Histone modifications and their role in epigenetics of atopy and allergic diseases

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Histone modifications and their role in epigenetics of atopy and allergic diseases

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Abstract
This review covers basic aspects of histone modification and the role of posttranslational histone modifications in the development of allergic diseases, including the immune mechanisms underlying this development. Together with DNA methylation, histone modifications (including histone acetylation, methylation, phosphorylation, ubiquitination, etc.) represent the classical epigenetic mechanisms. However, much less attention has been given to histone modifications than to DNA methylation in the context of allergy. A systematic review of the literature was undertaken to provide an unbiased and comprehensive update on the involvement of histone modifications in allergy and the mechanisms underlying this development. In addition to covering the growing interest in the contribution of histone modifications in regulating the development of allergic diseases, this review summarizes some of the evidence supporting this contribution. There are at least two levels at which the role of histone modifications is manifested. One is the regulation of cells that contribute to the allergic inflammation (T cells and macrophages) and those that participate in airway remodeling [(myo-) fibroblasts]. The other is the direct association between histone modifications and allergic phenotypes. Inhibitors of histone-modifying enzymes may potentially be used as anti-allergic drugs. Furthermore, epigenetic patterns may provide novel tools in the diagnosis of allergic disorders.

Keywords: Allergy, Asthma, Atopy, Epigenetic (-s), Histone acetylation, Histone methylation, Histone modification (-s), Histone phosphorylation, Inflammation, Immunity

Background
In the last few decades, there has been a substantial increase in the prevalence of allergic diseases in the industrialized countries [1–3]. Since this change could not be explained by a rather stable population genetic profile [2–4], increased exposure to harmful and reduced exposure to protective epigenetically-mediated environmental factors have been considered, at least in part, as a possible explanation for this epidemiological phenomenon [5–9]. While DNA methylation has been extensively studied as the epigenetic mechanism involved in the etiopathogenesis of allergic disorders, posttranslational histone modifications, another important classical epigenetic mechanism, have not been as widely investigated and discussed because it is not considered as important as DNA methylation [5–7, 10]. The review firstly describes the (bio-) chemical basics of epigenetic histone modifications. This is followed by an assessment of recent evidence that supports a role for histone modifications in the epigenetic regulation of the pathogenesis of allergy and related disorders, together with a description of the underlying cellular and molecular mechanisms.

Main text
Histone modifications: the basics
Similarly to DNA methylation, posttranslational histone modifications do not affect DNA nucleotide sequence but...
can modify its availability to the transcriptional machinery. Although histone modifications play also other roles, such as histone phosphorylation, best known for its contribution to DNA repair in response to cell damage, this review deals primarily with general mechanisms of histone modifications in the context of their role in epigenetic modulation of gene expression. Several types of histone modifications are known, amongst which acetylation, methylation, phosphorylation, and ubiquitination are the best studied and most important in terms of the regulation of chromatin structure and (transcriptional) activity [11–15]. In general, histone modifications are catalyzed by specific enzymes that act, predominantly, but not exclusively (e.g. some types of histone phosphorylation), at the histone N-terminal tails involving amino acids such as lysine or arginine as well as serine, threonine, tyrosine, etc. Histone acetylation usually leads to higher gene expression. This may not always be the case for histone H4 [16–18]. Histone methylation in turn has either transcriptionally permissive or repressive character, depending on the location of targeted amino acid residues in the histone tail and/or the number of modifying (e.g. methyl) groups added [5, 6, 14, 15, 19, 20]. Table 1 summarizes the various forms of histone modifications appearing in this review along with their effects on gene transcriptional activity.

### Histone acetylation

Histone acetylation status is regulated by two groups of enzymes exerting opposite effects, histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyze the transfer of an acetyl group from acetyl-CoA to an amino acid group of the target lysine residues in the histone tails, which leads to the removal of a positive charge on the histones, weakening the interaction between histones and (negatively charged phosphate groups of) DNA. This in turn typically makes the chromatin less compact and thus more accessible to the transcriptional machinery. HDACs remove acetyl groups from histone tail lysine residues and thereby work as repressors of gene expression [5, 14, 21–24]. HATs are classified into five (or sometimes six) families. The GCN5-related N-acetyltransferase (GNAT) family comprises KAT2A and KAT2B enzymes. They are involved in acetylation of histones and transcription

| Modification and site | Abbreviation | Effect on transcription |
|-----------------------|--------------|------------------------|
| Histone acetylation   | H3ac         | Activating/permissive  |
| Histone 3 panacetylation | H3ac        | Activating/permissive  |
| Histone 4 panacetylation | H4ac        | Activating/permissive  |
| Histone 3 lysine 4 acetylation | H3K4ac     | Activating/permissive  |
| Histone 3 lysine 9 acetylation | H3K9ac     | Activating/permissive  |
| Histone 3 lysine 14 acetylation | H3K14ac   | Activating/permissive  |
| Histone 3 lysine 18 acetylation | H3K18ac   | Activating/permissive  |
| Histone 3 lysine 27 acetylation | H3K27ac   | Activating/permissive  |
| Histone 4 lysine 16 acetylation | H4K16ac   | Activating/permissive  |
| Histone methylation   | H3K4me1      | Activating/permissive  |
| Histone 3 lysine 4 dimethylation | H3K4me2 | Activating/permissive  |
| Histone 3 lysine 4 trimethylation | H3K4me3  | Activating/permissive  |
| Histone 3 lysine 9 dimethylation | H3K9me2  | Repressive             |
| Histone 3 lysine 9 trimethylation | H3K9me3  | Repressive             |
| Histone 3 lysine 27 trimethylation | H3K27me3 | Repressive             |
| Histone 3 lysine 36 trimethylation | H3K36me3 | Activating/permissive  |
| Histone 3 lysine 79 methylation | H3K79me1 | Activating/permissive  |
| Histone phosphorylation | H3S10ph    | Activating/permissive  |
| Histone ubiquitination | H2Aub       | Repressive             |
| Histone 2B ubiquitination | H2Bub       | Activating/permissive  |

