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REVIEW

From allergens to epigenetics: how histone acetylation shapes immune gene expression in allergic diseases

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ABSTRACT

Allergic diseases are a significant global health concern. These disorders result from abnormal immune responses to environmental allergens, influenced by genetic, environmental, and epigenetic factors. Among these, histone acetylation has emerged as a key epigenetic mechanism influencing immune gene expression. Histone acetylation modulates chromatin structure and gene transcription, linking environmental exposures to immune responses. In this review, we explore how histone acetylation mechanisms regulate immune gene activation and contribute to the pathophysiology of allergic diseases and detail the role of histone acetylation in asthma, food allergy, atopic dermatitis, and other allergic conditions. Finally, we discuss therapeutic strategies targeting histone acetylation, highlighting their potential to mitigate allergic inflammation and improve patient outcomes. Understanding histone acetylation's role in allergic diseases provides a basis for developing epigenetic therapies, offering promising new approaches to managing these conditions.

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1. Introduction

Allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis, have become significant public health concerns globally, with rising prevalence attributed to genetic, environmental, and epigenetic factors [1]. At the heart of allergic pathophysiology lies the dysregulation of immune responses, particularly the skewing toward type 2 helper T-cell (Th2) dominance, which promotes the overproduction of immunoglobulin E (IgE) and the release of pro-inflammatory cytokines [2]. While allergens are well-established as triggers of these immune cascades, recent advancements in molecular biology have highlighted the critical role of epigenetic mechanisms, such as histone modifications, in shaping immune gene expression.

Histone acetylation, a reversible epigenetic modification, has emerged as a key regulator of chromatin accessibility and transcriptional activity in immune cells [3]. By adding acetyl groups to lysine residues on histones, histone acetyltransferases (HATs) reduce chromatin compaction, facilitating the recruitment of transcriptional machinery to immune-related genes [4]. Conversely, histone deacetylases (HDACs) remove these acetyl groups, repressing gene expression. This dynamic interplay between HATs and HDACs modulates the expression of cytokines, chemokines, and receptors critical for allergic inflammation [5].

Emerging evidence suggests that environmental factors, such as pollutants and dietary components, influence histone acetylation patterns, linking epigenetic regulation to allergen-induced immune responses [6]. Furthermore, aberrant histone acetylation has been implicated in the persistence of Th2 polarization and the suppression of regulatory T-cell (Treg) function, exacerbating allergic diseases [7]. This review explores the role of histone acetylation in allergic diseases, emphasizing its potential as a therapeutic target for modulating immune responses and improving patient outcomes.

2. The immune system responds to allergens

Allergic diseases are triggered by environmental substances known as allergens. Common allergens include environmental sources (e.g., pollen and dust mites), food allergens (e.g., peanuts, shellfish, and milk) and drug allergens. These allergens can originate from various sources and enter the body through inhalation, ingestion or skin contact. These allergens can trigger allergies like asthma, food allergies and atopic dermatitis, most of which lead to type 2 immune response in the human body, and type I hypersensitivity is a manifestation of type 2 immune response.

Allergic responses progress through two distinct phases: the sensitization phase and the elicitation phase. During sensitization, antigen-presenting cells (APCs), such as dendritic cells, capture allergens and present them to naïve T cells in lymphoid tissues. In predisposed individuals, this interaction induces the differentiation of Th2 cells, a hallmark of allergic hypersensitivity. The type 2 immune response involves a network of Th2 cells, IgE-producing B cells, group 2 innate lymphoid cells (ILC2s), basophils, mast cells, and their associated cytokines, including interleukin-4 (IL-4), IL-5, IL-9, and IL-13. These cytokines stimulate B cells to produce allergen-specific IgE antibodies [8,9]. IgE binds to high-affinity IgE

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Article highlights

- **Histone acetylation plays a pivotal role in regulating the transcription of genes associated with allergic diseases.**
- **Histone acetylation mechanism**
- Acetylation leads to a more open chromatin structure by neutralizing the positive charge of the lysine ε-amino group which enhances transcription factor binding to DNA.
- Acetylated lysine residues serve as docking sites for specific epigenetic readers to the transcript.
- **Epigenetic control of immune genes links acetylation to gene activation in allergic diseases via cytokines and Tregs**
- Histone acetylation regulates the expression of cytokines which are involved in allergic diseases like IL-4, IL-13 and IFN-γ.
- Histone acetylation regulates the Tregs differentiation and function that maintain immune tolerance and prevent excessive immune responses.
- **Explain the role of histone acetylation in asthma, food allergy, atopic dermatitis and other allergic diseases**
- **Histone acetylation as therapeutic targets in allergic disease**
- Therapeutic strategies targeting histone acetylation aim to restore immune balance by modulating the activity of HATs and HDACs.
- Defined compounds such as trichostatin A, I-BET762, sodium butyrate, and dietary interventions like curcumin, L-Sulforaphane may help correct abnormal gene expression and alleviate allergic symptoms.

receptors (FcεRI) on the surface of mast cells and basophils, "priming" these cells for subsequent allergen encounters. Upon re-exposure to the allergen, typically at barrier surfaces such as the skin or mucosa, the allergen cross-links IgE molecules bound to FcεRI on mast cells. This cross-linking induces mast cell degranulation, releasing preformed inflammatory mediators, such as histamine, tryptase, and leukotrienes, within seconds. Additionally, mast cells rapidly synthesize and release newly formed mediators. These mediators drive the acute symptoms of allergic reactions, including itching, swelling, flushing, nausea, vomiting, diarrhea, pain, wheezing, cough, sneezing, rhinorrhea, congestion, and syncope [10–13].

3. Histone acetylation

Epigenetics has grown rapidly over the past few decades, but researchers often define the term differently. For example, the US National Institutes of Health (2009) described epigenetics as both heritable changes in gene activity and expression (in the progeny of cells or individuals) and stable, long-term alterations in the transcriptional potential of a cell that are not necessarily heritable [14]. Deans and her colleague defined epigenetics as "the study of phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression that are not dependent on changes to DNA sequence" [15]. Despite these varying definitions, most agree that epigenetic regulation mainly involves four mechanisms: histone modifications, DNA methylation, chromatin remodeling, and non-coding RNA. In addition, Nicoglou *et al*. also suggested that transcription factors may play a role in epigenetic regulation [16]. These epigenetic mechanisms add another layer of control over gene expression, allowing cells to adapt to changing environments. This flexibility helps organisms respond quickly to external stimuli. Epigenetic changes can also affect physical traits and are involved in the development and progression of many diseases, including inflammation, cancer, cardiovascular and kidney diseases, metabolic disorders, and neuropsychiatric conditions [17]. The epigenetic changes are heritable. Environmental exposures in progenitors, such as diet, can induce epigenetic changes that are heritable through the germline and persist across cell divisions. A well-known example is the Dutch Hunger Winter cohort: children of fathers who were prenatally exposed to famine showed a higher risk of being overweight or obese compared to children of unexposed fathers and both exposed and unexposed mothers [18]. Recent studies in humans and mice have shown that epigenetic modifications in the paternal germline, such as changes in methylation at histone H3 lysine 4 (H3K4) and lysine 27 (H3K27), can affect chromatin structure and gene regulation. These alterations influence promoter regions of genes critical for embryonic development, further supporting the transgenerational impact of epigenetic regulation [19–21].

Among epigenetic modifications, histone modifications remain one of the most extensively studied modifications, particularly histone acetylation. Histone acetylation supports accessible and transcriptionally active chromatin, promoting critical genome regulation processes such as replication, repair, and transcription [22]. In general, the active state of genes correlates with increased levels of acetylated histones, and lysine acetylation on histones has two major consequences. First, acetylation leads to a more open chromatin structure by neutralizing the positive charge of the lysine ε-amino group. This charge neutralization disrupts electrostatic interactions between lysine residues and other macromolecules, such as DNA and proteins, thereby enhancing transcription factor binding to DNA [23]. Second, acetylated lysine residues serve as docking sites for specific epigenetic readers. These readers recognize acetylated histones and recruit transcriptional co-regulators and chromatin remodeling factors [24]. The most well-characterized families of epigenetic readers include proteins with bromodomains (BRDs), which recognize acetylated histones, and chromodomains [25]. These readers bind acetylated histones at promoter and enhancer regions, recruiting transcription factors, cofactors, and RNA polymerase II to regulate transcription and other DNA-templated processes in a highly context-dependent manner [26–29]. Histone acetylation is dynamically regulated by HATs, which act as "epigenetic writers" by acetylating lysine residues, and HDACs, which function as "epigenetic erasers" by removing these modifications (Figure 1). For example, A cryogenic electron microscopy study has provided insights into the molecular mechanism of p300/CBP, a key histone acetyltransferase. These studies revealed that p300/CBP propagates acetylation within H3-H4 tetramers and transfers it to H2A-H2B dimers, destabilizing nucleosomes and activating gene transcription [30]. Additionally, histone acetylation has been shown to facilitate transcription by recruiting bromodomain-containing proteins, such as BRD4 and TFIID subunit 1, which play pivotal roles in transcriptional initiation [31].

These processes are catalyzed by HATs and HDACs, respectively [32,33]. HDACs are grouped into four different classes: (1) class-I (HDAC1, HDAC2, HDAC3, HDAC8); (2) class-IIa

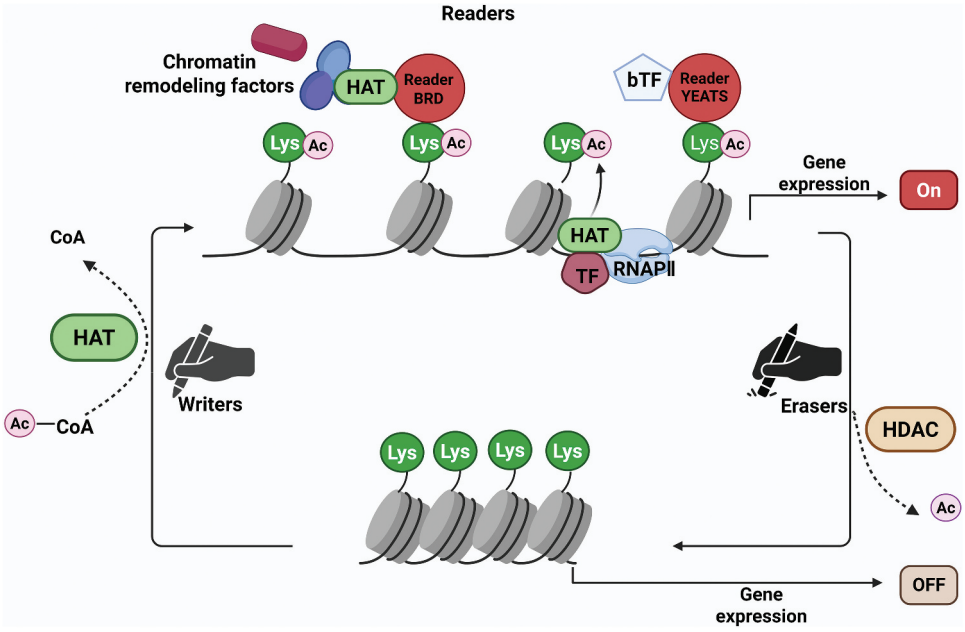

Figure 1. The mechanism of gene expression by reversible lysine acetylation process. Acetylation of lysine (lys) residues on substrate histone protein is carried out by histone acetyltransferases (HAT). These enzymes are the so-called "writers" able to add acetyl groups mostly on histone tails. The acetylation reaction converts acetyl coenzyme a (ac-CoA) into coenzyme a (CoA). The active state of genes correlates with increased levels of acetylated histones and has two major consequences. First, acetylation leads to a more open chromatin structure by neutralizing the positive charge of the lysine ε-amino group and thus allowing the recruitment of gene-specific transcription factors(tfs) to promote transcription. Second, acetylated lysine residues serve as docking sites for specific epigenetic readers like BRDs, these readers might recruit the basal TFs (bTfs) or chromatin remodeling complexes to activate gene expression. The process is reversible due to the action of histone deacetylases (HDAC), the "erasers" that remove the acetyl group from histone tails.

