

The role of histone deacetylases in asthma and allergic diseases

Pankaj Bhavsar, PhD, Tehireem Ahmad, BSc, and Ian M. Adcock, PhD *London, United Kingdom*

Diverse cellular functions, including inflammatory gene expression, DNA repair, and cell proliferation, are regulated by histone acetylation. Transcriptional coactivators possess intrinsic histone acetyltransferase activity, and this activity drives inflammatory gene expression and the development of tolerance in macrophages. Eleven histone deacetylases (HDACs) act to regulate the expression of distinct subsets of inflammatory/immune genes. Other proteins, particularly transcription factors, are also acetylated and are targets for deacetylation by HDACs and sirtuins, a group of protein deacetylases. HDAC inhibitors can further enhance inflammatory gene expression. However, the acetylation/deacetylation status of nonhistone proteins can also affect the overall expression pattern of inflammatory genes. HDAC2 expression and activity is reduced in lung macrophages, biopsy specimens, and blood cells from patients with severe asthma and smoking-induced asthma, as well as in patients with chronic obstructive pulmonary disease, perhaps accounting for the enhanced inflammation and reduced steroid responsiveness seen in these patients. Targeting specific enzymes involved in this process might lead to new therapeutic agents, particularly in situations in which current anti-inflammatory therapies are suboptimal. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Histone deacetylase, gene expression, inflammation, glucocorticoids, immune tolerance

All patients with asthma have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, an infiltration of eosinophils, and an increased number of activated T_H2 cells.¹ It is believed that this specific pattern of inflammation underlies the clinical features of asthma, including intermittent wheezing, dyspnea, cough, and chest tightness.¹ It has become evident that factors other than changes in the genetic code must determine cell function. DNA methylation and chromatin modifications, known as epigenetics, are now known to be not only critical for generating cellular diversity during development but also for maintaining distinct gene expression profiles.² Since the early studies of Allfrey, it was clear that one of the key modifications

Abbreviations used

Brg1: Brahma-related gene 1
COPD: Chronic obstructive pulmonary disease
DEP: Diesel exhaust particulate matter
GR: Glucocorticoid receptor
HASM: Human airway smooth muscle
HAT: Histone acetyltransferase
HDAC: Histone deacetylase
Hsp90: Heat shock protein 90
NF: Nuclear factor
OVA: Ovalbumin
TSA: Trichostatin A

associated with inflammatory gene induction and cell proliferation is histone acetylation.² This review summarizes some of the recent work elucidating the role of histone acetylation in *in vitro* and *in vivo* models and speculates on its potential as a therapeutic target in asthma and allergy.

HISTONE ACETYLATION

One hundred forty-six base pairs of DNA are wrapped around an octamer of core histone proteins (2 molecules each of H2A, H2B, H4, and H4) to form a nucleosome, the basic structure of chromatin.² Transcriptional coactivators, such as cyclic adenosine monophosphate response element binding protein (CBP), steroid receptor coactivator 1 (SRC-1), transcription intermediary factor 2 (TIF2), glucocorticoid-interacting protein 1 (GRIP-1), and p300/CBP-associated factor have intrinsic histone acetyltransferase (HAT) activity,² and increased inflammatory/immune gene transcription is associated with an increase in histone acetylation. Changes in the acetylation status of specific lysine residues in the N-terminal tails of histones 3 and 4 form a molecular tag for the recruitment of chromatin remodeling enzymes, such as Brg1,³ which allows local chromatin unwinding and the recruitment of other transcription factors, the basal transcriptional complex, and RNA polymerase II.² This molecular mechanism is common to all genes, including those involved in differentiation, proliferation, DNA repair, and activation of cells.²

Just as acetylation of histones is associated with gene induction, removal of acetyl groups by histone deacetylases (HDACs) is generally associated with a lack of gene expression or gene silencing.² The histone code hypothesis proposes that different combinations of histone modifications, including acetylation, methylation, and phosphorylation, can result in distinct outcomes in terms of chromatin-regulated functions.² Many stimuli can activate histone acetylation acting through induction of proinflammatory transcription factors, such as activator protein 1 and

From Cell and Molecular Biology, Airways Disease Section, National Heart and Lung Institute, Imperial College London.