*According to the cells signaling technology webpage [100] and/or other sources referenced in the "Main text" and/or Tables 2 and 3 of this review

b See also "Histone modifications: the basics"
| Study                          | Major epigenetic aims                                                                 | Major epigenetic results                                                                                                                                                                                                 |
|-------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Harb et al. [84]               | Analysis of the association between prenatal fish oil exposure (maternal fish oil intake) and CB CD4+ T-cell H3ac and H4ac levels at promoters of PRK2 and several other important T-cell genes (placebo n = 34; fish oil n = 36) | Significantly higher H3ac levels at the PRK2 and IFNG promoters, and lower H3/H4ac levels at the IL13 and TXK21 were observed in CB CD4+ T-cells obtained from newborns of mothers supplemented with fish oil during pregnancy compared to newborns of placebo-treated mothers. The infants born from the fish oil-supplemented mothers were at the lower risk of developing allergic diseases [81, 82] |
| Harb et al. [83]               | Comparison of H3ac and H4ac levels at gene promoters of Th1, Th2, Th17, and Treg cells between CB CD4+ T-cells obtained from neonates with either high (n = 12) or low (n = 11) maternal serum folate levels estimated during the last trimester selected form a larger cohort based on conventional extremes of exposure design | Significantly higher GATA3 promoter H3ac and H4ac levels were observed in the high folate group. Significantly higher IL9 promoter H4ac levels in high folate arm (and a tendency towards a similar association for H3ac) were also found. A tendency towards lower IFNG promoter H4ac was observed in high folate group. Statistical analyses included adjustment for CB serum vitamin D levels. |
| Stefanowicz et al. [66]       | Comparison of global and gene-specific [TP63 (ΔNp63 isoform), EGFR, and STAT6] histone acetylation and methylation status in alveolar epithelial cells (AECs) obtained from asthmatic (n = 5) and healthy (n = 5) non-transplantable teenage human lung donors | Higher global H3K18ac and H3K9me3 levels were observed in asthmatic subjects. Higher association of H3K18ac (but not H3K9me3) around the transcription start sites of TP63 (ΔNp63 isoform), EGFR, and STAT6 was found in asthmatics. Non-significant increase in protein expression of those three genes was detected in AECs treated with HDACi (TSA) |
| Cahill et al. [62]             | Analysis of the effect H3K27ac at the PTGER2 promoter on EP2-expression in polyfimbriated fibroblasts obtained from aspirin-exacerbated respiratory disease (AERD) patients (n = 18), aspirin-tolerant and asthma-free control subjects with chronic rhinosinusitis and polyposis (aspirin-tolerant controls; n = 9), and healthy control subjects undergoing sinus surgery for concha bullosa (n = 8) | Independent of disease state, the levels of H3K27ac at PTGER2 were variable (in contrast to the H3K27ac at PTGER4 that were constant across samples) and correlated significantly with EP2 receptor expression (PTGER2 mRNA levels). After HDACi (TSA) treatment, PTGER2 mRNA levels increased in fibroblasts obtained from subjects with AERD or aspirin-tolerant controls but not in those from healthy controls. |
| Marwick et al. [69]           | Analysis of oxidant-associated inflammation (such as observed in severe asthma)-induced H3S10ph at promoters of inflammatory genes on the anti-inflammatory effect of corticosteroids (CS) | The induction of H3S10ph at promoters of the IL6, CCL2, and CXCL8 in alveolar macrophages from severe asthmatic patients was not reduced by CS. Application of a selective p38α MAPK inhibitor, SB239063, and IKK-2 inhibitor, TPAC-1, resulted in reduced induction of H3S10ph; this inhibitory effect was even stronger when SB239063 or TPAC-1 were combined with CS. |
| Borriello et al. [68]          | Analysis of the effect IL-3 and IL-4 on STAT5 and STAT6 (respectively) binding and H3ac at the COX2 locus, encoding CCL17, a marker of the alternative activation of human monocytes | IL-3 and IL-4 together increased H3ac at CCL17 locus. IL-4 alone but not in combination with IL-3 induced STAT6 binding at the CCL17 locus. No identifiable STAT5 binding at the CCL17 locus was observed. |
| Harb et al. [72]               | Comparison of H3ac and H4ac levels at Th1, Th2 and Treg-cell-related genes in isolated CD4+ T-cells obtained from children with allergic asthma (n = 14) and form healthy control children (n = 18) | Higher H3ac and H4ac levels at the IL13 locus observed in children with allergic asthma when compared to healthy controls. This difference correlated with higher IL-13 protein levels in supernatants of anti-CD3/CD28-stimulated PBMCs of allergic asthmatic children compared with healthy controls. The levels of H3ac at the FOXP3 locus were higher in allergic asthmatics than in healthy controls. |
| Clifford et al. [54]          | Comparison of ASMCs H3ac and H4ac, H3K9me2/3, H3K4me2/3, and DNA methylation levels at the CXC2 promoter between asthmatic (n = 7) and non-asthmatic subjects (n = 6) | No differences in H4ac, H3K9me2/3 and H3K4me2/3 or in DNA methylation levels were detected between asthmatic and non-asthmatic subjects. However, significantly higher H3ac levels, specifically H3K18ac, and higher binding of bromodomain-containing HATs, p300 and PCAF, were observed in asthmatics. BET inhibitors reduced CXC2 secretion |
| Perry et al. [55]             | Analysis of the effect of BET bromodomains on the TGF-β-induced proliferation and cytokine release in ASMCs from healthy (n = 9), non-severe asthmatic (n = 9), and severe asthmatic (n = 9) subjects | An inhibition of FCS-β-inducible cell proliferation as well as IL-6 and CXC2 expression (IL6 and CXC2 mRNA levels, and IL-6 and CXC2 protein release) after treatment with BET bromodomain mimics JQ1/GCB801 and I-BET762 was observed. A higher concentration of both mimics was needed depending on the asthma severity |
| Study                  | Major epigenetic aims                                                                                                                                                                                                 | Major epigenetic results                                                                                                                                                                                                 |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comer et al. [56]     | Comparison of H3ac and H4ac levels at the COX2 locus in ASMCs obtained from asthmatic (n=7) and non-asthmatic subjects (n=5) before and after treatment with cytokim (IL-1β, TNF-α, and IFN-γ) | No differences in histone acetylation between the asthmatic and non-asthmatic ASMCs were detected. Moreover, no differences in histone acetylation were observed after the cytokim treatment in both groups. Higher COX-2 protein levels were found in asthmatics, most likely due to posttranslational regulation (miR-155) |
| Seumois et al. [73]   | Comparison of global H3K4me2-marked cis-regulatory regions in naïve, Th1, and Th2 CD4+ T-cells obtained from asthmatic (n=12) and non-asthmatic subjects (n=12)                                                                 | Differential enrichment of H3K4me2 was observed in 200 enhancer regions in the three cell types when comparing asthmatic vs. non-asthmatic subjects. 163 of 200 asthma-associated enhancers were Th2-specific and 84 of them contained binding sites for transcription factors involved in T-cell differentiation (e.g. GATA3, TBX21 and RUNX3) |
| Zhang et al. [67]     | Analysis of the anti-inflammatory and steroid-enhancing effects of vitamin D in monocytes obtained from patients with steroid-resistant (SR; n=11) and with steroid-sensitive (SS; n=8) asthma | Significant increase in H4ac levels at the glucocorticoid response element upstream of the DUSP1 locus (encoding for MKP-1) occurred after treatment of the monocytes obtained from both SS and SR patients with dexamethasone. Preincubation with calcitriol resulted in a significant enhancement in the dexamethasone-mediated H4ac. Higher H4ac was observed in SS patients than in SR patients |
| Kobayashi et al. [85] | Analysis of the effect of passive smoking on HDAC2 expression and activity and on corticosteroid sensitivity in alveolar macrophages (AMs) obtained from children with severe asthma exposed (n=9) or not exposed (n=10) to passive smoking | Significantly lower HDAC2 protein expression and HDAC2 activity in passive smoking-exposed group. Higher levels of phosphorylation of Akt1 in AMs of the passive smoking-exposed group correlated negatively with HDAC2 activity. Significant inhibition (40%) of the TNFa-induced CXCL8 production in AMs from subjects not exposed to passive smoking after treatment with dexamethasone was observed. In contrast, no significant inhibition was detected in AMs from passive smoking-exposed subjects |
| Cho et al. [63]       | Analysis of the effect of HDACi (TSA) on myofibroblast differentiation and extracellular matrix (ECM) accumulation in nasal polypsis (18 patients)                                                                           | Suppression of the TGF-β1-induced myofibroblast differentiation and ECM production after treatment with TSA was observed (α-SMA, fibronectin, and collagen type I expression was diminished). This was due to decreased expression of both HDAC2 and HDAC4 and increased histone four acetylation |
| Clifford et al. [57]  | Comparison of H3ac and H4ac, H3K4me3, H3K9me3, and DNA methylation levels at the VEGFA promoter in ASMCs obtained from asthmatic (n=7) and non-asthmatic (n=6) subjects                                                   | No differences in the DNA methylation or H3ac or H4ac at the VEGFA locus were identified between asthmatic and non-asthmatic subjects. Nevertheless, slightly but consistently higher H3K4me3 (a mark associated with transcription activation) levels and much lower H3K9me3 (marked associated with transcription repression) levels were detected in ASMCs obtained from asthmatic subjects. The low H3K9me3 was an aftermath of abortive recruitment of G9a in asthmatic ASMCs. After treatment with BIX-01294, a histone methyltransferase (HMT) G9a inhibitor, VEGF expression increased in cells obtained from non-asthmatics to near asthmatic levels |
| Cho et al. [64]       | Analysis of the effect of HDACi (TSA) on myofibroblast differentiation and ECM accumulation in nasal polypsis (7 patients with chronic rhinosinusitis with nasal polyps vs. normal inferior turbinate tissues) | Increased expression (mRNA/protein) of HDAC2, α-SMA and TGF-β1 was observed in nasal polyp tissues. In addition to its suppressive effect on the TGF-β1-induced myofibroblast differentiation and ECM production (α-SMA and collagen type I expression was diminished after TSA treatment), TSA also reversed TGF-β1-induced morphological changes in nasal polyp-derived fibroblasts (NPDFs). Inhibition of the HDAC2 expression and increased H3ac and H4ac were also a TSA application aftermath. Inhibiting HDAC2 with siRNA had a similar effect to TSA. The TSA suppressive effect was produced by inhibiting the TGF-β1-induced phosphorylation and translocation of Smad2/3 (to nucleus). Moreover, TSA blocked NPDFs proliferation with no cytotoxic effects |
### Table 2 (continued)