(HDAC4, HDAC5, HDAC7, HDAC9) and class-IIb (HDAC6, HDAC10); (3) class-III (the NAD-dependent protein deacetylase sirtuin 1–7 (SIRT1–7) and (4) class-IV (HDAC11) [34,35]. And HATs can be grouped into three main families: (1) the general control non-derepressible5 (Gcn5)/PCAF family; (2) the p300/CBP family; (3) the MYST family are involved in the control of transcription and cell growth and survival [35].

4. Epigenetic control of immune genes links acetylation to gene activation in allergic diseases via cytokines and Tregs

Histone acetylation plays a pivotal role in regulating the transcription of genes associated with allergic diseases. Acetylation at the promoter regions of allergy-related immune genes has been identified as a significant risk factor for sensitization to food or inhaled allergens [36]. Su *et al*. demonstrated that HAT activity was increased in nuclear lysates of PBMCs from children with allergic asthma, whereas HDAC activity was reduced compared to atopic non-asthmatic controls. Moreover, the extent of histone acetylation positively correlated with the severity of bronchial hyperresponsiveness [37]. Allergen-specific memory T cells from the spleens of asthma mouse models had histone hyperacetylation caused by reduced HDAC7, HDAC9, and HDAC10 expression. They contribute to eosinophilic airway inflammation when these cells are adoptively transferred into naïve mice's lungs [38]. HAT activity is essential for the transcription of numerous immune molecules. For example, Tat-interactive protein 60 (Tip60), a key HAT, facilitates chromatin remodeling and IgE/IgG1 expression in B cells. Inhibition of Tip60 significantly attenuated allergic inflammation [39,40]. Conversely, mice with HDAC1-deficient T cells exhibited heightened Th2-type responses, including increased eosinophilic recruitment, mucus hypersecretion, lung inflammation, and enhanced airway resistance [41].

4.1. Histone acetylation regulates cytokines which are involved in allergic diseases

Cytokines are critical mediators of immune responses, and their expression is tightly regulated by histone acetylation. Th2 differentiation is accompanied by dynamic alterations in histone acetylation at cytokine gene loci. IL-4 and IL-13 are hallmarks of Th2 cytokines that orchestrate many allergic processes, including IgE production, eosinophil recruitment, and mucus hypersecretion. In contrast, IFN-γ, a critical Th1 cytokine that counterbalances Th2 responses, shows reduced expression in allergic diseases. Fields *et al* [42]. reported profound increases in histone acetylation at both IFN-γ and IL-4 loci during Th1/2 differentiation and found that these changes were locus and lineage-specific. Increased H3 acetylation at the IL-4 locus in Th2 cells was associated with elevated IL-4 expression, whereas reduced histone acetylation at the IFN-γ locus led to diminished expression of IFN-γ in Th2 cells [43]. Overexpression of the HDAC1, HDAC2 and HDAC3 inhibited transcription driven by the IL-4 promoter [44]. Whereas, the binding of the HAT p300/CBP to the CNS1 region further enhances histone acetylation and IL-4 expression [45].

STAT6 is a key transcription factor in Th2-mediated immune responses. When IL-4 binds to its receptor, it activates JAK2, which then phosphorylates STAT6. This phosphorylation

allows STAT6 to promote the transcription of its target genes, including those encoding inflammatory mediators and cytokines. Tripartite motif-containing 24 (TRIM24) is a CBP-associated E3 ubiquitin ligase. TRIM24 promotes the ubiquitination of CBP at lysine 119 and strengthens the interaction between CBP and STAT6. This interaction leads to STAT6 acetylation at lysine 383, and this modification reduces its ability to bind DNA, which means it suppresses its transcriptional activity. Liyan and colleagues found reduced TRIM24 expression in PBMCs and $CD4^+$ T cells from patients with allergic rhinitis. This reduction in TRIM24 was associated with lower acetylation at lysine 383 of STAT6, which enhanced STAT6 activity. As a result, transcription of STAT6 target genes, such as *GATA3*, was increased. Together, these findings suggest that TRIM24 regulates STAT6-mediated GATA3 expression by modulating STAT6 acetylation. This mechanism promotes IL-4 production, Th2 cell differentiation, and more severe allergic rhinitis symptoms [46,47].

Similarly, PBMCs from patients with Henoch-Schönlein purpura exhibited marked increases in histone H3 acetylation and H3 lysine 4 trimethylation at the IL-4 loci. This was accompanied by elevated expression of IL-4, IL-6, IL-13, GATA-3, TIM-1, and CXCL4 [48]. IL-13 treatment has been shown to induce global histone H3 acetylation and promote CBP-STAT6 complex formation. This increases histone acetylation at the eotaxin-3 promoter which increases transcription of IL-13-induced chemokines such as eotaxin-3 [49]. Conversely, activation of STAT4 allows for histone acetylation to accumulate at the conserved regions of the IFN-γ promoter, facilitating STAT4 transcription factor binding, thereby committing naïve T cells toward a Th1 lineage while suppressing Th2 differentiation [50].

4.2. Histone acetylation regulates Tregs which are involved in allergic diseases

Tregs are a subset of $CD4^+$ T cells that maintain immune tolerance and prevent excessive immune responses. They play a critical role in suppressing inflammation and immune hyperreactivity associated with allergic disorders. Importantly, the suppressive function of Tregs is regulated epigenetically. Harb *et al*. observed that in the *FoxP3* locus of Tregs, histone H3 acetylation was significantly increased, with a trend toward elevated H4 acetylation at the *IL-13* locus, in children with allergic asthma compared to healthy controls [51]. Treatment with HDAC inhibitors increased FoxP3 expression, enhanced Treg-cell numbers, and improved the suppressive function of Tregs [52]. Genetic deletion of HDAC6 or HDAC9 increases the expression of FoxP3. In addition, both HDAC6 and HDAC9 deacetylate other proteins directly or indirectly involved in FoxP3 expression and Treg-cell function, such as HSP90 and STAT5 [53–55]. Consistent with this, HDAC9 activity in T cells restricts Treg-cell numbers and function by suppressing the conversion of effector T cells (Teffs) into Tregs [53]. Additionally, the FoxP3 protein itself is directly and functionally regulated by HDAC-mediated deacetylation. Treatment of Tregs with either Trichostatin A (TSA) or nicotinamide, a sirtuin inhibitor, induced FoxP3 acetylation and increased FoxP3 protein expression [56,57]. Notably, SIRT1 uniquely deacetylates FoxP3 at specific lysine residues (K31, K262, K267), acting as a negative regulator of Treg function. SIRT1 inhibitors have been shown to restore FoxP3 acetylation and strengthen Treg suppressive activity [25,57,58]. In IgE-mediated cow's milk allergy models, decreased H3/H4 acetylation at Treg loci coincided with lower Treg and Th17%s, reflecting an epigenetic state favoring lower gene expression [59].

5. Role of histone acetylation in specific allergic diseases

5.1. Histone acetylation in asthma

Asthma is a common chronic respiratory disease characterized by inflammation, airway hyperresponsiveness, and airway restriction, resulting in breathing difficulties [60]. It is one of the primary allergic diseases affecting millions of people worldwide, and about 1000 people die from it every day [61]. Recent research shows the critical role of epigenetic modifications, particularly histone acetylation, in the progression of asthma [62–68].

Several studies have shown that various HATs such as P300 and KAT8 promote different asthma symptoms [69–71]. In particular, it was shown that activation of the orosomucoid 1-like protein 3 (*ORMDL3*) gene, which is closely associated with asthma progression, switches on the NLRP3 inflammasome and further facilitates the inflammatory response of asthma in a murine model [69,70,72]. The effective use of C646, a selective inhibitor of P300, in alleviating asthma was also shown in the same study [69,72]. Similarly, a study conducted by Zhou *et al*. investigated the impact of $PM_{2.5}$, a highly studied environmental risk factor for asthma, on disease progression. The findings show that P300 contributes to asthma by hyperacetylating H3K9 and H3K14 within the promoter region of IL-4 in $CD4^+$ T cells. This modification enhances IL-4 production, which plays a crucial role in asthma progression by activating plasma cells [73,74]. Additionally, KAT8, a HAT, acetylates the IL-33 promoter, enhancing cytokine stability and contributing to asthma progression. Inhibition of HAT activity with MG149 alleviates allergic airway inflammation [71,75].

In contrast to HATs, HDACs play critical roles in regulating inflammation and remodeling in asthma by histone deacetylation. In particular, HDAC1 [76], HDAC2 [77–79], HDAC8 [80,81] and several SIRTs [82–85] have emerged as key regulators in asthma progression. HDACs influence cytokine production, mucus secretion, airway fibrosis, and immune cell polarization [76–81,83–85]. HDAC1 suppresses IL-6, a major pro-inflammatory cytokine linked to asthma. The protein C-ets-2 recruits HDAC1 to the IL-6 promoter following TLR activation, enhancing histone deacetylation and epigenetically suppressing IL-6 production. This mechanism highlights HDAC1 as a potential target for controlling inflammation in asthma [76].

Similarly, HDAC2 plays a massive role in asthma progression. HDAC2 is recruited by glucocorticosteroids, an asthma drug, to deacetylate activated inflammatory genes such as tumor necrosisfactor-α (*TNF-α*), *IL-8* and granulocyte-macrophage colony stimulating factor (*GM-CSF*), thereby reducing inflammation and enhancing the efficacy of corticosteroid therapy [77]. Additionally, HDAC2 regulates mucus production

by interacting with the TGFβ-activated Smad3 complex. This complex suppresses MUC5AC expression, a gene involved in mucus production, by promoting NF-κB deacetylation at K310, thereby reducing its transcription [78]. Moreover, HDAC2 suppresses connective tissue growth factor (CTGF) expression in lung fibroblasts. HDCA2 deacetylates the promoter region of *CTGF* gene. Since *CTGF* plays a critical role in fibrosis by involving in extracellular matrix production and tissue remodeling, its upregulation contributes to the progression of asthma [86]. The observed reduction in HDAC2 in asthma patients further highlights its potential as a target for mitigating fibrotic remodeling in asthma [79]. In the same way, HDAC8 interacts with Galectin 3 to promote M2 macrophage polarization, contributing to asthma progression. Inhibition of HDAC8 by PCI-34051 reduces M2 macrophage activity, thereby alleviating airway hyperresponsiveness and asthma [80,81].

On a different note, SIRT6, an HDAC, has shown dual function in asthma progression. On one hand, SIRT6 plays a protective role in airway remodeling associated with asthma, where overexpression of SIRT6 suppressed TGF-β1-induced phosphorylation of Smad3, reducing histone H3K9 acetylation, and inhibiting the transcription of the c-Jun promoter. The later was linked to epithelial-mesenchymal transition and airway remodeling [83]. Conversely, SIRT6 contributed to asthma progression by promoting airway inflammation via IL-17A production. It was found that SIRT6 facilitated IL-17A production by interacting with transcription factor RORγt in a mouse model of allergic inflammation. Using SIRT6 inhibitors reduced IL-17A expression and alleviated asthma symptoms, indicating the potential of inhibitors as a therapeutic target for asthma [84].