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Reprint requests: Ian M. Adcock, PhD, Cell and Molecular Biology, Airways Disease Section, National Heart and Lung Institute, Imperial College London, Dovehouse St, London SW3 6LY, United Kingdom. E-mail: ian.adcock@imperial.ac.uk.

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nuclear factor (NF) κ B.² Evidence for a key role of HDACs in inflammatory gene expression is provided by the fact that HDAC inhibitors, such as trichostatin A (TSA), enhance NF- κ B–driven inflammatory gene transcription in different cell types with many distinct stimuli.²

HDACs

HDACs are divided into 4 classes: class I (HDAC1, HDAC2, HDAC3, and HDAC8), class II (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10), class III (Sirt1, Sirt2, Sirt3, Sirt4, Sirt5, Sirt6, and Sirt7), and class IV (HDAC11).² The widely expressed class I HDACs are predominantly localized to the nucleus, whereas the more restricted class II HDACs shuttle between the nucleus and the cytoplasm, although this distinction is becoming blurred. There is evidence that the different HDACs target different patterns of acetylation and regulate different genes.² The different HDACs are also likely to be regulated differently. HDACs interact with corepressor molecules, which aid HDACs in gene repression and might provide specificity by selecting which genes are regulated by individual HDACs.²

HISTONE ACETYLATION AND INFLAMMATORY GENE EXPRESSION

Changes in histone acetylation are involved in the induction of numerous proinflammatory genes in human lung epithelial and smooth muscle cells.² Thus in human airway smooth muscle (HASM) cells TNF- α –stimulated CCL11 release from HASM cells is associated with NF- κ B binding and histone H4 acetylation of the native CCL11 promoter.⁴ Furthermore, IFN- γ markedly inhibited TNF- α –induced expression of the NF- κ B–sensitive genes IL-6, IL-8, and eotaxin. IFN- γ did not affect TNF- α –induced inhibitor of kappaB kinase (IKK) 2 phosphorylation or inhibitor of kappaB α (I κ B α) degradation or NF- κ B/DNA interaction⁵ but decreased TNF- α –induced p65-associated HAT activity and p65 acetylation and increased total nuclear HDAC activity. Importantly, TSA prevented the inhibitory effect of IFN- γ on TNF- α –induced gene expression. Therefore inhibition of TNF- α –induced cytokine and chemokine expression is mediated through HDAC activity, expression in HASM cells, or both.⁵

Diesel exhaust particulate matter (DEP) induces pulmonary inflammation and exacerbates asthma *in vivo* and is a potent inducer of inflammatory responses in human airway epithelial cells.⁶ DEP induces the expression of COX-2 in BEAS-2B cells at both the transcriptional and protein levels. The induction of COX-2 gene expression is associated with HAT p300–mediated induction of histone H4 acetylation at the native COX-2 promoter start site. DEP also caused the degradation of HDAC1 and selective knockdown of HDAC1 by using small interfering RNA, and overexpression of HDAC1 confirmed a role for HDAC1 in regulating DEP-induced COX-2 transcription (Fig 1).⁶

Recent evidence also suggests that HDACs maintain pre-established T_H1-like and T_H2-like immunity in human T cells.⁷ PHA activation selectively stimulates antigen-experienced CD45RO(+) T cells, eliciting recall cytokine responses. The HDAC inhibitor TSA provoked total cell hyperacetylation and led to increased IL-13 and IL-5 cytokine expression and reduced IFN- γ and CXCL10-associated recall responses. In addition, IL-2 and IL-10 production was also reduced. Interestingly, this was associated with increased expression of GATA3 and the T_H1

negative regulator sphingosine kinase 1. TSA treatment shifted T_H1/T_H2 ratios 3- to 8-fold, skewing the recall responses more toward a T_H2-like phenotype, independent of the stimulus used and highlighting the role of HDACs in the development and maintenance of T_H1/T_H2 immunity.⁷

Overall, inflammatory stimuli, including environmental agents, viral infection, and allergen exposure, can lead to enhanced inflammatory gene expression and T_H2 skewing as a result of changes in histone acetylation status. Enhanced histone acetylation is associated with inflammation and reduced acetylation with decreased inflammation.