| Study         | Major epigenetic aims                                                                 | Major epigenetic results                                                                                                                                 |
|---------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kuo et al. [101] | Analysis of the effect of iloprost, a prostaglandin I2 (PGI2) analog, on the expression of TNF-α in human myeloid dendritic cells (mDCs) obtained from 6 healthy subjects via histone modifications | Downregulation of the poly I:C-induced H3K4me3 in the TNF promoter region was observed after treatment with iloprost. This suppressive effect was produced by inhibiting the poly I:C-induced translocation of H3K4-specific methyltransferase MLL (mixed lineage leukemia) and WDR5 (WD repeat domain 5) proteins from the cytoplasm to the nucleus. |
| Yang et al. [65] | Analysis of the effect of TGF-β on the ADAM33 mRNA expression and ADAM33 protein in bronchial fibroblasts obtained from asthmatic (n = 7) and healthy (n = 6) subjects during their differentiation into myofibroblasts via histone modifications | Although no difference in transcript levels of ADAM33 between asthmatic and healthy control cells was detected, a suppression of ADAM33 mRNA expression after treatment with TGF-β was observed. This was caused by chromatin condensation at the ADAM33 promoter via histone modification (deacetylation of H3ac, demethylation of H3K4, and hypermethylation of H3K9) and not by DNA methylation. Stimulation of ADAM33 ectodomain shedding was also caused by TGF-β. |

For criteria of the selection, please, refer to Fig. 1 and “Systematic search: methodology” section of “Main text.”

α-SMA, denotes alpha smooth muscle actin; ADAM33, ADAM metallopeptidase domain 33 (ADAM33) gene; ASMC, airway smooth muscle cell; Akt1, RAC-alpha serine/threonine-protein kinase; BET, bromodomain and extra-terminal (proteins); CCL2/17, C–C motif chemokine ligand 2 (CCL2/17) gene; CB, cord blood; COX2, cytochrome c oxidase subunit II (COX2) gene; CXCL8/10, C–X–C motif chemokine ligand 8/10 (CXCL8/10) gene; DUSP1, dual specificity phosphatase 1 gene; EGFR, epidermal growth factor receptor (EGFR) gene; FCS, fetal calf serum; FOXP3, forkhead box P3 (FOXP3) gene; G9a, euchromatic histone-lysine N-methyltransferase 2; GATA3, GATA binding protein 3 (GATA3) gene; HAT, histone acetyltransferase; HDAC, histone deacetylase (HDAC) inhibitor; IFNG, interferon gamma (IFN-γ) gene; IKK-2, IκB kinase 2; IL-1β, interleukin 1 beta; IL6/9/13, interleukin 6 (IL-6/-9/-13) gene; MAPK, p38 mitogen-activated protein kinase; MKP-1, MAPK phosphatase 1; p300, E1A binding protein p300; PBMC, peripheral blood mononuclear cell; PCAF, P300/CBP-associated factor; PRKCZ, protein kinase C zeta (PKCζ) gene; PTGER2/4, prostaglandin E receptor 2/4 (EP2/4) gene; RUNKL, runt-related transcription factor 3; STAT1/3/5/6, signal transducer and activator of transcription 1/3/5/6; TBX21, T-box 21 (TBX21) gene; TGF-β, transforming growth factor beta; Th1/2/17, cells, helper T-cells/T-helper cells type 1/2/17; TNF, tumor necrosis factor (TNF-α) gene; TP63, tumor protein p63 (TP63) gene; Treg, cells, regulatory T-cells; TSA, trichostatin A; VEGFA, vascular endothelial growth factor A (VEGF) gene

