy," *Drug Discovery Today*, vol. 16, no. 13-14, pp. 543–547, 2011.

[101] M. J. Peart, G. K. Smyth, R. K. van Laar et al., "Identification and functional significance of genes regulated by structurally different histone deacetylase inhibitors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 10, pp. 3697–3702, 2005.

[102] C. Campàs-Moya, "Romidepsin for the treatment of cutaneous t-cell lymphoma," *Drugs of Today*, vol. 45, no. 11, pp. 787–795, 2009.

[103] P. A. Marks and R. Breslow, "Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug," *Nature Biotechnology*, vol. 25, no. 1, pp. 84–90, 2007.

[104] M. Duvic and J. Vu, "Vorinostat: a new oral histone deacetylase inhibitor approved for cutaneous T-cell lymphoma," *Expert Opinion on Investigational Drugs*, vol. 16, no. 7, pp. 1111–1120, 2007.

[105] C. Grant, F. Rahman, R. Piekarz et al., "Romidepsin: a new therapy for cutaneous T-cell lymphoma and a potential

therapy for solid tumors," *Expert Review of Anticancer Therapy*, vol. 10, no. 7, pp. 997–1008, 2010.

[106] M. Yoshida, M. Kijima, M. Akita, and T. Beppu, "Potent and specific inhibition of mammalian histone deacetylase both in vivo and in vitro by trichostatin A," *The Journal of Biological Chemistry*, vol. 265, no. 28, pp. 17174–17179, 1990.

[107] P. A. Marks, "The clinical development of histone deacetylase inhibitors as targeted anticancer drugs," *Expert Opinion on Investigational Drugs*, vol. 19, no. 9, pp. 1049–1066, 2010.

[108] R. A. Blaheta and J. Cinatl, "Anti-tumor mechanisms of valproate: a novel role for an old drug," *Medicinal Research Reviews*, vol. 22, no. 5, pp. 492–511, 2002.

[109] C. U. Johannessen, "Mechanisms of action of valproate: a commentatory," *Neurochemistry International*, vol. 37, no. 2-3, pp. 103–110, 2000.

[110] G. Rosenberg, "The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?" *Cellular and Molecular Life Sciences*, vol. 64, no. 16, pp. 2090–2103, 2007.

[111] B. G. Cosío, B. Mann, K. Ito et al., "Histone acetylase and deacetylase activity in alveolar macrophages and blood mononocytes in asthma," *American Journal of Respiratory and Critical Care Medicine*, vol. 170, no. 2, pp. 141–147, 2004.

[112] K. Ito, G. Caramori, S. Lim et al., "Expression and activity of histone deacetylases in human asthmatic airways," *American Journal of Respiratory and Critical Care Medicine*, vol. 166, no. 3, pp. 392–396, 2002.

[113] M. Hew, P. Bhavsar, A. Torrego et al., "Relative corticosteroid insensitivity of peripheral blood mononuclear cells in severe asthma," *American Journal of Respiratory and Critical Care Medicine*, vol. 174, no. 2, pp. 134–141, 2006.

[114] P. J. Barnes, "How corticosteroids control inflammation: quintiles Prize Lecture 2005," *British Journal of Pharmacology*, vol. 148, no. 3, pp. 245–254, 2006.

[115] K. Ito, S. J. Getting, and C. E. Charron, "Mode of glucocorticoid actions in airway disease," *The Scientific World Journal*, vol. 6, pp. 1750–1769, 2006.

[116] K. Ito, S. Lim, G. Caramori et al., "A molecular mechanism of action of theophylline: induction of histone deacetylase activity to decrease inflammatory gene expression," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 13, pp. 8921–8926, 2002.

[117] P. J. Barnes and R. A. Pauwels, "Theophylline in the management of asthma: time for reappraisal?" *European Respiratory Journal*, vol. 7, no. 3, pp. 579–591, 1994.

[118] Z. H. Jaffar, P. Sullivan, C. Page, and J. Costello, "Low-dose theophylline modulates T-lymphocyte activation in allergen-challenged asthmatics," *European Respiratory Journal*, vol. 9, no. 3, pp. 456–462, 1996.