EPIGENETIC REGULATION OF TOLERANCE

Repeated LPS exposure results in a dampened response, and initially this was thought to occur with all genes.⁸ Recent results in murine macrophages indicate that these cells are tolerized to the proinflammatory effects of repeated LPS challenge but maintain sensitivity to antimicrobial actions, thereby preventing systemic inflammation and septic shock.⁸ Tolerant (proinflammatory) and nontolerant (antimicrobial) genes have distinct patterns of histone acetylation and methylation within their promoters that remains after the initial LPS challenge, and this is maintained on repeated LPS stimulation. Thus antibacterial genes have increased levels of histone H4 acetylation and H3 K4 trimethylation, both markers of gene activation, which act to prime these genes in response to subsequent LPS stimulation, resulting in similar or even greater levels of gene expression. In contrast, anti-inflammatory genes are no longer induced in response to LPS, do not obtain these epigenetic marks, cannot recruit RNA polymerase II, and fail to respond to TSA.⁸ Similar processes might occur *in vivo*, where prolonged inhaled allergen exposure can lead to persistent tolerance in murine models of asthma,⁸ although the precise mechanism for this effect remains to be elucidated.

NONHISTONE SUBSTRATES OF HDACs

The simplistic view of HDAC inhibitors as only targeting acetylated histones to modulate gene expression cannot be totally correct because studies show that equal numbers of genes are suppressed by these agents as are enhanced.² An expanding list of nonhistone proteins have been identified as substrates for HDACs, including transcription factors and cytoplasmic signaling and structural proteins.² Consequently, the stability, localization, protein dimerization, and protein–protein interaction of these acetylated nonhistone proteins can be altered. Although in many cases the HATs involved in acetylating these nonhistone proteins are known, often the specific protein deacetylases that regulate the reverse process remain unclear. As a result, treatment of cells or animals with nonselective HDAC inhibitors can often result in paradoxical changes in mediator expression, cell function, or both (Fig 1).

HDACs AND GLUCOCORTICOID FUNCTION

Glucocorticoids are very effective in suppressing inflammatory gene expression in most chronic inflammatory diseases, either alone or in concert with other drugs. Thus in HASM cells the combination of salmeterol, fluticasone, or both further enhanced the ability of the peroxisome proliferator–activated receptor γ