For the remaining abbreviations please refer to Table 1.
Zheng et al. [103] After treatment with TSA, a significant increase of the (lower) transcription of STAT3-dependent genes (Zhong et al. [102] Significantly decreased expression of Th2-related cytokines (IL-4, IL-5) in human CD4+ T-cells and PBMCs was observed after treatment with chemically synthesized PIWI interacting RNA (piRNA), piR30840. Accordingly, antisense inhibition of the endogenous piR30840 resulted in CD4+ T-cells with upregulated IL-4 expression. As no differences in histone methylation levels at the IL-4 promoter region between piR30840-transfected and -untransfected CD4+ T-cells were detected, the functioning of piR30840 was not attributed to this type of histone modification but rather to pre-mRNA decay through nuclear exosomes

Zheng et al. [103] After treatment with TSA, a significant increase of the (lower) transcription of STAT3-dependent genes (IL-17A and IL-22) in IL-23-stimulated PBMCs from chronic mucocutaneous candidiasis (CMC) patients (n = 16) (back) to control (n = 37) levels was observed. Conversely, TSA significantly decreased the enhanced transcription of STAT1-dependent genes (CXCL10 and IRF1) in IFN-γ-stimulated gain-of-function STAT1-mutation Epstein-Barr virus (EBV)-transformed B cell line back to control levels

Vicente et al. [104] Noticeable regulatory activity characterized by H3K4me1/2 peak identified four putative regulatory elements (PREs) in the 8q21 core region of genetic association (with allergies) in lymphoblastoid cell lines. Significant correlation between the allergy-associated SNP rs7009110 located on the 8q21 and PAG1 expression

Naranbhai et al. [105] Significant enrichment of peak cis-eQTL was detected in DNA-hypomethylated regions, and in regions marked by H3K4me3 (associated with promoter activity), H3K27ac and H3K4me1 (associated with active or poised enhancers), and H3K36me3 (associated with gene activation) in neutrophils. Correspondingly, a depletion of peak cis-eQTL was observed in DNA-hypermethylated regions and in regions marked by H3K27me3 and H3K9me3 (repressive histone modifications). A SNP rs2240335, an eQTL in PAD4 (a locus associated with rheumatoid arthritis), was shown to be located within regions marked by H3K27ac and H3K4me1

Lin et al. [106] Increased H4ac levels at the VCAM1 promoter region correlating with higher VCAM1 expression (protein/mRNA) and promotor activity in human tracheal smooth muscle cells were observed upon pretreatment with ET-1, mediated via Elk-1/p300 interaction, in an ET receptor/Src/RTK/PI3K/AKT/p42/p44 MAPK-dependent manner

Castellucci et al. [70] Abolition of the IL-10-mediated deacetylation of H4ac at the CXCL8 promoter in LPS-stimulated monocytes was observed after Cl-994, a class I HDACi, treatment. Concordantly, IL-10-mediated inhibition of CXCL8 transcription in LPS-stimulated PBMCs obtained from COPD patients (n = 6), due to reduced HDAC2 expression, was dampened compared to acute respiratory failure patients (n = 4) and healthy controls (n = 6)

Hsieh et al. [71] Noticeable suppression of the LPS-induced MDC/CCL2 expression in THP-1 cells (human monocyte cell line) and human primary monocytes was observed after treatment with sesamin, a class of phytoestrogen isolated from sesame seed Sesamum indicum, due to dampened recruitment of a HAT, CREBBP, and a subsequent decrease in H3ac and H4ac levels at the CCL2 promoter

Sharma et al. [107] Significant enrichment of active histone marks H3K4me1 and H3K27ac at the regions near to two asthma-associated SNPs in the FADS2 rs968567 and the NAGA (rs1801311) loci was observed in three different cell lines: Jurkat (human T lymphocyte cell line), Beas-2B (human bronchial epithelial cell line) and A549 (human lung epithelial cell line). Consistently, both SNPs showed significant enrichment of formaldehyde-assisted isolation of regulatory elements (FAIRE) signals in all three cell lines

Escobar et al. [108] Markedly increased Jumonji, AT Rich Interactive Domain 2 (Jarid2), a DNA-binding protein that recruits the polycomb gene family accompanied with increased expression of the histone demethylase JMJD3. JMJD3 knockdown with siRNA led to an increase in H3K27me3 levels and lower AMP production

Huber et al. [74] Significantly elevated levels of the repressive H3K27me3 mark at the conserved noncoding sequence (CNS-1) located 5 kb upstream of exon 1A of the GATA3 gene in primary naive human CD4+ T-cells after treatment with IFN-α (both, with or without IL-4 co-stimulation) were observed, resulting in a consequential inhibition of GATA3 binding to exon 1A (i.e. down-regulation of a positive-feedback loop of GATA3/GATA3 autoregulation and thus reduced gene expression)

Gschwandtner et al. [109] When compared to both neonatal and adult human keratinocytes (KC), fetal human KCs produced more AMPs, and had lower global H3K27me3 levels and higher expression of a histone demethylase JMJD3. JMJD3 knockdown with siRNA led to an increase in H3K27me3 levels and lower AMP production

Coward et al. [58] Markedly increased H3K9me3 and H3K27me3 levels at the COX2 promoter were detected in primary human fibroblasts from IPF lung (stimulated or not with the COX2 inducer, IL-2β) when compared to fibroblasts from non-fibrotic lung, which were related to the recruitment of HMTs, G9a and EZH2. Substantially decreased H3K9me3 and H3K27me3, and increased H3ac and H4ac levels at the COX2 promoter resulting in COX2 mRNA and protein re-expression were observed in fibroblasts from IPF lung after treatment with G9a or EZH2 inhibitors (more significant effect with IL-2β stimulation)