In addition to the above, several studies have shown various differential histone acetylation sites specifically involved in asthma progression. Movassagh *et al*. discovered that $PM_{2.5}$ induces trained immunity in monocytes, which is characterized by the release of proinflammatory mediators such as TNF, IL-8, and IL-6 upon secondary stimulation with LPS or house dust mite *in vitro*. Epigenetic regulation of this trained immunity is through enhanced H3K27ac in monocytes. This type of proinflammatory monocyte was observed in children with asthma compared to healthy children. In children with asthma, exposure to $PM_{2.5}$ appears to prime monocytes toward a more proinflammatory state. This suggests that trained immunity after $PM_{2.5}$ exposure could be exacerbating the already increased inflammation typically seen in asthma [87]. Another study by Ren *et al*. also showed 15 differentially modified acetylation sites including 13 upregulated namely, H3K9ac, H3K14ac, H3K18ac, H3K23ac, H3K27ac, H3K36ac, H2B1KK120ac, H2B2BK20ac, H2BK16ac, H2BK20ac, H2BK108ac, H2BK116ac, and H2BK120ac and 2 downregulated sites H2BK5ac and H2BK11ac were identified linked to asthma pathogenesis and progression [88]. Similarly, a small pilot study on the epigenome of asthma and healthy controls showed H3K27ac enrichment in genes associated with epithelial-mesenchymal transition [89]. In another study on the Ovalbumin (OVA)-induced allergic airway inflammation mouse model, proteome and acetylproteome analyses identified significant alterations in 154 proteins and 68 acetylation sites by asthma. Sequence motif preference analysis shows a novel lysine acetylation motif, -KAXXK-, which can be a key regulatory unit of histone acetylation. The progression of asthma could be modulated by histone acetylation via this KAXXK motif [90]. A summary of the key histone acetylation mechanisms involved in asthma is illustrated in Figure 2.

5.2. Histone acetylation in food allergy

Food allergy is defined as an adverse health issue that emerges upon a specific immune response, which is consistently triggered by a particular food [91]. Histone acetylation is influenced by diet and impacts immune responses that influence food allergy. It has been reported as one of the main histone modifications driven by food.

Exposure to cow's milk protein, especially whey protein, caused immediate histone modifications in key T cell and B cell genes. The reduction of acetylation can downregulate the *tbx21* gene, the main transcription factor for Th1 cells, leading to a reduction in numbers and activation of these cells. In the same study, histone acetylation at the STAT6 locus in B cells was increased and this was associated with higher proallergic responses and corresponded to the presence of whey-specific IgE [59]. Moreover, administrating Short Chain Fatty acids (SCFAs) to both humans and rodents, correlated with a reduction of global HDAC activity, increased the global histone acetylation, and eventually reduced the expression of IL-6, IL-8 and TNF-α. On the other hand, SCFAs can positively regulate the tolerogenic activity in the mesenteric lymph node dendritic cells, increase the number of Tregs in the intestine and increase the production of IgA in the intestinal lumen [92–94]. Furthermore, SCFAs administration in mice increased S6 kinase acetylation, which allowed for the activation of the mTOR pathway in CD4 T cells. mTOR is crucial for T cell differentiation, and the expression of IL-10, IFN-γ and IL-17 [94]. Furthermore, butyrate in mice and rats suffering from colitis reduced the Th17/Treg ratio by inhibiting HDAC1 deacetylation activity [95]. Moreover, in human enterocytes, butyrate can be a protective factor by increasing tolerogenic effects. It significantly reduces HDAC activity in a dose-dependent manner, which increases the level of histone acetylation, and tolerogenic factors expression, such as human β-defensin 3 (HBD-3), which is crucial for Tregs induction and immune tolerance maintenance in the gut [96]. In addition to that, butyrate can modulate the acetylation of histones at the *FoxP3* gene, increasing the FoxP3 protein stabilization and the number of intestinal Treg cells [97–99]. On the other hand, *in vitro*, lamina propria CD4 T cell activation, proliferation, and function were reduced upon treatment with butyrate, through histone acetylation and possibly via G-protein coupled receptor 43 (GPR43) signaling, where GPR43 agonism can mimic the butyrate's impact on CD4 T cell proliferation. This highlights the butyrate's potential role in modulating the immune response in the gut mucosa [100].

Furthermore, in humans and mice, butyrate and propionate can inhibit the degranulation of mast cells, which is mediated by IgE-dependent and IgE-independent pathways. These effects are associated with the inhibition of HDACs but not the SCFA receptors such as GPR41, GPR43 and PPAR. These HDACs inhibition decreased acetylation at the promoter

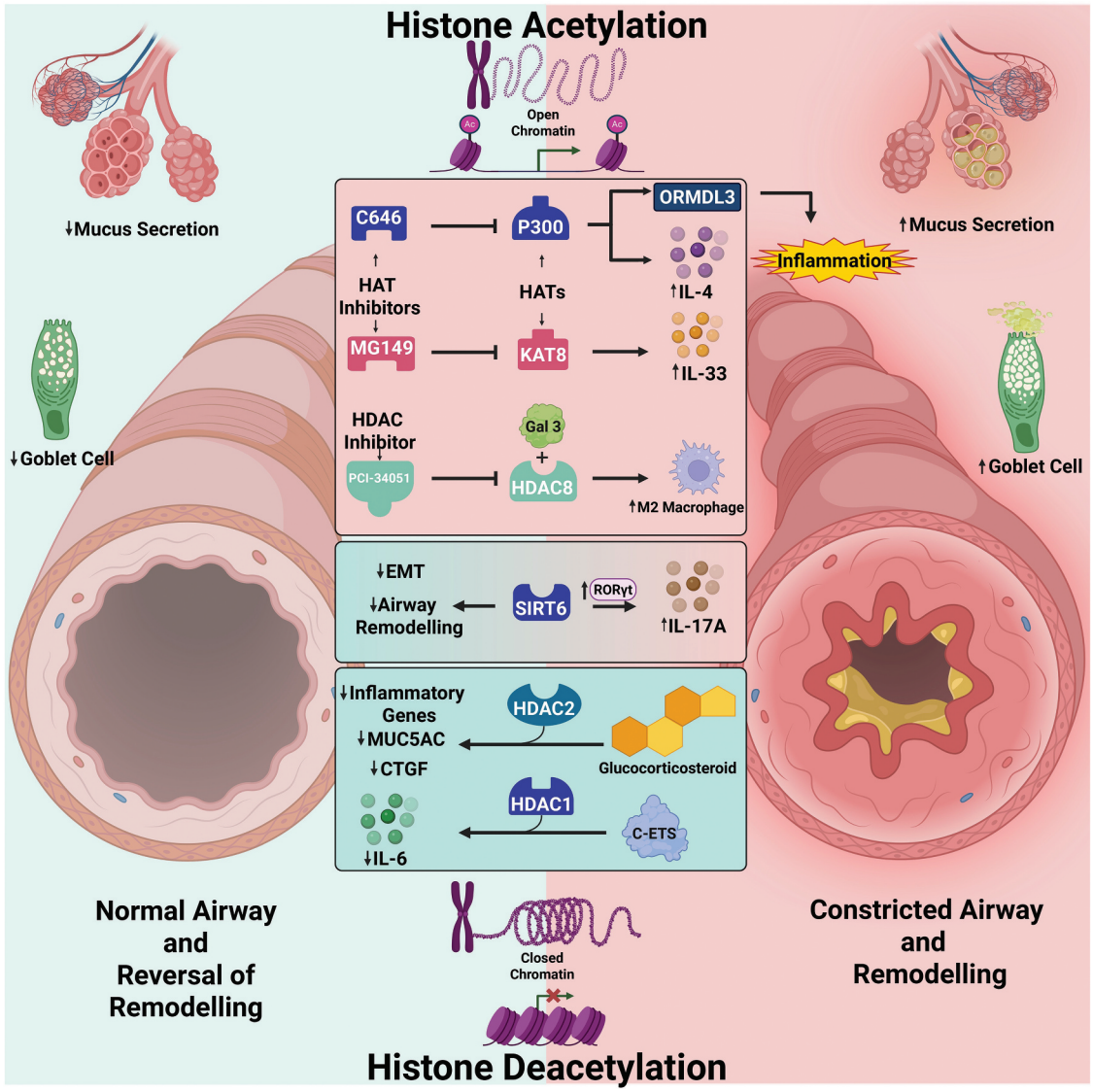

Figure 2. Histone acetylation significantly influences asthma progression through the regulation of genes involved in inflammation and airway remodeling. HATs, P300 and KAT8, promote asthma by activating genes like *ORMDL3* and *IL-4* gene. Similarly, KAT8 stabilizes IL-33, another pro-inflammatory cytokine. HAT inhibitors, such as C646 and MG149, have shown promise in reducing asthma symptoms by suppressing these pathways. HDACs regulate inflammation and airway remodeling through histone deacetylation. HDAC1 suppresses IL-6 production, while HDAC2 reduces inflammation and mucus production and enhances the efficacy of corticosteroids. HDAC8 promotes M2 polarization of macrophages along with galectin 3 protein and exacerbating asthma, similarly use of HDAC8 inhibitor PCI-34051 reduces the polarization relieving asthma symptoms. SIRT6, exhibit dual roles, either mitigating airway remodeling or exacerbating inflammation by promoting IL-17A production.

region of the genes of tyrosine kinases *BTK, SYK*, and *LAT*. These genes encode for tyrosine kinases that are crucial transducers of FcεRI-mediated signals for mast cell activation [101]. On another note, a reduction of HDAC6 activity and an increase of GPR43 expression in mice administrated with a propionic acid diet have suggested a higher histone acetylation linked to a higher percentage of $CD4^+$ $FoxP3^+$ T cells compared with the baseline percentage [102]. Figure 3 illustrates the histone acetylation in food allergy to visually clarify its role in disease progression.

5.3. Histone acetylation in atopic dermatitis

Atopic dermatitis is a persistent inflammatory skin condition characterized by a compromised skin barrier, chronic itching, and an increased susceptibility to secondary infections. Due to its early onset, sensitization patterns, and overlap with other allergic conditions, atopic dermatitis plays a central role in the allergic disease spectrum [103]. Environmental influences, particularly allergen exposure, like exposure to ultraviolet radiation, house dust mites, and pollen, are crucial in precipitating this condition [104,105]. In Europe and the United States, the prevalence of atopic dermatitis is approximately 20% in children and ranges from 7% to 14% in adults [106], with an impressive 95% of cases manifesting symptoms prior to age five [107]. Notably, children diagnosed with atopic dermatitis face a higher likelihood of developing asthma and allergic rhinitis, a phenomenon known as the "atopic march" [108].

Epigenetic changes play an important role in atopic dermatitis, affecting inflammation, gene expression, and skin barrier function. While many studies have explored DNA methylation in atopic dermatitis, histone modifications are less studied

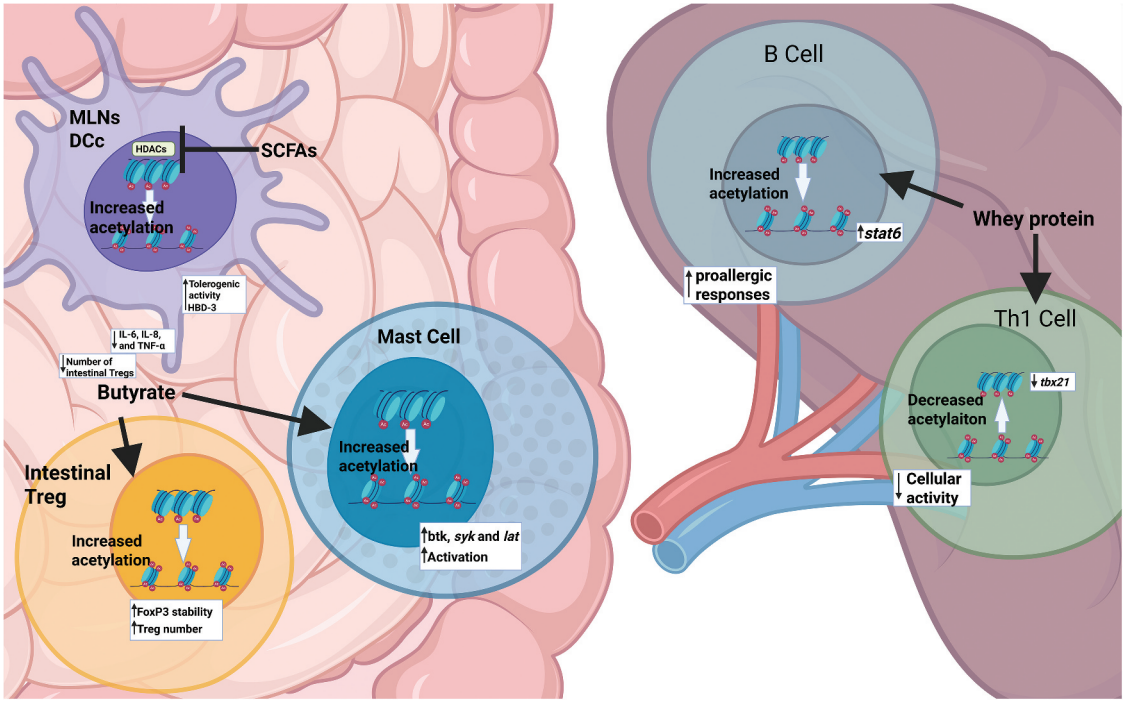

Figure 3. Illustration shows the change in the histone acetylatio/deacetylation and the change of cellular activity of several cell types upon interaction with different diet components. Arrows show the level of expression (↑ upregulation, and ↓ downregulation).