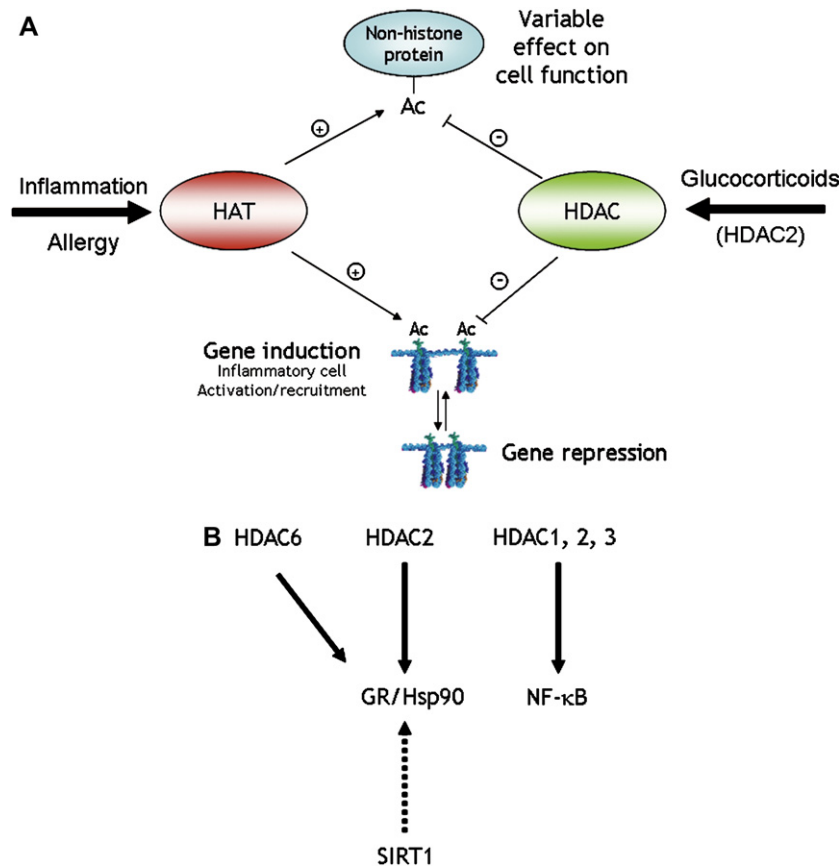


FIG 1. **A**, Allergen exposure or inflammatory stimuli lead to histone acetylation (histones shown protruding through pale blue DNA loops) by HATs and gene induction/cell activation. This process is reversed by specific HDACs, which mediate the actions of glucocorticoids. Nonhistone proteins are also targets for lysine acetylation and deacetylation by HATs and HDACs, with the effect on cell function depending on stimulus, readout, and cell type. **B**, Selective HDACs and sirtuins (*SIRT1*) can target acetylated proteins' GR functions either directly or indirectly through Hsp90 or by blocking HAT/NF-κB interactions (see main text for details).

agonists 15d-PGJ2 and troglitazone to suppress TNF- α -induced CCL11 transcription.⁹ Peroxisome proliferator-activated receptor γ and glucocorticoid receptor (GR) formed a complex at the native CCL11 promoter and suppressed histone acetylation and NF- κ B p65 DNA binding⁹ events shown previously to involve HDACs.⁴

Nonselective HDAC inhibitors are able to prevent GR repression of inflammatory genes, implicating a role for HDACs in GR function.² In lung epithelial cells we demonstrated that HDAC2 was important in GR-mediated GM-CSF and CXCL8 gene repression¹⁰ and did not affect GR nuclear translocation, DNA binding, or transactivation.¹⁰ GR is rapidly acetylated on ligand binding at amino acids 492 to 495, and only the deacetylated form of GR is able to associate with p65. Thus recruitment of HDAC2 by acetylated GRs leads to deacetylation of the GR, interaction with the p65 NF- κ B-activated complex, reversal of local histone acetylation, and subsequent suppression of inflammatory gene expression. This mechanism provides a molecular explanation for the ability of the GR to distinguish between recruitment of coactivator and corepressor proteins and the subsequent ability to transactivate or repress gene transcription.¹⁰

In addition, other HDACs have also been implicated in GR actions (Fig 1). Thus dexamethasone-induced repression of T_H2

cytokines required the GR to bring HDAC1 to GATA3 located on the promoters of T_H2 genes.¹¹ Heat shock protein 90 (Hsp90) and its accessory cochaperones ensure the correct structure of client proteins, including GRs.¹² The function of Hsp90 is regulated by reversible acetylation under the control of HDAC6. Inactivation of HDAC6 leads to Hsp90 hyperacetylation, its dissociation from the essential cochaperone p23, and a loss of chaperone activity.^{2,12} Changes in Hsp90 acetylation alters the dynamic GR-hsp90 heterocomplex assembly/disassembly and results in a reduction in GR ligand binding and nuclear translocation and a 100-fold reduction in glucocorticoid responsiveness.^{2,12} HDAC6 also has tubulin deacetylase activity and has been implicated in lymphocyte polarity, motility, and transmigration. However, it is clear that the action of HDAC6 on T-cell chemotaxis was probably dependent on a structural role rather than on its enzymic activity against acetylated tubulin.¹²

Recently, sirtuin 1 has been reported to act as a major repressor of dexamethasone-induced uncoupling protein 3 expression through deacetylation of the uncoupling protein 3 promoter. This effect is indirect through impairing the association of p300 with GR.¹³

In summary, the anti-inflammatory actions of glucocorticoids require the presence or activation of a number of distinct HDACs that each target different aspects of glucocorticoid actions.