Sanders et al. [59] Markedly increased H3K9ac and decreased H3K9me3 at the pro-apoptotic BAK1 gene accompanied with increased expression (mRNA) and substantially decreased H3K9ac and increased H3K9me3 levels at the anti-apoptotic BCL2L1 gene accompanied by a decrease in gene expression (mRNA) were observed in primary human IPF fibroblasts after treatment with a HDACi, SAHA

Han et al. [110] Significantly reduced H3K27me3 levels at the ALOX15 promoter were detected in AS49 cells after treatment with IL-4, coinciding with higher ALOX15 mRNA levels. More potent induction of ALOX15 was observed in human monocytes. Significant increase in H3K27me3 levels after depletion of a lysine demethylase UTX (with siRNA) was observed, resulting in reduced IL-4-induced ALOX15 expression. Inhibition of the IL-4-mediated ALOX15 expression in UTX-depleted human monocytes with no changes in the H3K27me3 levels when compared to control monocytes was found
### Table 3 (continued)

| Study | Major epigenetic findings (in the context of major study results) |
|-------|---------------------------------------------------------------|
| Lakshmi et al. [111] | Markedly reduced expression of PPARy correlated with downregulated HDAC2 expression in lung and human bronchial epithelial cells (HBE) obtained from COPD patients compared with healthy controls. Noticeable suppressed GR-α expression in H292 cells (human lung epithelial cell line) after CSE treatment due to dampened expression of PPARy and HDAC2 was also observed. The suppressive effect of CSE on GR-α and HDAC expression was attenuated with PPARy agonists |
| Zhang et al. [60] | Downregulation of COL3A1 expression in primary human IPF myofibroblasts with concomitant increases of H3ac, H4ac, H3K9ac, and H3K27me3 levels at COL3A1 promoter was observed after SAHA treatment |
| Wiegman et al. [112] | Significantly increased HAT activity levels and decreased HDAC2 activity levels (due to protein modification: nuclear phosphorylation and cytoplasmic carbonylation) were observed in lung extracts obtained from mice after ozone exposure compared to air-exposed animals |
| Che et al. [113] | Inhibition of the sphingosine-1-phosphate (S1P)-induced IL-6 secretion by primary human ASMCs via MKP-1-mediated repression of MAPK-driven activation of mitogen and stress-activated protein kinase 1 (MSK1) and phosphorylation at H3510 (H3S10ph; global, putatively at IL6 promoter as well) was observed after the treatment of the cells with demethylase |
| Liu et al. [61] | Significantly higher H3K9ac levels at the TERT promoter region were detected in primary human lung fibroblasts from patients with IPF (n = 70) compared with healthy control subjects (n = 117). After treatment of the cells with a HDACi (TSA), significantly elevated TERT mRNA and TERT protein levels (time and dose-dependent increase) were detected in both human lung fibroblasts from patients with IPF and mouse lung fibroblasts from a murine model of bleomycin-induced pulmonary fibrosis |
| Gerasimova et al. [75] | Noticeable enrichment of asthma-associated non-coding SNPs and H3K4me1 peaks (enhancers) in the Th2 cytokine locus of CD4+ T-cells (when compared with other cell/tissue types) was observed |
| Li et al. [76] | Significantly decreased LAT expression consistent with decreased H3ac and H4ac levels and increased H3K9me2 levels at the LAT (Lat) upstream region in lung T-cells obtained from ovalbumin-induced allergic airway inflammation rat model when compared with control animals were found. H3ac and H4ac as well as LAT expression noticeably increased after treatment of the cells with TSA |
| Luo et al. [77] | Increased global H3ac and H3K4me levels were observed in PBMCs of HSP patients with kidney damage (n = 16) compared to HSP patients without kidney damage (n = 8) and healthy controls (n = 22). Higher CD4+ T-cell H3ac and H3K4me levels were detected at IL4 regulatory regions of HSP patients when compared to control subjects. Higher expression (mRNA) of several HATs (CREBBP, PCAF, and p300) and HMTs (SETD1A, SETD81, SUV39H1, and SUV39H2) and lower expression of a few HDACs (HDAC1, HDAC2, HDAC3, and SIRT1) were found in PBMCs of both HSP groups compared to healthy controls |
| Kallsen et al. [114] | Markedly increased H3ac and H3K4me3 levels at the DEFB1 promoter in A549 cells coinciding with enhanced DEFB1 expression after treatment with class I HDACi (MS-275) were found |
| Han et al. [78] | Noticeable DNA hypomethylation at 26 unique regions (10–70 kb) was found in naive CD4+ T-cells obtained from psoriasis patients (n = 12) compared to atopic dermatitis patients (n = 15) and healthy controls (n = 10). These regions coincided incidentally with various strong epigenomic signals, including histone modifications (H3K4me1, H3K27ac, and H3K4me3), and transcription factor binding sites |
| Robertson et al. [115] | Significantly increased HDAC activity (only at the protein level) was observed in ARNT-depleted N-TERT keratinocytes (15–20% increase) and in ARNT-depleted immortalized human HaCaT keratinocytes (~50% increase). After treating ARNT-depleted N-TERT keratinocytes with TSA, the negative effect of ARNT-deficiency on transcription of amphiregulin gene (AREG), an important ligand of EGFR, was abolished |
| Vazquez et al. [116] | A novel inducible hypersensitive region was identified in human and mouse lymphocytes that is located in intron 1 of CD69, H3K4me2, H3ac, H3K14ac, and/or H3K4ac levels within this region were found to be dynamically regulated during thymocyte development and/or to be constitutively high in mature T lymphocytes |
| Zijlstra et al. [117] | Reduced glucocorticoid sensitivity and dampened HDAC activity were observed in 16HBE cells (human bronchial epithelial cell line) after treatment with IL-17A. Overexpression of HDAC2 reversed IL-17A-induced glucocorticoid insensitivity |

For criteria of the selection, please, refer to Fig. 1 and “Systematic search: methodology” section of “Main text”.