[109]. Indirect evidence suggests their involvement in atopic dermatitis. For example, Liew *et al*. found reduced miR-335 levels in atopic dermatitis lesions, which could be restored by belinostat, a histone deacetylase inhibitor [110]. This highlights the role of acetylation in atopic dermatitis. Besides, histone modifications may influence gut bacteria that produce short-chain fatty acids, and reduced microbiota diversity has been linked to increased atopic dermatitis severity, suggesting a gut-skin connection [111]. Additionally, much research which focuses on atopic dermatitis also provides reliable support for the study of histone acetylation in atopic dermatitis.

Recent research has uncovered significant insights into how repeated exposure to allergens can lead to enduring modifications in the gene expression profiles of immune cells, particularly Th cells and dendritic cells. These alterations are linked to the activation of pro-inflammatory cytokines, such as IL-4 and IL-13, which promote a Th2-dominant immune response. This response is a defining characteristic of atopic dermatitis [112]. One of the critical regulators of inflammation in atopic dermatitis is NF-κB [113]. NF-κB regulates the expression of a multitude of pro-inflammatory genes [114]. However, SIRT1 deacetylated transcription factors, affecting signaling pathways like NF-κB, reducing these inflammatory cytokines, thereby alleviating inflammation [115].

Furthermore, a compromised skin barrier results in increased trans-epidermal water loss and heightened allergen penetration, provoking inflammation [116]. Histone acetylation is crucial in regulating the expression of the filaggrin (*FLG*) gene, which encodes a protein vital for skin barrier integrity [117]. FLG, a histidine-rich protein in the stratum corneum, aggregates keratin filaments into tight arrays, enhancing skin resilience [118]. Acetylation plays a vital role in opening the chromatin structure, thereby allowing easier access for the transcriptional machinery and enhancing the expression of FLG. The precise regulation of FLG through histone acetylation is essential for maintaining the integrity of the skin barrier, and any dysregulation can lead to reduced FLG levels, thereby worsening the symptoms of atopic dermatitis [117]. Several key epidermal barrier genes – including *FLG, FLG2*, hornerin, and desmogleins are subject to epigenetic regulation. Among them, the transcription factor OVOL1 plays a pivotal role in promoting *FLG* expression and supporting epidermal homeostasis. Notably, activation of the aryl hydrocarbon receptor (AHR), a pathway associated with epigenetic modulation, induces OVOL1 expression, thereby enhancing *FLG* expression and reinforcing skin barrier integrity [119,120].

Excitingly, recent studies have delved into the influence of microbiome-mediated epigenetic changes in the pathogenesis of atopic dermatitis. For instance, butyric acid (BA), a fermentation by-product of the skin probiotic *Staphylococcus epidermidis*, demonstrated inhibitory effects against the pathogenic bacterium *Staphylococcus aureus (S. aureus)*, known to be implicated in atopic dermatitis [121]. BA acted as an inhibitor of HDAC, promoting histone acetylation and enhancing gene expression. Pre-treating mouse skin wounds with BA or its derivative before exposure to *S. aureus* effectively suppressed bacterial growth [122]. Notably, Trompette *et al*. highlighted several key genes that play a crucial role in skin function and were upregulated following butyrate treatment in mice. Among these genes are those involved in keratinocyte differentiation and skin barrier function, including FLG, involucrin, loricrin, late cornified envelope 1 m, and calmodulin-like skin protein [123].

A compelling aspect of allergen-induced epigenetic changes is the concept of epigenetic memory, which contributes to long-lasting alterations in gene expression and helps explain the chronic and relapsing nature of atopic dermatitis. Kuriakose and Miller [50] discuss how early-life environmental exposures can lead to persistent epigenetic modifications that influence immune responses later in life. More recently, Onrust-van Schoonhoven *et al* [124]. demonstrated that allergen-driven 3D chromatin reorganization in memory Th2 cells primes them for rapid transcriptional activation upon re-exposure, even in the absence of ongoing inflammation. Together, these findings support the notion that epigenetic memory plays a central role in sustaining heightened immune reactivity in atopic dermatitis. The histone acetylation-related mechanisms underlying atopic dermatitis are synthesized in Figure 4

5.4. Histone acetylation in other allergic diseases

Allergic rhinitis is a noninfectious inflammatory disease of the nasal mucosa [125] and is primarily driven by an IgE-mediated type 1 hypersensitivity response due to an allergen exposure [126]. The main symptoms of allergic rhinitis are nasal congestion, watery rhinorrhea, pruritus and paroxysmal sneezing [127]. Inhaled allergies are the most common due to aeroallergens like grass and tree pollens, molds, pests, house dust mites and animal dander [128,129].

A study examining patients with perennial allergic rhinitis (sensitized to mite allergens) revealed a significant upregulation of HDAC1 expression in nasal epithelial cells compared to healthy controls [130]. In contrast, the expression of the potassium channel TWIK-related K+ channel 1 (TREK-1) was markedly reduced in allergic rhinitis. However, antigen-specific immunotherapy (AIT) was found to restore TREK-1 expression while concurrently reducing HDAC1 levels, indicating a potential therapeutic mechanism through epigenetic modulation. The interplay between HDAC1 and TREK-1 May be critical in allergic rhinitis, as increased HDAC1 activity has been implicated in the suppression of TREK-1, contributing to the development of the disease. Moreover, the inhibition of HDAC1 promotes anti-inflammatory mediators like IL-10 and FoxP3, while reducing pro-inflammatory TNF-α. These findings collectively highlight the role of HDAC1 in the exacerbation of allergic rhinitis by amplifying inflammatory pathways while suppressing anti-inflammatory mechanisms [131].

Further supporting the role of HDACs in allergic rhinitis, another study explored the potential regulatory interactions between HDAC1, HDAC3, and thymic stromal lymphopoietin (TSLP). TSLP is a cytokine that plays a pivotal role in initiating and perpetuating allergic immune responses. The study hypothesized that both HDAC1 and HDAC3 May act as upstream regulators of TSLP, thus influencing the pathophysiology of allergic rhinitis. Although direct evidence for this regulatory relationship is limited, the study provided

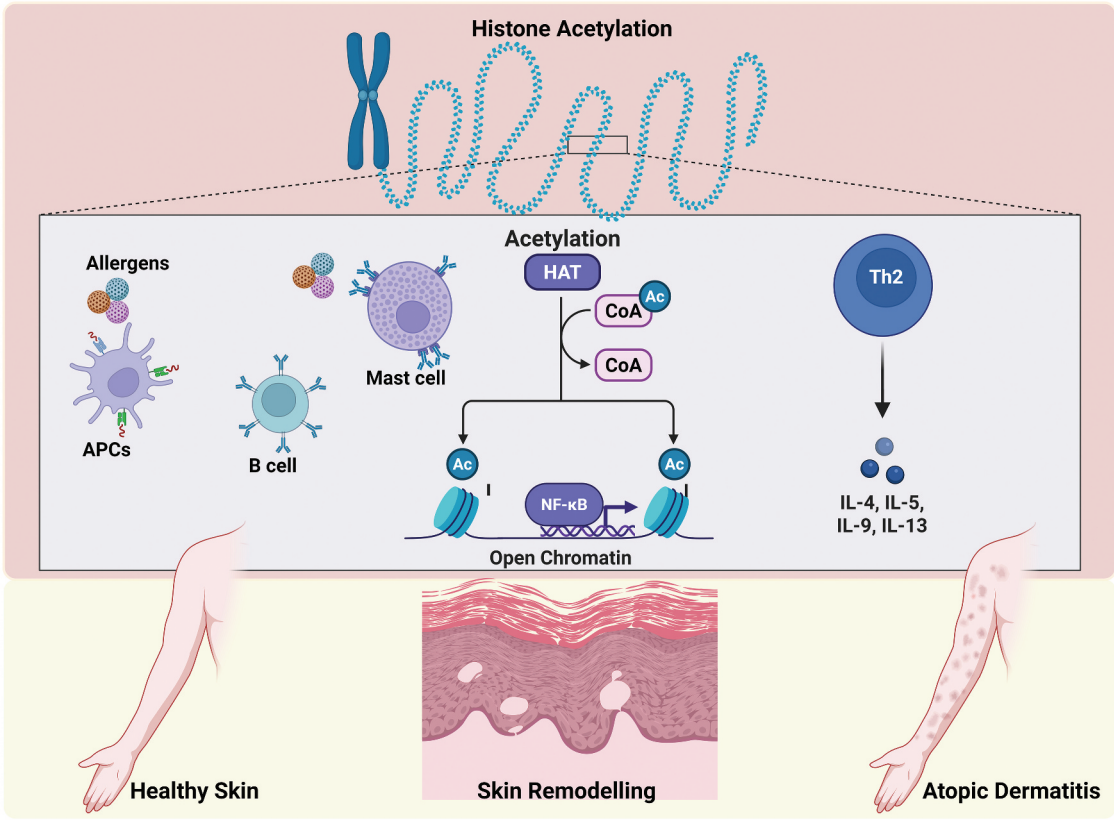

Figure 4. This figure illustrates how exposure to allergens, such as dust mites and pollen, triggers epigenetic changes that contribute to the development of atopic dermatitis (AD). Histone acetylation at promoter regions enhances the expression of key genes involved in skin barrier function, inflammatory cytokines, and the Th2 immune response. The activation of NF-κB and Th2 cytokines, such as IL-4, IL-5, IL-9, and IL-13, leads to inflammation, while compromised skin barrier integrity further exacerbates the condition.

compelling insights into the potential therapeutic implications. The use of sodium butyrate, an HDAC inhibitor, was found to suppress TSLP expression, leading to a marked improvement in clinical symptoms of allergic rhinitis. This underscores the therapeutic promise of targeting HDAC activity to modulate TSLP-driven allergic inflammation [132].