HDACs IN ALLERGIC DISEASE

HDAC/HAT activities might also be involved in glucocorticoid insensitivity in patients with severe steroid-insensitive asthma.² Thus the suppression of LPS-induced cytokine release (monocyte chemoattractant protein 1, macrophage inflammatory protein 1 α , RANTES, TNF- α , IL-1 β , IL-8, IFN- γ , IL-6, IL-10, and GM-CSF) by dexamethasone from PBMCs of subjects with severe steroid-insensitive asthma was reduced compared with that seen in subjects with mild steroid-sensitive asthma.¹⁴ Nuclear HDAC and HAT activities were reduced in patients with severe steroid-insensitive asthma compared with patients with mild steroid-sensitive asthma, and importantly, the reduced HDAC activity correlated directly with steroid insensitivity. In contrast, the reduction in HAT activity related to corticosteroid use rather than asthma severity.¹⁴ However, reduced HDAC2 expression has not been seen in all patients with severe steroid-insensitive asthma, perhaps reflecting the heterogeneity of the severe asthma phenotype.¹⁵

Recent data from Kelly et al¹⁶ reconcile these differences to some extent. GR β usually acts as a dominant-negative isoform of GR α . However, using transient transfections, Kelly et al¹⁶ demonstrated that GR β acts as a transcriptional repressor of T_H2 genes and mediates its function through the recruitment of HDAC complexes. The authors conclude that GR β might have a dominant-negative role on GR transactivation rather than repression.¹⁶

HDAC2 expression and activity are also decreased in asthmatic subjects, smokers, smoking asthmatic subjects,² and patients with chronic obstructive pulmonary disease (COPD).^{2,10} all of whom are known to be insensitive to the anti-inflammatory effects of glucocorticoids.² In addition, there is a negative correlation between the repressive effect of dexamethasone on cytokine production and total HDAC activity in alveolar macrophages from smokers and nonsmokers.² Overexpression of HDAC2, but not HDAC1, in primary macrophages from patients with COPD restored dexamethasone efficacy toward suppressing LPS-induced GM-CSF release to levels seen in cells from healthy control subjects.¹⁰ Furthermore, knockdown of HDAC2 in sputum macrophages from healthy nonsmokers by RNA interference reduced the inhibitory effect of dexamethasone.¹⁰

In support of a major role for HDAC2 in GR function, Bilodeau et al³ have reported that GR-mediated repression of proopiomelanocortin requires the adenosine triphosphatase-dependent chromatin remodeling enzyme Brg1 and the recruitment of HDAC2 to enable deacetylation of the proopiomelanocortin promoter. A lack of Brg1 expression, HDAC2 expression, or both was reported in 50% of glucocorticoid-resistant human and dog corticotroph adenomas, which are a hallmark of Cushing's disease.³

EFFECT OF HDAT/HDAC MODULATORS *IN VIVO*

Selective HAT inhibitors have only recently been developed,¹⁷ although suppressing the expression of many genes also induced the expression of several others. This might again reflect the combined actions of acetylation on both histones and nonhistone proteins. As stated earlier, HDAC inhibitors have both positive and negative effects *in vitro* and *ex vivo* depending on the cell type and stimulus used.² For example, TSA represses IL-1 β and LPS plus IFN- γ -induced nitric oxide synthase 2 expression in murine mesangial and macrophage-like cells¹⁸ but increases LPS-stimulated nitric oxide synthase 2 expression in murine N9 and primary rat microglial cells.¹⁸ Furthermore, respiratory syncytial virus-induced CXCL8 expression attenuates after 24 hours in