ALOX15, arachidonate 15-lipoxygenase (ALOX15) gene; AMP, antimicrobial peptide; ARNT, aryl hydrocarbon receptor nuclear translocator; BAK1, BCL2 antagonist/killer (Bak) gene; Bcl-xL, B-cell lymphoma-extra large (Bcl-xL) gene; CBP, CREB binding protein; COL3A1, collagen type III alpha 1 chain (COL3A1) gene; COPD, chronic obstructive pulmonary disease; CREBBP, CREB binding protein; CSE, cigarette smoke extract; DEFB1, defensin beta 1 (DEFB1) gene; eQTL, expression quantitative trait loci; Elk-1, ETS transcription factor; ET-1, endothelin-1, E2H2, enhancer of zeste 2 polycomb repressive complex 2 subunit; FAD2, fatty acid desaturase 2 (FAD2) gene; GR-α, glucocorticoid receptor alpha; HMT, histone methyltransferase; HSP, Henoch-Schönlein purpura; IL17A/22, interleukin 17A/22 (IL17A/22) gene; IL9/10/22, mouse interleukin 9/10/20 (IL-9/10/20) gene; IL23/2β, interleukin 23/2β; INF-α, interferon alpha; IPF, Idiopathic pulmonary fibrosis; IRF1, interferon regulatory factor 1; LAT, linker for activation of T-cells; MDC/CCL22, macrophage-derived chemokine/C-C motif chemokine ligand 22 (CCL22) gene; NAGA, alpha-N-acetylgalactosaminidase (NAGA) gene; PADI4, peptidylarginine deiminase 4 (PADI4) gene; PAG1, phosphoprotein membrane anchor with glycosphingolipid microdomains 1 (PAG1) gene; PCAF, lysine acetyltransferase 2B; P30K, phosphoprotein membrane anchor with glycosphingolipid microdomains 1 (PAG1) gene; PPARγ, peroxisome proliferator activated receptor gamma; RTR, Receptor tyrosine kinase; SNA, suberoylanilide hydroxamic acid; sIRNA, small interfering RNA; SNP, single-nucleotide polymorphism; Src, SRC proto-oncogene, non-receptor tyrosine kinase; TERT, telomerase transcriptase (TERT) gene; VCAM1, vascular cell adhesion molecule 1 (VCAM1) gene; For the remaining abbreviations please refer to Tables 1 and 2
factors and thus cell cycle regulation, and DNA replication and repair [25, 26]. Moreover, these enzymes have been recently identified to be important for centrosome function as well [27]. The MYST family is in turn composed of KAT6A/MOZ/MYST3, KAT6B/MORF/MYST4, KAT7/HBO1/MYST2, KAT8/hMOF/MYST1, and KAT5/Tip60. It contributes to transcription regulation and is also responsible for DNA repair [28–30]. Interestingly, autoacetylation of MYST family protein enzymes participates in their regulation, which makes them distinct from other acetyltransferases, drawing at the same time similarities to the phosphoregulation of protein kinases [31, 32]. The other HAT families are much smaller. KAT3A and KAT3B enzymes belong to p300/CBP family, and KAT4/TAFI1/TBP and KAT12/TIFIIIC90 are members of the general transcriptional factor-related HAT family [23, 28, 33]. Steroid receptor co-activators family comprises KAT13A/SRC1, KAT13B/SCR3/AIB1/ACTR, KAT13C/p600, and KAT13D/CLOCK [23, 34]. Finally, KAT1/HAT1 and HAT4/NAAl60 are cytoplasmatic HATs [23].

Eighteen enzymes belonging to the HDAC superfamily have been identified. They are further subdivided into four classes, including class I (HDAC1, HDAC2, HDAC3, and HDAC8), class IIa (HDAC4, HDAC5, HDAC7, and HDAC9), class IIb (HDAC6 and HDAC10), class III, so-called sirtuins (SIRTs; SIRT 1–7; enzymes evolutionally related to yeast Sir2p), and class IV (HDAC11) [35–37]. Class I HDACs are characterized by a ubiquitous nuclear expression in all tissues, class IIb HDACs are present both in the nucleus and cytoplasm, and class IIa HDACs show mainly cytosolic localization. Not much is known about HDAC11, and sirtuins which localize in nucleus, cytosol and/or mitochondria [36].

**Histone methylation**

Histone methylation is mediated by histone methyltransferases (HMTs), including lysine methyltransferases (KMTs) and arginine methyltransferases (PRMTs), and histone demethylation by histone demethylases (HDMs).

Whereas acetylation of the histone lysine affects the electrical charge of the histones and thus their interaction with DNA, methylation of histone lysine or arginine does not affect this electrostatic bond, but instead indirectly influences the recruitment and binding of different regulatory proteins to chromatin [19, 38, 39]. KMTs can transfer up to three methyl groups from the cofactor S-adenosyl-l-methionine (SAM) to lysine or arginine residues of the histones [19, 38]. More than 50 human KMTs are known at the moment, which, based on their catalytic domain sequence, can be further subdivided into the SET domain-containing and the DOT1-like protein family, the latter having only one representative in humans, with a catalytic domain structurally more similar to the PRMTs [19, 38, 39]. KMTs are more specific than HATs and they generally target a specific lysine residue. Methylation of H3K4 residue (for the description of histone modifications including their location, character and effect on transcription, please, refer to Table 1) is mediated in mammals by KMTs such as KMT2A/MLL1, KMT2A/MLL2, KMT2F/hSET1A, KMT2G/hSET1B, or KMT2H/ASH1. Examples of KMTs responsible for H3K9 methylation include KMT1A/SUV39H1, KMT1B/SUV39H2, KMT1C/G9a, or KMT1D/EuHMTase/GLP. H3K36 methylation is catalyzed by e.g. KMT3B/NSD1, KMT3C/SMYD2, or KMT3A/SET(D)2. KMT6A/EZH2 methylates H3K27, and KMT4/DOT1L targets H3K79. Etc. [19, 38, 39].

Based on the catalytic mechanism and sequence homology, HDMs can be divided into two classes. Firstly, amine-oxidase type lysine-specific demethylases (LSDs or KDM1 s), including KDM1A/LSD1/AOF2 and KDM1B/LSD2/AOF1. These remove the methyl groups from mono- and dimethylated H3K4. Secondly, the JumonjiC (JMC) domain-containing HDMs, in turn, catalyze the demethylation of mono-, di-, and trimethylatedlysine residues at various histone amino acid residues. Over thirty members of this group can be further subdivided, based on the JMC domain homology, into seven/eight subfamilies (KDM2–7/8) [19, 38–41].