Histone acetylation also plays a role in the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP) [133]. Another remarkable study demonstrated that TSA suppresses TGF-β1-induced myofibroblast differentiation and extracellular matrix (ECM) production in nasal polyp tissue [134]. This effect was mediated through the inhibition of HDAC2 and HDAC4 activity, leading to increased histone acetylation and subsequent alterations in the expression of fibrosis-related genes. By targeting this pathway, TSA effectively reduced the fibrotic response and ECM accumulation, highlighting its potential as a therapeutic candidate for managing CRSwNP [134]. These findings underscore the importance of histone acetylation as a regulatory mechanism and a promising target for treating this inflammatory condition.On the other side, Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease driven by food allergies and characterized by eosinophilic inflammation of the esophagus accompanied by symptoms of esophageal dysfunction [135]. Recent advances in epigenetic research have provided insights into the molecular mechanisms underlying EoE pathogenesis. Notably, elevated levels of histone H3 acetylation in the esophageal tissue of EoE patients have been identified as a critical epigenetic alteration [49]. This modification is closely linked to the activation of CBP histone acetyltransferase activity, which is mediated by IL-13. IL-13, a cytokine known for its central role in allergic inflammation, enhances CBP activity, thereby promoting histone acetylation at specific genomic loci. This epigenetic remodeling facilitates the transcription of pro-inflammatory genes, leading to increased eosinophil recruitment and sustained inflammation in the esophageal tissue. Modulating histone acetylation or disrupting the IL-13–CBP signaling axis could offer novel strategies for controlling eosinophilic inflammation.

6. Histone acetylation as therapeutic targets in allergic disease

In the past few years, there have been multiple trials targeting histone acetylation as a therapeutic strategy aiming to restore immune balance by modulating the activity of HATs and HDACs (Table 1).

6.1. Defined compounds

HDAC inhibitors have emerged as promising therapeutic agents for allergic diseases. Preclinical studies demonstrate their ability to suppress Th2 responses, enhance Treg differentiation, and mitigate allergic inflammation. Pretreatment with TSA, a well-studied HDAC inhibitor, can reduce secretion of IL-4, IL-6, TNF-α and IL-13 in IgE-mediated marrow-derived mast cell activation. This was accompanied by decreased expression of FcεRI and mast cell degranulation. Interestingly, TSA also impacts responses to non-IgE stimuli, such as IL-33 [136]. Additionally, TSA treatment in mice increased the number of functionally improved Tregs in the thymus and spleen and decreased inflammatory bowel disease through Treg-dependent effects [137].

Allopurinol is a xanthine oxidase inhibitor. It ameliorated toluene diisocyanate-induced oxidative stress, DNA damage, and mixed granulocytic airway inflammation. It also modulated Th1, Th2 and Th17 immunity and regulated HMGB1 acetylation and secretion. This suggests a novel link between purine metabolism and asthma pathogenesis [138].

Acetate, propionate, and butyrate belong to SCFAs that are fermentation products of dietary components. Moreover, these compounds are also as defined chemicals which can be produced chemically or via microbial fermentation for industry. These chemicals exert epigenetic effects primarily through

Table 1. Histone acetylation as therapeutic targets in allergic disease.

Category	Name	Target	Mechanism in allergic diseases	Reference
Defined compounds	Trichostatin A	HDAC	Interfere with the removal of HDAC to suppress Th2 responses, enhance Treg differentiation, and mitigate allergic inflammation	[136,137]
	Allopurinol	Xanthine Oxidase	Ameliorate oxidative stress, DNA damage, and inflammation. regulated HMGB1 acetylation, modulated Th1, Th2 and Th17 immunity	[138]
	Propionate and butyrate	HDACs	Inhibit HDACs activity to regulate basophils and mast cell activation and degranulation; reduce type 2 cytokines; downregulates key tyrosine kinases	[40,101,139,140]
	Sodium butyrate	HDAC1, HDAC8	Reduce the expression of HDAC1 and HDAC8 and increase acetylation of H3AcK9	[132,142]
	I-BET762	BET bromodomain	Block the binding of BET proteins to acetylated histones, inhibited IL-6 and CXCL8 release	[25,144,145]
	iBET151	Bromodomain family	Interfere with the recruitment of BET proteins to acetylated histones	[146]
	MG149	HAT8	Inhibit HAT8-mediated IL-33 acetylation	[71]
Dietary interventions	Curcumin	p300/CBP HAT; HDAC1, HDAC3	Inhibit p300/CBP HAT activity to decrease the binding efficiency of histones H3 and H4 and acetyl CoA. Decreases in HDAC1 and HDAC3 levels	[150–153]
	L-Sulforaphane	HDAC	Inhibit HDAC activity and interact with HDAC catalytic domains to alleviate asthma	[154]
	Pterostilbene	glucose-Glut1	inhibits glycolysis by Glut1/mTOR/GATA3 axis, leads to histone acetylation reduction	[155]

HDAC inhibition, influencing immune cells integral to the immune tolerance network [99]. For example, propionate and butyrate induced histone acetylation of basophils and mast cell suppression of HDACs, and they may play a complex role in regulating these cells' activation and degranulation via inhibiting HDACs activity [101,139]. *In vivo* butyrate secretion ameliorated allergen-induced airway eosinophilia, reduced type 2 cytokines in bronchial fluid, and improved airway hyperresponsiveness [40,140]. Transcriptome analyses revealed that butyrate downregulates key tyrosine kinases, including BTK, SYK, and LAT, which are critical transducers of FcεRI-mediated signals essential for mast cell activation [101]. Moreover, Mice treated orally with SCFAs acetate and butyrate showed reductions in anaphylactic clinical scores and serum IgE levels compared to controls following the induction of peanut allergy [136,141]. Sodium butyrate treatment significantly reduced the increased levels of OVA-specific IgE, increased serum IL-2 and IFN-γ levels, and decreased IL-4 and IL-10 levels. These treatments corrected the Th1/Th2 imbalance and improved clinical symptoms in mouse models of allergic rhinitis [132]. Moreover, Sodium butyrate exhibited a preventive effect. It reduced the expression of HDAC1 and HDAC8 and increased OVA-induced acetylation of H3AcK9 [142].

In addition to the above, reader proteins, such as the BRD family, recognize specific histone modifications and present opportunities for pharmacological intervention [143]. BET inhibitor I-BET762(also named GSK525762A), a compound that mimics acetylated histones, binds to bromodomain and BET proteins in the BRD family, including BRD2, BRD3, and BRD4 [25,144]. It inhibited FCS+TGF-β-induced airway smooth muscle cell proliferation and IL-6 and CXCL8 release in healthy individuals and nonsevere and severe asthma patients [145]. Another BET inhibitor, iBET151, profoundly suppressed the expression of genes critical for type 2 immunity, including type 2 cytokines, cell surface receptors, and regulators of ILC2 differentiation and activation following IL-33 stimulation. *In vivo*, iBET151 administration in experimental mouse models of allergic lung inflammation significantly reduced lung inflammation and airway resistance in response to cytokine or allergen exposure [146].

Interestingly, HAT can also be a therapeutic target in allergic disease. The study found that mice exposed to house dust mite (HDM) developed airway hyperresponsiveness. However, treatment with MG149, a KAT8 inhibitor, in this HDM-challenged mouse model significantly reduced airway resistance, inflammatory cell infiltration, and mucus production [71]. The researchers also discovered that IL-33 is a substrate of KAT8, and KAT8 can acetylate IL-33 and enhance protein stability via reducing its polyubiquitination. In HDM-treated Il33−/− mice, MG149 had no additional effect, indicating that the anti-inflammatory role of MG149 depends on the presence of IL-33. Overall, the data suggest that KAT8 contributes to asthma through IL-33 regulation, and its inhibition may offer a new therapeutic approach for allergic airway inflammation [71].

6.2. Dietary interventions

Dietary interventions that influence histone acetylation are emerging as potential therapeutic strategies in allergic diseases. A very interesting compound is Curcumin. Curcumin, a bioactive compound derived from the spice turmeric, has been shown to modulate both HDAC and HAT activity in allergic diseases. A study showed that oral treatment with curcumin for two months markedly reduced the levels of IL-4, TNF-α and IL-8 in patients with allergic rhinitis. However, curcumin also increased the level of IL-10. Clinically, curcumin greatly alleviated nasal symptoms like rhinorrhea, sneezing, itching, and obstruction [147,148]. In another clinical study involving patients with asthma, curcumin administration (500 mg/day) for one month significantly decreased the total number of leukocytes, eosinophils, lymphocytes, and neutrophils [149]. Mechanistically, curcumin is a specific inhibitor of p300/CBP HAT activity *in vitro* and *in vivo* but not of p300/CBP-associated factor [150]. Curcumin's binding site on p300/CBP was specific and that binding led to a conformational change, resulting in a decrease in the binding efficiency of histones H3 and H4 and acetyl CoA [151,152]. Additionally, Chen *et al*. reported significant decreases in HDAC1 and HDAC3 levels following curcumin treatment, further underscoring its epigenetic regulatory potential [153].

In addition to the well-known compounds mentioned above, many more natural compounds have been found to have therapeutic effects. For example, L-Sulforaphane, a naturally occurring isothiocyanate compound primarily from plant origin, has shown protective effects in an OVA-induced allergic airway murine model. It inhibits HDAC activity and interacts with HDAC catalytic domains, alleviating asthma [154].

Another study on pterostilbene, a compound derived from blueberry extract, has been shown to reduce histone acetylation of transcription factors such as GATA3 and STAT6, thereby suppressing Th2 cell activation, eosinophilic inflammation, and cytokine release (IL-4, IL-5, and IL-13). However, pterostilbene doesn't target HDACs, it inhibits glycolysis by blocking glucose-Glut1 and downregulates the mTOR-GATA3 axis, which leads to histone acetylation reduction and ultimately a decrease in IL-4 and IL-13 [155].

7. Future perspectives

Histone acetylation represents a pivotal epigenetic mechanism that affects immune gene expression and plays a key role in the immune responses involved in allergic diseases. By controlling the accessibility of chromatin, histone acetylation helps activate genes that are essential for immune cells and the production of pro-inflammatory cytokines. Environmental factors, such as allergens, pollutants, and dietary components, can influence histone acetylation, exacerbating or mitigating allergic inflammation.

Targeting histone acetylation could provide a promising therapeutic approach to managing allergic diseases. Drugs that inhibit HATs or activate HDACs may help correct abnormal gene expression and alleviate allergic symptoms. However, due to the complex and context-specific nature of histone acetylation, careful consideration is needed. Over-targeting these pathways could lead to unintended immune suppression or off-target effects.

Future research should prioritize identifying specific histone acetylation patterns and their associated gene networks in allergic diseases. Advanced techniques, such as multi-omics approaches – including transcriptomics and single-cell analyses, offer powerful tools to deepen our understanding of how histone acetylation influences immune gene expression. These methods can also clarify how genetic predispositions and environmental factors interact to drive disease progression. Longitudinal studies are essential to investigate the long-term effects of histone acetylation changes, including their stability over time and potential inheritance across generations.