A549 cells, despite ongoing viral replication through recruitment of HDAC1 to the CXCL8 promoter, and this effect is lost in the presence of TSA, suggesting that HDAC inhibitors might enhance virus-induced inflammation.¹⁸ The differential effects of nonselective HDAC inhibitors on distinct gene targets is highlighted by the fact that TSA further enhanced LPS-stimulated IL-8 but repressed IL-12 p40 expression in BEAS-2B cells.¹⁸

In contrast, in an ovalbumin (OVA)-challenged murine model of asthma, prophylactic TSA (1 mg/kg) suppressed OVA-induced airway inflammation and airway hyperresponsiveness.¹⁹ TSA was given to animals every other day for 3 weeks in the 21-day acute OVA model and caused an approximately 30% to 40% reduction in bronchoalveolar lavage eosinophils and lymphocytes and a 24% reduction in infiltrating mucosal inflammatory cells. Bronchoalveolar lavage IL-4 and IL-5 levels were also significantly reduced in this model. Importantly, no adverse effects were reported. This article suggests that TSA or an HDAC inhibitor with greater bioavailability and longer-lasting effects might have the potential to act as anti-inflammatory agents in the treatment of allergic airways disease. However, which is the key HDAC targeted by TSA in this model and whether it targets a histone or nonhistone protein remain to be elucidated.¹⁹ This might reflect a general effect on cell death seen with nonselective HDAC inhibitors.¹⁸ However, treatment with nonselective HDAC inhibitors is detrimental in some animal models of inflammation.¹⁸

Conversely, because HDAC2 expression and activity are reduced in patients with asthma, smokers, and smoking asthmatic patients, as well as in patients with COPD, increase of HDAC2 activity by drugs, such as theophylline, might be beneficial in these diseases, particularly in combination with corticosteroids.² Studies are currently ongoing to determine whether the beneficial effect of combined steroid/theophylline treatment observed in these patients relates to the effects on HDAC activity.¹

CLINICAL IMPLICATIONS

In the context of inflammatory gene expression, it is likely that specific upregulation of HDAC2 will restore glucocorticoid responsiveness. Drugs, such as theophylline and selective phosphoinositide kinase-3 inhibitors, which increase HDAC2 activity suppressed by oxidative stress, might act in concert to restore steroid sensitivity in patients with severe asthma, smokers with asthma, and patients with COPD. The expression and activity of individual HDAC enzymes in primary cells from patients with distinct allergic diseases might suggest the need to target other HDAC enzymes. Currently, nonselective HDAC inhibitors are being developed for the treatment of cancer because of their ability to induce cell apoptosis. However, the nonselective nature of these agents might account for their limited clinical effectiveness and potential to cause metastasis. This is akin to using nonselective kinase inhibitors, which also induce cell death, whereas selective inhibitors can be potentially beneficial. More data are required to determine whether selective HDAC inhibitors might have the ability to act on specific cells, such as eosinophils, T cells, or macrophages, thereby increasing their potential for use in allergic diseases.

SUMMARY

Reversible histone acetylation regulates inflammatory gene expression and also plays a role in diverse functions, such as DNA repair and cell proliferation, in several diseases. However, the

effect of nonselective HDAC inhibitors on gene expression is often confounded by their action on nonhistone proteins, particularly transcription factors and chaperone proteins. Furthermore, it is evident that selective HDACs are required to control specific gene panels after different stimuli. Additional work is required to examine the expression and activity of individual HDACs in asthma and other allergic diseases to compare with the reduced expression of HDAC2 seen in some studies. The development of selective HDAC inhibitors, activators, or both might reveal the role of individual HDACs in the regulation of inflammation and the immune response in cell and animal models and lead to new therapeutic agents, particularly in situations in which current anti-inflammatory therapies are suboptimal.

The literature in this area is extensive, and many important studies were omitted because of space constraints, for which we apologize. We would like to thank other members of the Cell and Molecular Biology Group for their helpful discussions. The support of Asthma UK, the Medical Research Council (UK), the Wellcome Trust, AstraZeneca, GlaxoSmithKline, and Sirtris is acknowledged for supporting ongoing research in our laboratories.

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