**Histone phosphorylation**

Histone phosphorylation status is controlled by two types of enzymes having opposing modes of action. While kinases add phosphate groups, phosphatases remove the phosphates [13, 15]. At least three functions of phosphorylated histones are known, DNA damage repair, the control of chromatin compaction associated with mitosis and meiosis, and the regulation of transcriptional activity (similar to histone acetylation) [13, 15]. In comparison to histone acetylation and methylation, histone phosphorylation works in conjunction with other histone modifications, establishing the platform for mutual interactions between them. This cross-talk results in a complex downstream regulation of chromatic status and its consequences [13, 15, 42]. For example, histone H3 phosphorylation (specifically H3S10ph) can directly affect acetylation levels at two amino acid residues of the same histone (H3K9ac and H3K14ac) [43, 44]. Furthermore, H3S10ph can induce transcriptional activation by interaction with H4K16ac [42].
Histone ubiquitination
Protein ubiquitination is an important post-translational modification that regulates almost every aspect of cellular function in many cell signaling pathways in eukaryotes. Ubiquitin is an 8.5 kD protein which is conjugated to substrate proteins by the ubiquitin–proteasome system thereby regulating the stability and turnover of the target proteins. Histone ubiquitination is carried out by histone ubiquitin ligases and can be removed by ubiquitin-specific peptidases, the latter known as deubiquitinating enzymes (DUBs) [45–47]. Monoubiquitination has a critical role in protein translocation, DNA damage signaling, and transcriptional regulation. Histone 2A monoubiquitination (H2Aub) is more often associated with gene silencing. Monoubiquitination of histone 2B (H2Bub) is typically correlated with transcription activation. Polyspecific ubiquitination marks the protein for degradation or activation in certain signaling pathways [45–48]. Similarly to histone phosphorylation, there is also crosstalk between histone ubiquitination and other histone modifications [46–48]. For instance, monoubiquitination of histone H3 is able to induce acetylation of the same histone [49].

Epigenetic readers
In addition to epigenetic writers, i.e. enzymes adding epigenetic marks on histones (HATs, HMTs/KMTs, PRMTs, kinases, ubiquitin ligases) and epigenetic erasers (HDACs, HDMs/KDMs, phosphatases, DUBs), there are also epigenetic readers, which are the molecules that recognize and bind to the epigenetic marks created by writers, thereby determining their functional consequences. They include proteins containing bromodomains, chromodomains, or Tudor domains [50, 51]. Some enzymes with primary activities different from epigenetic reading possess bromodomains as well, for example certain HATs [51].

Systematic search: methodology
In order to cover the area of interest, a systematic literature search was conducted (Fig. 1). In brief, On January 23, 2017, the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) was searched by using the input “(allergy OR atopy OR asthma OR dermatitis OR eczema OR food allergy OR rhinitis OR conjunctivitis) AND (histone modifications OR histone modification OR histone acetylation OR histone methylation OR histone phosphorylation OR histone ubiquitination)”, restricting the results with “5 years” (“Publication dates”) and “Humans” (“Species”) filters, which yielded a total of 170 hits. These were subsequently subjected to full text-based screening to exclude articles not reporting original data (reviews, editorials, commentaries, etc.), which resulted in elimination of 54 publications. From the remaining 116 papers, a further 72 were excluded as not being directly or at least indirectly relevant to the topic of the present review (not reporting data on histone modifications, reporting histone modification data but not in the context of allergic or related disorders, or both). The remaining 44 articles were divided into two groups. The group that met the primary selection criterion contained 17 papers reporting the data on the role of histone modifications in allergic diseases obtained in material collected from allergic subjects and thus directly relevant to allergies is presented in Table 2. Another 27 articles of potential interest comprised the additional group (Table 3). These did not necessarily target allergic disorders but allergy-like diseases or related conditions, did not report histone modification data obtained in primary human cells/tissues, or indeed a combination of those. This included also those reporting data on epigenetic mechanisms likely playing a role in allergies but not directly related to/associated with this group of diseases.

Systematic search: review
Epigenetic mechanisms are thought to play an important regulatory role in allergic inflammation and the development of allergic disorders. DNA methylation is the classical epigenetic modification that has been most widely studied in this context. However, histone modifications, which contribute to the lineage commitment, differentiation and maturation of immune cells, including those strongly involved in allergic inflammation such as CD4+ T-helper (Th) cells, are likely to play a crucial role in the predisposition to developing atopic diseases as well as in the effector phase of allergic inflammation [5, 6, 10, 52, 53]. Indeed, our systematic search identified a number of recent studies that sought to define the relationships between histone modifications and allergic inflammation or related immune mechanisms, and/or allergic diseases or disorders sharing some of the pathophysiology. The results reported in those 44 original articles are summarized in Tables 2 and 3.

Several studies investigated the relationships between histone modifications in airway smooth muscle cells (ASMCs) and the respiratory tract allergic inflammatory disease. For instance, increased binding of bromodomain-containing HATs [E1A binding protein p300 (p300) and p300/CREBBP-associated factor (PCAF)] accompanied by significantly higher H3ac levels (specifically H3K18ac) at the C–X–C motif chemokine ligand 8 (CXCL8) gene (CXCL8) promoter were observed in ASMCs obtained from asthmatics compared to healthy controls [54]. Furthermore, treatment of cultured cells with bromodomain and extra-terminal (BET) protein inhibitors reduced CXCL8 secretion [54]. The application of BET
PubMed search:
i. For “(allergy OR atopy OR asthma OR dermatitis OR eczema OR food allergy OR rhinitis OR conjunctivitis) AND (histone modifications OR histone modification OR histone acetylation OR histone methylation OR histone phosphorylation OR histone ubiquitination)”
ii. Using “5 years” (“Publication dates”) and “Humans” (“Species”) filters
iii. On January 23, 2017

Excluded if:
i. Not reporting original data (reviews, editorials, commentaries, etc.)

Excluded if:
i. Not reporting data on histone modifications
ii. Reporting histone modification data but not in the context of allergic or related disorders
iii. Combination of those reasons

Finally included
44 Records

As meeting primary criterion (Table 2) if:
i. Reporting the data on the role of histone modifications in allergic diseases obtained in (martialis collected from) allergic subjects

As meeting secondary criteria (Table 3), of potential interest though:
i. Not really targeting allergic diseases but allergy-like disorders or related conditions
ii. Not reporting the histone modification data obtained in primary human cells/tissues
iii. A combination of those
iv. Reporting data on epigenetic mechanisms (likely) playing a role in allergies but not directly related to/associated with this group of diseases
v. Others

Fig. 1 Strategy of systematic literature search and its results
bromodomain mimics reduced in turn fetal calf serum plus transforming growth factor beta (TGF-β) -induced ASMC proliferation and interleukin 6 (IL-6) gene (IL6) and CXCL8 expression, with the required dose depending on asthma severity of cell donor [55]. On the other hand, no differences in H3ac and H4ac levels at the cytochrome c oxidase subunit II (COX2) gene (COX2) between the asthmatic and non-asthmatic ASMCs were detected, regardless of whether they were stimulated with proinflammatory cytokines [56]. Although asthmatic and non-asthmatic ASMCs did not differ in their H3ac or H4ac levels at the vascular endothelial growth factor A (VEGF) locus (VEGFA), the cells obtained from affected individuals displayed slightly but consistently higher H3K4me3 and a low H3K9me3 levels [57]. Moreover, treatment with an inhibitor of a HMT (HMTi), euchromatic histone-lysine N-methyltransferase 2 (G9a), increased VEGF expression in non-asthmatic ASMCs to near asthmatic levels [57].