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Author contributions

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References

1. von Mutius E. The "hygiene hypothesis" and the lessons learnt from farm studies. Front Immunol. 2021;12:635522. doi: 10.3389/fimmu.2021.635522
2. Lambrecht BN, Hammad H. The immunology of the allergy epidemic and the hygiene hypothesis. Nat Immunol. 2017 Sep 19;18(10):1076–1083. doi: 10.1038/ni.3829
3. Kouzarides T. Chromatin modifications and their function. Cell. 2007 Feb 23;128(4):693–705. doi: 10.1016/j.cell.2007.02.005
4. Alaskhar Alhamwe B, Khalaila R, Wolf J, et al. Histone modifications and their role in epigenetics of atopy and allergic diseases. Allergy Asthma Clin Immunol. 2018;14(1):39. doi: 10.1186/s13223-018-0259-4
5. Shakespear MR, Halili MA, Irvine KM, et al. Histone deacetylases as regulators of inflammation and immunity. Trends Immunol. 2011 Jul;32(7):335–343. doi: 10.1016/j.it.2011.04.001
6. Yang F, Zhang X, Xie Y, et al. The pathogenesis of food allergy and protection offered by dietary compounds from the perspective of epigenetics. J Nutr Biochem. 2024 Jun;128:109593. doi: 10.1016/j.jnutbio.2024.109593
7. Kuo CH, Hsieh CC, Lee MS, et al. Epigenetic regulation in allergic diseases and related studies. Asia Pac Allergy. 2014 Jan;4(1):14–18. doi: 10.5415/apallergy.2014.4.1.14
8. Boonpiyathad T, Sözener ZC, Satitsuksanoa P, et al. Immunologic mechanisms in asthma. Semin Immunol. 2019 Dec;46:101333. doi: 10.1016/j.smim.2019.101333
9. Maeda K, Caldez MJ, Akira S. Innate immunity in allergy. Allergy. 2019 Sep;74(9):1660–1674. doi: 10.1111/all.13788
10. Miranda-Waldetario MCG, Curotto de Lafaille MA. Making good of a tricky start: how IgE and mast cells manage a protective sway in food allergy. Immunity. 2023 Sep 12;56(9):1988–1990. doi: 10.1016/j.immuni.2023.08.010
11. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. Can Med Assoc. 2016 Oct 18;188(15):1087–1093. doi: 10.1503/cmaj.160124
12. Renz H, Allen KJ, Sicherer SH, et al. Food allergy. Nat Rev Dis Primers. 2018 Jan 4;4(1):17098. doi: 10.1038/nrdp.2017.98
13. Del Giacco SR, Bakirtas A, Bel E, et al. Allergy in severe asthma. Allergy. 2017 Feb;72(2):207–220. doi: 10.1111/all.13072
14. Gibney ER, Nolan CM. Epigenetics and gene expression. Heredity (edinb). 2010 Jul;105(1):4–13. doi: 10.1038/hdy.2010.54
15. Deans C, Maggert KA. What do you mean, "epigenetic"? Genetics. 2015 Apr;199(4):887–896. doi: 10.1534/genetics.114.173492
16. Nicolaou N, Renkema KY, Bongers EM, et al. Genetic, environmental, and epigenetic factors involved in CAKUT. Nat Rev Nephrol. 2015 Dec;11(12):720–731. doi: 10.1038/nrneph.2015.140
17. Yao W, Hu X, Wang X. Crossing epigenetic frontiers: the intersection of novel histone modifications and diseases. Signal transduction and targeted therapy. Signal Transduct Target Ther. 2024 Sep 16;9(1):232. doi: 10.1038/s41392-024-01918-w
18. Costa DL. Overweight grandsons and grandfathers' starvation exposure. J Health Econ. 2023 Sep;91:102796. doi: 10.1016/j.jhealeco.2023.102796
19. Hammoud SS, Nix DA, Zhang H, et al. Distinctive chromatin in human sperm packages genes for embryo development. Nature. 2009 Jul 23;460(7254):473–478. doi: 10.1038/nature08162
20. Brykczynska U, Hisano M, Erkek S, et al. Repressive and active histone methylation mark distinct promoters in human and mouse spermatozoa. Nat Struct Mol Biol. 2010 Jun;17(6):679–687. doi: 10.1038/nsmb.1821
21. Xavier MJ, Roman SD, Aitken RJ, et al. Transgenerational inheritance: how impacts to the epigenetic and genetic information of parents affect offspring health. Hum Reprod Update. 2019 Sep 11;25(5):519–541. doi: 10.1093/humupd/dmz017
22. Haws SA, Leech CM, Denu JM. Metabolism and the epigenome: a dynamic relationship. Trends Biochem Sci. 2020 Sep;45(9):731–747. doi: 10.1016/j.tibs.2020.04.002
23. Shvedunova M, Akhtar A. Modulation of cellular processes by histone and non-histone protein acetylation. Nat Rev Mol Cell Biol. 2022 May;23(5):329–349. doi: 10.1038/s41580-021-00441-y
24. Cochran AG, Conery AR, Sims RJ. Bromodomains: a new target class for drug development. Nat Rev Drug Discov. 2019 Aug;18(8):609–628. doi: 10.1038/s41573-019-0030-7
25. Grabiec AM, Reedquist KA. The ascent of acetylation in the epigenetics of rheumatoid arthritis. Nat Rev Rheumatol. 2013 May;9(5):311–318. doi: 10.1038/nrrheum.2013.17
26. Filippakopoulos P, Knapp S. Targeting bromodomains: epigenetic readers of lysine acetylation. Nat Rev Drug Discov. 2014 May;13(5):337–356. doi: 10.1038/nrd4286
27. Andrews FH, Shanle EK, Strahl BD, et al. The essential role of acetyllysine binding by the YEATS domain in transcriptional regulation. Transcription. 2016;7(1):14–20. doi: 10.1080/21541264.2015.1125987

28. Barbieri I, Cannizzaro E, Dawson MA. Bromodomains as therapeutic targets in cancer. Brief Funct Genomics. 2013 May;12(3):219–230. doi: 10.1093/bfgp/elt007
29. Ellmeier W, Seiser C. Histone deacetylase function in CD4(+) T cells. Nat Rev Immunol. 2018 Oct;18(10):617–634. doi: 10.1038/s41577-018-0037-z
30. Kikuchi M, Morita S, Wakamori M, et al. Epigenetic mechanisms to propagate histone acetylation by p300/CBP. Nat Commun. 2023 Jul 17;14(1):4103. doi: 10.1038/s41467-023-39735-4
31. Narita T, Ito S, Higashijima Y, et al. Enhancers are activated by p300/CBP activity-dependent PIC assembly, RNAPII recruitment, and pause release. Mol Cell. 2021 May 20;81(10):2166–2182.e6. doi: 10.1016/j.molcel.2021.03.008
32. Hansen BK, Gupta R, Baldus L, et al. Analysis of human acetylation stoichiometry defines mechanistic constraints on protein regulation. Nat Commun. 2019 Mar 5;10(1):1055. doi: 10.1038/s41467-019-09024-0
33. Millán-Zambrano G, Burton A, Bannister AJ, et al. Histone post-translational modifications - cause and consequence of genome function. Nat Rev Genet. 2022 Sep;23(9):563–580. doi: 10.1038/s41576-022-00468-7
34. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. Cold Spring Harb Perspect Biol. 2014 Apr 1;6(4):a018713. doi: 10.1101/cshperspect.a018713
35. Shen F, Zhuang S. Histone acetylation and modifiers in renal fibrosis. Front Pharmacol. 2022;13:760308. doi: 10.3389/fphar.2022.760308
36. Harb H, Alashkar Alhamwe B, Acevedo N, et al. Epigenetic modifications in Placenta are associated with the Child's sensitization to allergens. Biomed Res Int. 2019;2019:1–11. doi: 10.1155/2019/1315257
37. Su RC, Becker AB, Kozyrskyj AL, et al. Altered epigenetic regulation and increasing severity of bronchial hyperresponsiveness in atopic asthmatic children. J Allergy Clin Immunol. 2009 Nov;124(5):1116–1118. doi: 10.1016/j.jaci.2009.08.033
38. Zhang HP, Wang L, Fu JJ, et al. Association between histone hyperacetylation status in memory T lymphocytes and allergen-induced eosinophilic airway inflammation. Respirol. 2016 Jul;21(5):850–857. doi: 10.1111/resp.12774
39. Yang G, Cheng BH, Yang SB, et al. Targeting histone-acetyltransferase tat-interactive protein 60 inhibits intestinal allergy. Allergy. 2018 Feb;73(2):387–394. doi: 10.1111/all.13304
40. Agache I, Cojanu C, Laculiceanu A, et al. Genetics and epigenetics of allergy. Curr Opin Allergy Clin Immunol. 2020 Jun;20(3):223–232. doi: 10.1097/ACI.0000000000000634
41. Grausenburger R, Bilic I, Boucheron N, et al. Conditional deletion of histone deacetylase 1 in T cells leads to enhanced airway inflammation and increased Th2 cytokine production. J Immunol. 2010 Sep 15;185(6):3489–3497. doi: 10.4049/jimmunol.0903610
42. Fields PE, Kim ST, Flavell RA. Cutting edge: changes in histone acetylation at the IL-4 and IFN-gamma loci accompany Th1/Th2 differentiation. J Immunol. 2002 Jul 15;169(2):647–650. doi: 10.4049/jimmunol.169.2.647
43. van Panhuys N, Le Gros G, McConnell MJ. Epigenetic regulation of Th2 cytokine expression in atopic diseases. Tissue Antigens. 2008 Aug;72(2):91–97. doi: 10.1111/j.1399-0039.2008.01068.x
44. Valapour M, Guo J, Schroeder JT, et al. Histone deacetylation inhibits IL4 gene expression in T cells. J Allergy Clin Immunol. 2002 Feb;109(2):238–245. doi: 10.1067/mai.2002.121145
45. Strempel JM, Vercelli D. Functional dissection identifies a conserved noncoding sequence-1 core that mediates IL13 and IL4 transcriptional enhancement. J Biol Chem. 2007 Feb 9;282(6):3738–3746. doi: 10.1074/jbc.M606615200
46. Yue L, Jia Q, Dong J, et al. TRIM24-mediated acetylation of STAT6 suppresses Th2-induced allergic rhinitis. Allergy Asthma Immunol Res. 2023 Sep;15(5):603–613. doi: 10.4168/aair.2023.15.5.603
47. Yu T, Gan S, Zhu Q, et al. Modulation of M2 macrophage polarization by the crosstalk between Stat6 and Trim24. Nat Commun. 2019 Sep 25;10(1):4353. doi: 10.1038/s41467-019-12384-2
48. Luo S, Liang G, Zhang P, et al. Aberrant histone modifications in peripheral blood mononuclear cells from patients with Henoch-Schönlein purpura. Clin Immunol. 2013 Mar;146(3):165–175. doi: 10.1016/j.clim.2012.12.009
49. Lim EJ, Lu TX, Blanchard C, et al. Epigenetic regulation of the IL-13-induced human eotaxin-3 gene by CREB-binding protein-mediated histone 3 acetylation. J Biol Chem. 2011 Apr 15;286(15):13193–13204. doi: 10.1074/jbc.M110.210724
50. Kuriakose JS, Miller RL. Environmental epigenetics and allergic diseases: recent advances. Clin Exp Allergy. 2010 Nov;40(11):1602–1610. doi: 10.1111/j.1365-2222.2010.03599.x
51. Harb H, Raedler D, Ballenberger N, et al. Childhood allergic asthma is associated with increased IL-13 and FOXP3 histone acetylation. J Allergy Clin Immunol. 2015 Jul;136(1):200–202. doi: 10.1016/j.jaci.2015.01.027
52. Xiao Y, Li B, Zhou Z, et al. Histone acetyltransferase mediated regulation of FOXP3 acetylation and Treg function. Curr Opin Immunol. 2010 Oct;22(5):583–591. doi: 10.1016/j.coi.2010.08.013
53. Beier UH, Wang L, Han R, et al. Histone deacetylases 6 and 9 and sirtuin-1 control Foxp3+ regulatory T cell function through shared and isoform-specific mechanisms. Sci Signal. 2012 Jun 19;5(229):ra45. doi: 10.1126/scisignal.2002873
54. de Zoeten EF, Wang L, Sai H, et al. Inhibition of HDAC9 increases T regulatory cell function and prevents colitis in mice. Gastroenterology. 2010 Feb;138(2):583–594. doi: 10.1053/j.gastro.2009.10.037
55. de Zoeten EF, Wang L, Butler K, et al. Histone deacetylase 6 and heat shock protein 90 control the functions of Foxp3(+) T-regulatory cells. Mol Cell Biol. 2011 May;31(10):2066–2078. doi: 10.1128/MCB.05155-11
56. van Loosdregt J, Vercoulen Y, Guichelaar T, et al. Regulation of Treg functionality by acetylation-mediated Foxp3 protein stabilization. Blood. 2010 Feb 4;115(5):965–974. doi: 10.1182/blood-2009-02-207118
57. van Loosdregt J, Brunen D, Fleskens V, et al. Rapid temporal control of Foxp3 protein degradation by sirtuin-1. PLOS ONE. 2011 Apr 20;6(4):e19047. doi: 10.1371/journal.pone.0019047
58. Kwon HS, Lim HW, Wu J, et al. Three novel acetylation sites in the Foxp3 transcription factor regulate the suppressive activity of regulatory T cells. The J Immunol. 2012 Mar 15;188(6):2712–2721. doi: 10.4049/jimmunol.1100903
59. Alashkar Alhamwe B, Meulenbroek L, Veening-Griffioen DH, et al. Decreased histone acetylation levels at Th1 and regulatory loci after induction of food allergy. Nutrients. 2020 Oct 19;12(10):3193. doi: 10.3390/nu12103193
60. Fanta CH. Asthma. N Engl J Med. 2009 Mar 5;360(10):1002–1014. doi: 10.1056/NEJMra0804579
61. International Union Against Tuberculosis and Lung Disease. The global asthma report 2022. Int J Tuberc Lung Dis. 2022 Nov 25;26(Supp 1):1–104. doi: 10.5588/ijtld.22.1010
62. Potaczek DP, Bazan-Socha S, Wypasek E, et al. Recent developments in the role of histone acetylation in asthma. Int Arch Allergy Immunol. 2024;185(7):641–651. doi: 10.1159/000536460
63. Lin Y, Qiu T, Wei G, et al. Role of histone post-translational modifications in inflammatory diseases. Front Immunol. 2022;13:852272. doi: 10.3389/fimmu.2022.852272
64. Ntontsi P, Photiades A, Zervas E, et al. Genetics and epigenetics in asthma. Int J Mol Sci. 2021 Feb 27;22(5):2412. doi: 10.3390/ijms22052412
65. Sotty J, Garcon G, Denayer FO, et al. Toxicological effects of ambient fine (PM(2.5–0.18)) and ultrafine (PM(0.18)) particles in healthy and diseased 3D organo-typic mucocilary-phenotype models. Environ Res. 2019 Sep;176:108538. doi: 10.1016/j.envres.2019.108538
66. Theodorou J, Nowak E, Bock A, et al. Mitogen-activated protein kinase signaling in childhood asthma development and environment-mediated protection. Pediatr Allergy Immunol. 2022 Jan;33(1):e13657. doi: 10.1111/pai.13657