[119] S. Lim, K. Tomita, G. Carramori et al., "Low-dose theophylline reduces eosinophilic inflammation but not exhaled nitric oxide in mild asthma," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 2, pp. 273–276, 2001.

[120] P. Sullivan, S. Bekir, Z. Jaffar, C. Page, P. Jeffery, and J. Costello, "Anti-inflammatory effects of low-dose oral theophylline in atopic asthma," *The Lancet*, vol. 343, no. 8904, pp. 1006–1008, 1994.

[121] A. J. M. Ward, M. McKenniff, J. M. Evans, C. P. Page, and J. F. Costello, "Theophylline—an immunomodulatory role in asthma?" *American Review of Respiratory Disease*, vol. 147, no. 3, pp. 518–523, 1993.

[122] D. J. Evans, D. A. Taylor, O. Zetterstrom, K. F. Chung, B. J. O'Connor, and P. J. Barnes, "A comparison of low-dose inhaled budesonide plus theophylline and high- dose inhaled budesonide for moderate asthma," *The New England Journal of Medicine*, vol. 337, no. 20, pp. 1412–1418, 1997.

[123] A. Markham and D. Faulds, "Theophylline. A review of its potential steroid sparing effects in asthma," *Drugs*, vol. 56, no. 6, pp. 1081–1091, 1998.

[124] D. Ukena, U. Harnest, R. Sakalauskas et al., "Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma," *European Respiratory Journal*, vol. 10, no. 12, pp. 2754–2760, 1997.

[125] Y. To, K. Ito, Y. Kizawa et al., "Targeting phosphoinositide-3-kinase-δ with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease," *American Journal of Respiratory and Critical Care Medicine*, vol. 182, no. 7, pp. 897–904, 2010.

[126] N. Mercado, Y. To, K. Ito, and P. J. Barnes, "Nortriptyline reverses corticosteroid insensitivity by inhibition of phosphoinositide-3-kinase-δ," *Journal of Pharmacology and Experimental Therapeutics*, vol. 337, no. 2, pp. 465–470, 2011.

[127] J. H. Choi, S. W. Oh, M. S. Kang, H. J. Kwon, G. T. Oh, and D. Y. Kim, "Trichostatin A attenuates airway inflammation in mouse asthma model," *Clinical and Experimental Allergy*, vol. 35, no. 1, pp. 89–96, 2005.

[128] E. S. K. Assem, K. H. Peh, B. Y. C. Wan, B. J. Middleton, J. Dines, and C. M. Marson, "Effects of a selection of histone deacetylase inhibitors on mast cell activation and airway and colonic smooth muscle contraction," *International Immunopharmacology*, vol. 8, no. 13-14, pp. 1793–1801, 2008.

[129] H. Dombrowsky, M. Barrenschee, M. Kunze, and S. Uhlig, "Conserved responses to trichostatin A in rodent lungs exposed to endotoxin or stretch," *Pulmonary Pharmacology and Therapeutics*, vol. 22, no. 6, pp. 593–602, 2009.

[130] A. Banerjee, C. M. Trivedi, G. Damera et al., "Trichostatin a abrogates airway constriction, but not inflammation in 2 mouse and human asthma models," *American Journal of Respiratory Cell and Molecular Biology*, vol. 46, no. 2, pp. 132–138, 2012.

[131] M. Lomia, Z. Chapichadze, M. Pruidze, and P. Platonov, "Efficacy of monotherapy with carbamazepine and valproic acid in patients with bronchial asthma: is asthma a neurological disease?" *The Internet Journal of Neurology*, vol. 4, no. 1, 2005.

[132] B. Sayar and O. Polvan, "Epilepsy and bronchial asthma," *The Lancet*, vol. 1, no. 7550, p. 1038, 1968.

[133] H. Stevens, "Allergy and epilepsy," *Epilepsia*, vol. 6, no. 3, pp. 205–216, 1965.

[134] S. G. Royce, W. Dang, K. Ververis et al., "Protective effects of valproic acid against airway hyperresponsiveness and airway remodeling in a mouse model of allergic airways disease," *Epigenetics*, vol. 6, no. 12, pp. 1463–1470, 2011.