67. Afthab M, Hambo S, Kim H, et al. Particulate matter-induced epigenetic modifications and lung complications. Eur Respir Rev. 2024 Oct;33(174):240129. doi: 10.1183/16000617.0129-2024
68. Mijač S, Banić I, Genc AM, et al. The effects of environmental exposure on epigenetic modifications in allergic diseases. Medicina (Kaunas). 2024 Jan 7;60(1):110. doi: 10.3390/medicina60010110
69. Cheng Q, Shang Y, Huang W, et al. p300 mediates the histone acetylation of ORMDL3 to affect airway inflammation and remodeling in asthma. Int Immunopharmacol. 2019 Nov;76:105885. doi: 10.1016/j.intimp.2019.105885
70. Cheng Q, Shang Y. ORMDL3 may participate in the pathogenesis of bronchial epithelial-mesenchymal transition in asthmatic mice with airway remodeling. Mol Med Rep. 2017 Jan;17(1):995–1005. doi: 10.3892/mmr.2017.7972
71. Liu Y, Du J, Liu X, et al. MG149 inhibits histone acetyltransferase KAT8-mediated IL-33 acetylation to alleviate allergic airway inflammation and airway hyperresponsiveness. Signal transduction and targeted therapy. Signal Transduct Target Ther. 2021 Sep 8;6(1):321. doi: 10.1038/s41392-021-00667-4
72. Cheng Q, He F, Zhao W, et al. Histone acetylation regulates ORMDL3 expression-mediated NLRP3 inflammasome overexpression during RSV-allergic exacerbation mice. J Cell Physiol. 2023 Dec;238(12):2904–2923. doi: 10.1002/jcp.31141
73. Nakagome K, Nagata M. The possible roles of IL-4/IL-13 in the development of eosinophil-predominant severe asthma. Biomolecules. 2024 May 2;14(5):546. doi: 10.3390/biom14050546
74. Zhou J, Geng F, Xu J, et al. PM(2.5) exposure and cold stress exacerbates asthma in mice by increasing histone acetylation in IL-4 gene promoter in CD4(+) T cells. Toxicol Lett. 2019 Nov;316:147–153. doi: 10.1016/j.toxlet.2019.09.011
75. van den Bosch T, Leus NGJ, Wapenaar H, et al. A 6-alkylsalicylate histone acetyltransferase inhibitor inhibits histone acetylation and pro-inflammatory gene expression in murine precision-cut lung slices. Pulm Pharmacol Ther. 2017 Jun;44:88–95. doi: 10.1016/j.pupt.2017.03.006
76. Zhao J, Huang K, Peng HZ, et al. Protein C-ets-2 epigenetically suppresses TLRs-induced interleukin 6 production in macrophages. Biochem Biophys Res Commun. 2020 Feb 19;522(4):960–964. doi: 10.1016/j.bbrc.2019.11.123
77. Barnes PJ. Glucocorticosteroids. Handb Exp Pharmacol. 2017;237:93–115.
78. Lee SU, Kim MO, Kang MJ, et al. Transforming growth factor beta inhibits MUC5AC expression by Smad3/HDAC2 complex formation and NF-kappaB deacetylation at K310 in NCI-H292 cells. Mol Cells. 2021 Jan 31;44(1):38–49. doi: 10.14348/molcells.2020.0188
79. Hua HS, Wen HC, Lee HS, et al. Endothelin-1 induces connective tissue growth factor expression in human lung fibroblasts by disrupting HDAC2/Sin3A/MeCP2 corepressor complex. J Biomed Sci. 2023 Jun 14;30(1):40. doi: 10.1186/s12929-023-00931-5
80. Zuberi RI, Hsu DK, Kalayci O, et al. Critical role for galectin-3 in airway inflammation and bronchial hyperresponsiveness in a murine model of asthma. Am J Pathol. 2004 Dec;165(6):2045–2053. doi: 10.1016/S0002-9440(10)63255-5
81. Li ML, Su XM, Ren Y, et al. HDAC8 inhibitor attenuates airway responses to antigen stimulus through synchronously suppressing galectin-3 expression and reducing macrophage-2 polarization. Respir Res. 2020 Feb 28;21(1):62. doi: 10.1186/s12931-020-1322-5
82. Ma K, Lu N, Zou F, et al. Sirtuins as novel targets in the pathogenesis of airway inflammation in bronchial asthma. Eur J Pharmacol. 2019 Dec 15;865:172670. doi: 10.1016/j.ejphar.2019.172670
83. Liu F, Shang YX. Sirtuin 6 attenuates epithelial-mesenchymal transition by suppressing the TGF-beta1/Smad3 pathway and c-jun in asthma models. Int Immunopharmacol. 2020 Mar 3;82:106333. doi: 10.1016/j.intimp.2020.106333
84. Quan J, Wen X, Su G, et al. Epithelial SIRT6 governs IL-17A pathogenicity and drives allergic airway inflammation and remodeling. Nat Commun. 2023 Dec 22;14(1):8525. doi: 10.1038/s41467-023-44179-x
85. Lai T, Wen X, Wu D, et al. SIRT1 protects against urban particulate matter-induced airway inflammation. Int J Chron Obstruct Pulmon Dis. 2019;14:1741–1752. doi: 10.2147/COPD.S202904
86. Leask A, Parapuram SK, Shi-Wen X, et al. Connective tissue growth factor (CTGF, CCN2) gene regulation: a potent clinical bio-marker of fibroproliferative disease? J Cell Commun Signal. 2009 Jun;3(2):89–94. doi: 10.1007/s12079-009-0037-7
87. Movassagh H, Prunicki M, Kaushik A, et al. Proinflammatory polarization of monocytes by particulate air pollutants is mediated by induction of trained immunity in pediatric asthma. Allergy. 2023 Jul;78(7):1922–1933. doi: 10.1111/all.15692
88. Ren Y, Li M, Bai S, et al. Identification of histone acetylation in a murine model of allergic asthma by proteomic analysis. Exp Biol Med (maywood). 2021 Apr;246(8):929–939. doi: 10.1177/1535370220980345
89. McErlean P, Kelly A, Dhariwal J, et al. Profiling of H3K27Ac reveals the influence of asthma on the epigenome of the airway epithelium. Front Genet. 2020;11:585746. doi: 10.3389/fgene.2020.585746
90. Su XM, Ren Y, Li ML, et al. Proteomics profiling asthma induced-lysine acetylation. Excli J. 2020;19:734–744. doi: 10.17179/excli2019-1508
91. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored expert panel report. J Am Acad Dermatol. 2011 Jan;64(1):175–192. doi: 10.1016/j.jaad.2010.11.020
92. Goverse G, Molenaar R, Macia L, et al. Diet-derived short chain fatty acids stimulate intestinal epithelial cells to induce mucosal tolerogenic dendritic cells. J Immunol. 2017 Mar 1;198(5):2172–2181. doi: 10.4049/jimmunol.1600165
93. Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From dietary fiber to Host physiology: short-chain fatty acids as key bacterial metabolites. Cell. 2016 Jun 2;165(6):1332–1345. doi: 10.1016/j.cell.2016.05.041
94. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. Mucosal Immunol. 2015 Jan;8(1):80–93. doi: 10.1038/mi.2014.44
95. Zhou L, Zhang M, Wang Y, et al. Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. Inflamm Bowel Dis. 2018 Aug 16;24(9):1926–1940. doi: 10.1093/ibd/izy182
96. Paparo L, Nocerino R, Ciaglia E, et al. Butyrate as a bioactive human milk protective component against food allergy. Allergy. 2021 May;76(5):1398–1415. doi: 10.1111/all.14625
97. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 2013 Dec 19;504(7480):451–455. doi: 10.1038/nature12726
98. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013 Dec 19;504(7480):446–450. doi: 10.1038/nature12721
99. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013 Aug 2;341(6145):569–573. doi: 10.1126/science.1241165
100. Kibbie JJ, Dillon SM, Thompson TA, et al. Butyrate directly decreases human gut lamina propria CD4 T cell function through histone deacetylase (HDAC) inhibition and GPR43 signaling. Immunobiology. 2021 Sep;226(5):152126. doi: 10.1016/j.imbio.2021.152126
101. Folkerts J, Redegeld F, Folkerts G, et al. Butyrate inhibits human mast cell activation via epigenetic regulation of FcεRI-mediated signaling. Allergy. 2020 Aug;75(8):1966–1978. doi: 10.1111/all.14254
102. Du HX, Yue SY, Niu D, et al. Gut microflora modulates Th17/Treg cell differentiation in experimental autoimmune prostatitis via the short-chain fatty acid propionate. Front Immunol. 2022;13:915218. doi: 10.3389/fimmu.2022.915218
103. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. Immunol Allergy Clin North Am. 2015 Feb;35(1):161–183. doi: 10.1016/j.iac.2014.09.008
104. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert Rev Clin Immunol. 2017 Jan;13(1):15–26. doi: 10.1080/1744666X.2016.1212660

105. Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. Allergy. 2020 Jan;75(1):63–74. doi: 10.1111/all.13946
106. Bylund S, Kobyletzki LB, Svalstedt M, et al. Prevalence and incidence of atopic dermatitis: a systematic review. Acta Derm Venereol. 2020 Jun 9;100(12):adv00160. doi: 10.2340/00015555-3510
107. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. ISRN Allergy. 2014;2014:1–7. doi: 10.1155/2014/354250
108. Hahn EL, Bacharier LB. The atopic march: the pattern of allergic disease development in childhood. Immunol Allergy Clin North Am. 2005 May;25(2):231–246. doi: 10.1016/j.iac.2005.02.004
109. da Silva Duarte AJ, Sanabani SS, da Silva Duarte AJ. Deciphering epigenetic regulations in the inflammatory pathways of atopic dermatitis. Life Sci. 2024 Jul 1;348:122713. doi: 10.1016/j.lfs.2024.122713
110. Liew WC, Sundaram GM, Quah S, et al. Belinostat resolves skin barrier defects in atopic dermatitis by targeting the dysregulated miR-335: SOX6 axis. J Allergy Clin Immunol. 2020 Sep;146(3):606–-620.e12. doi: 10.1016/j.jaci.2020.02.007
111. Nylund L, Nermes M, Isolauri E, et al. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. Allergy. 2015 Feb;70(2):241–244. doi: 10.1111/all.12549
112. León B. Understanding the development of Th2 cell-driven allergic airway disease in early life. Front Allergy. 2023;3:1080153. doi: 10.3389/falgy.2022.1080153
113. Angelini F, Di Matteo G, Balestrero S, et al. Nuclear factor kappaB activity is increased in peripheral blood mononuclear cells of children affected by atopic and non-atopic eczema. Int J Immunopathol Pharmacol. 2007 Jan;20(1):59–67. doi: 10.1177/039463200702000107
114. Barnes PJ, Karin M, Epstein FH. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. N Engl J Med. 1997 Apr 10;336(15):1066–1071. doi: 10.1056/NEJM199704103361506
115. Lu Y, Tang X, Wang W, et al. The role of deacetylase SIRT1 in allergic diseases. Front Immunol. 2024;15:1422541. doi: 10.3389/fimmu.2024.1422541
116. Dizon MP, Yu AM, Singh RK, et al. Systematic review of atopic dermatitis disease definition in studies using routinely collected health data. Br J Dermatol. 2018 Jun;178(6):1280–1287. doi: 10.1111/bjd.16340
117. Moosbrugger-Martinz V, Leprince C, Méchin MC, et al. Revisiting the roles of filaggrin in atopic dermatitis. Int J Mol Sci. 2022 May 10;23(10):5318. doi: 10.3390/ijms23105318
118. Dale BA, Vadlamudi B, DeLap LW, et al. Similarities between stratum corneum basic protein and histidine-rich protein II from newborn rat epidermis. Biochim Biophys Acta. 1981 Mar 27;668(1):98–106. doi: 10.1016/0005-2795(81)90153-7
119. Nedoszytko B, Reszka E, Gutowska-Owsiak D, et al. Genetic and epigenetic aspects of atopic dermatitis. Int J Mol Sci. 2020 Sep 4;21(18):6484. doi: 10.3390/ijms21186484
120. Jia Q, Liu P, Wang X, et al. Benvitimod upregulates filaggrin, involucrin and loricrin expressions via aryl hydrocarbon receptor-OVO-like 1 axis. Arch Dermatol Res. 2024 Aug 29;316(8):585. doi: 10.1007/s00403-024-03268-7
121. Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res. 2012 May;22(5):850–859. doi: 10.1101/gr.131029.111
122. Traisaeng S, Herr DR, Kao HJ, et al. A derivative of butyric acid, the fermentation metabolite of staphylococcus epidermidis, inhibits the growth of a staphylococcus aureus strain isolated from atopic dermatitis patients. Toxins (Basel). 2019 May 31;11(6):311. doi: 10.3390/toxins11060311
123. Trompette A, Pernot J, Perdijk O, et al. Gut-derived short-chain fatty acids modulate skin barrier integrity by promoting keratinocyte metabolism and differentiation. Mucosal Immunol. 2022 May;15(5):908–926. doi: 10.1038/s41385-022-00524-9
124. Onrust-van Schoonhoven A, de Bruijn MJW, Stikker B, et al. 3D chromatin reprogramming primes human memory T(H)2 cells for rapid recall and pathogenic dysfunction. Sci Immunol. 2023 Jul 14;8(85):eadg3917. doi: 10.1126/sciimmunol.adg3917
125. Lan YA, Guo JX, Yao MH, et al. The role of neuro-immune interactions in the pathology and pathogenesis of allergic rhinitis. Immunol Invest. 2024 Oct;53(7):1013–1029. doi: 10.1080/08820139.2024.2382792
126. Wise SK, Damask C, Rola Nd LT, et al. International consensus statement on allergy and rhinology: allergic rhinitis - 2023. Int Forum Allergy Rhinol. 2023 Apr;13(4):293–859. doi: 10.1002/alr.23090
127. Bousquet PJ, Demoly P, Devillier P, et al. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol. 2013;160(4):393–400. doi: 10.1159/000342991
128. Siddiqui ZA, Walker A, Pirwani MM, et al. Allergic rhinitis: diagnosis and management. Br J Hosp Med. 2022 Feb 2;83(2):1–9. doi: 10.12968/hmed.2021.0570
129. Wheatley LM, Togias A, Solomon CG. Clinical practice Allergic Rhinitis. N Engl J Med. 2015 Jan 29;372(5):456–463. doi: 10.1056/NEJMcp1412282
130. Wang Y, Lv L, Zang H, et al. Regulation of Trek1 expression in nasal mucosa with allergic rhinitis by specific immunotherapy. Cell Biochem Funct. 2015 Jan;33(1):23–28. doi: 10.1002/cbf.3075
131. Choi BY, Han M, Kwak JW, et al. Genetics and epigenetics in allergic rhinitis. Genes (Basel). 2021 Dec 17;12(12):2004. doi: 10.3390/genes12122004
132. Wang J, Wen L, Wang Y, et al. Therapeutic effect of histone deacetylase inhibitor, sodium butyrate, on allergic rhinitis in vivo. DNA Cell Biol. 2016 Apr;35(4):203–208. doi: 10.1089/dna.2015.3037
133. Jiao YX, Zhou YM, Zhou ZW, et al. Histone acetylation alteration by KAT6A inhibitor WM-1119 suppresses IgE-mediated mast cell activation and allergic inflammation via reduction in AP-1 signaling. Biochem Pharmacol. 2024 Dec 19;232:116732. doi: 10.1016/j.bcp.2024.116732
134. Cho JS, Moon YM, Park IH, et al. Effects of histone deacetylase inhibitor on extracellular matrix production in human nasal polyp organ cultures. Am J Rhinol Allergy. 2013 Jan;27(1):18–23. doi: 10.2500/ajra.2013.27.3827
135. Lucendo A, Groetch M, Gonsalves N. Dietary management of eosinophilic esophagitis. Immunol Allergy Clin North Am. 2024 May;44(2):223–244. doi: 10.1016/j.iac.2023.12.009
136. Krajewski D, Kaczenski E, Rovatti J, et al. Epigenetic regulation via altered histone acetylation results in suppression of mast cell function and mast cell-mediated food allergic responses. Front Immunol. 2018;9:2414. doi: 10.3389/fimmu.2018.02414
137. Tao R, de Zoeten EF, Ozkaynak E, et al. Deacetylase inhibition promotes the generation and function of regulatory T cells. Nat Med. 2007 Nov;13(11):1299–1307. doi: 10.1038/nm1652
138. Wang Y, Le Y, Wu J, et al. Inhibition of xanthine oxidase by allopurinol suppresses HMGB1 secretion and ameliorates experimental asthma. Redox Biol. 2024 Apr;70:103021. doi: 10.1016/j.redox.2023.103021
139. Shi Y, Xu M, Pan S, et al. Induction of the apoptosis, degranulation and IL-13 production of human basophils by butyrate and propionate via suppression of histone deacetylation. Immunology. 2021 Oct;164(2):292–304. doi: 10.1111/imm.13370
140. Theiler A, Bärnthaler T, Platzer W, et al. Butyrate ameliorates allergic airway inflammation by limiting eosinophil trafficking and survival. J Allergy Clin Immunol. 2019 Sep;144(3):764–776. doi: 10.1016/j.jaci.2019.05.002
141. Tan J, McKenzie C, Vuillermin PJ, et al. Dietary fiber and bacterial SCFA enhance oral tolerance and protect against food allergy through diverse cellular pathways. Cell Rep. 2016 Jun 21;15(12):2809–2824. doi: 10.1016/j.celrep.2016.05.047
142. Wang J, Cui M, Sun F, et al. HDAC inhibitor sodium butyrate prevents allergic rhinitis and alters lncRNA and mRNA expression profiles in the nasal mucosa of mice. Int J Mol Med. 2020 Apr;45(4):1150–1162. doi: 10.3892/ijmm.2020.4489

143. Yun M, Wu J, Workman JL, et al. Readers of histone modifications. Cell Res. 2011 Apr;21(4):564–578. doi: 10.1038/cr.2011.42
144. Nicodeme E, Jeffrey KL, Schaefer U, et al. Suppression of inflammation by a synthetic histone mimic. Nature. 2010 Dec 23;468(7327):1119–1123. doi: 10.1038/nature09589
145. Perry MM, Durham AL, Austin PJ, et al. BET bromodomains regulate transforming growth factor-β-induced proliferation and cytokine release in asthmatic airway smooth muscle. J Biol Chem. 2015 Apr 3;290(14):9111–9121. doi: 10.1074/jbc.M114.612671
146. Kerscher B, Barlow JL, Rana BM, et al. BET bromodomain inhibitor iBET151 impedes human ILC2 activation and prevents experimental allergic lung inflammation. Front Immunol. 2019;10:678. doi: 10.3389/fimmu.2019.00678
147. Wu S, Xiao D. Effect of curcumin on nasal symptoms and airflow in patients with perennial allergic rhinitis. Annals of allergy, asthma & immunology: official publication of the American college of allergy. Asthma Immunol. 2016 Dec;117(6):697–702.e1. doi: 10.1016/j.anai.2016.09.427
148. Haftcheshmeh SM, Mirhafez SR, Abedi M, et al. Therapeutic potency of curcumin for allergic diseases: a focus on immunomodulatory actions. Biomed Pharmacother. 2022 Oct;154:113646. doi: 10.1016/j.biopha.2022.113646
149. Abidi A, Gupta S, Agarwal M, et al. Evaluation of efficacy of curcumin as an add-on therapy in patients of bronchial asthma. J Clin And Diagnostic Res. 2014 Aug;8(8):Hc19–24. doi: 10.7860/JCDR/2014/9273.4705
150. Balasubramanyam K, Varier RA, Altaf M, et al. Curcumin, a novel p300/CREB-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. J Biol Chem. 2004 Dec 3;279(49):51163–51171. doi: 10.1074/jbc.M409024200
151. Marcu MG, Jung YJ, Lee S, et al. Curcumin is an inhibitor of p300 histone acetylatransferase. Med Chem. 2006 Mar;2(2):169–174. doi: 10.2174/157340606776056133
152. Reuter S, Gupta SC, Park B, et al. Epigenetic changes induced by curcumin and other natural compounds. Genes Nutr. 2011 May;6(2):93–108. doi: 10.1007/s12263-011-0222-1
153. Chen Y, Shu W, Chen W, et al. Curcumin, both histone deacetylase and p300/CBP-specific inhibitor, represses the activity of nuclear factor kappa B and Notch 1 in raji cells. Basic Clin Pharma Tox. 2007 Dec;101(6):427–433. doi: 10.1111/j.1742-7843.2007.00142.x
154. Royce SG, Licciardi PV, Beh RC, et al. Sulforaphane prevents and reverses allergic airways disease in mice via anti-inflammatory, antioxidant, and epigenetic mechanisms. Cell Mol Life Sci. 2022 Nov 1;79(11):579. doi: 10.1007/s00018-022-04609-3
155. Liu CT, Song YC, Wu TC, et al. Targeting glycolysis in Th2 cells by pterostilbene attenuates clinical severities in an asthmatic mouse model and IL-4 production in peripheral blood from asthmatic patients. Immunology. 2022 Jun;166(2):222–237. doi: 10.1111/imm.13469