Histone modifications at several of the above-mentioned loci contribute also to the pathophysiology of some other inflammatory disorders of the lung. For example, H3K9me3 and H3K27me3 levels at the COX2 promoter were found to be substantially higher in primary human fibroblasts isolated from lung tissue of idiopathic pulmonary fibrosis (IPF) patients compared to non-IPF fibroblasts. This was accompanied by the recruitment of HMTs, G9a and enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) [58]. Interestingly, after treatment with G9a or EZH2 inhibitors, the levels of H3K9me3 and H3K27me3 markedly decreased and H3ac and H4ac levels increased at the COX2 promoter [58]. Several other studies observed the involvement of histone modifications in the regulation of gene expression in (human) IPF lung (myo-) fibroblasts, the effects of which were sensitive to HDAC inhibitor (HDACi) treatment [59–61]. Histone acetylation and/or methylation in (myo-) fibroblasts were also demonstrated to regulate expression of the loci involved in the pathogenesis of nasal chronic rhinosinusitis and polyposis, such as prostaglandin E receptor 2 (EP2) gene (PTGER2) [62]. Furthermore, HDACi treatment influenced HDAC expression and histone acetylation at several loci, thus affecting nasal polyp myofibroblast differentiation and extracellular matrix production [63, 64]. Finally, although no differences in ADAM metalloproteinase domain 33 (ADAM33) gene (ADAM33) expression were observed between asthmatic and healthy control bronchial fibroblasts, treatment with TGF-β suppressed ADAM33 mRNA expression through chromatin condensation related to deacetylation of H3ac, demethylation of H3K4, and hypermethylation of H3K9 at the ADAM33 promoter [65]. Asthmatic and non-asthmatic histone acetylation levels were compared also in alveolar epithelial cells [66]. Global H3K18ac and H3K9me3 levels were higher in cells from asthmatics, which was also the case for gene-specific H3K18ac (but not H3K9me3) around transcription start sites of the loci encoding tumor protein p63 (TP63; ΔNp63 isoform), epidermal growth factor receptor (EGFR), and signal transducer and activator of transcription 6 (STAT6) [66]. The latter effect was ablated upon HDACi treatment [66].

Several studies were conducted on the biology of monocytes, the mechanisms of epigenetic modulation controlling production of cytokines, and their role in the onset/severity of allergic diseases. H4ac levels at the glucocorticoid response element upstream of the dual specificity phosphatase 1 gene (DUSP1) encoding for MAPK phosphatase 1 (MKP-1) substantially increased in dexamethasone-treated cells obtained from both steroid-sensitive and steroid-resistant asthmatics patients [67]. Furthermore, preincubation with calcitriol led to a significant enhancement of the dexamethasone-induced H4ac, with higher H4ac levels observed in monocytes obtained from steroid-sensitive than those from steroid-resistant individuals [67]. The involvement of histone acetylation or phosphorylation in regulation of gene expression in monocytes/macrophages was also demonstrated for C–C motif chemokine ligand 2/17/22 (CCL2/17/22), CXCL8, or IL6 loci [68–71]. In addition, in monocytes, histone modification changes were susceptible to pharmacological modification ex vivo, demonstrated by the effect of HDACi on CXCL8 H4ac levels [70].

Several studies have focused on T-cells. For example, differences in H3ac and H4ac levels at the interleukin 13 (IL-13) gene (IL13) that were observed in CD4+ T-cells from children with allergic asthma and healthy controls correlated with serum IL-13 concentrations [72]. Differential enrichment of H3K4me2 in 200 cis-regulatory enhancer regions in naïve, Th1, and Th2 CD4+ T-cells was observed between asthmatic and non-asthmatic subjects. Moreover, 163 of those 200 asthma-associated enhancers were Th2-specific and 84 of them contained binding sites for transcription factors involved in T cell differentiation [e.g. GATA binding protein 3 (GATA3), T-box 21 (TBX21) and RUNX3] [73]. Most of the other studies identified by our literature search were also supportive for the importance of histone modifications, such as acetylation and methylation, in (CD4+) T-cell biology and/or related pathophysiology of allergic disorders [74–78].

Some prenatal dietary exposures, previously demonstrated to modulate the infant’s immune responses and/ or risk of allergy development in offspring [79–82], have recently been shown to be associated with the alterations in histone acetylation profiles in neonatal cells. For
instance, cord blood (CB) CD4+ T-cells obtained from children born from mothers with highest serum folate levels during pregnancy were characterized by significantly higher histone H3ac and H4ac levels at the GATA3 gene (GATA3) promoter, markedly lower H4ac levels at the analogous region of the interferon gamma (IFNγ) gene (IFNG), and significantly higher interleukin-9 (IL-9) gene (IL9) promoter H4ac levels when compared to the lowest folate level group [83]. In CB CD4+ T-cells obtained from newborns of mothers supplemented with fish oil (ω-3 fatty acids) during pregnancy in turn, significantly higher H3ac levels were observed at the protein kinase C zeta (PKCζ) gene (PRKCKZ) and IFNG locus, and lower H3/H4ac levels at the IL-13 and TBX21 genes (IL13 and TBX21, respectively) [84]. The infants from the fish oil-supplemented women were found to have lower risk of developing allergic diseases [81, 82].

Both passive (prenatal and postnatal) and active tobacco smoke exposures are a well-known extrinsic factors affecting the risk of allergic disorders, especially asthma, and this effect was found to be associated with (and thus is thought to be at least partly mediated by) changes in DNA methylation patterns [5, 6]. Exposure to passive smoking diminished corticosteroid sensitivity of alveolar macrophages obtained from children with severe asthma and was accompanied by lower HDAC2 expression and activity. This possibly explains the unfavorable effect [85] and suggests that histone modifications, specifically histone acetylation, are also involved.

The text in this review has been selective in discussing the field and the reader is advised to consult Tables 2 and 3 for a more comprehensive appreciation of the wider literature review.

Conclusions and future perspectives
The results of our systematic literature assessment demonstrate a growing interest in the contribution of histone modifications in regulating the development of allergic disorders and, at the same time, provide evidence supporting this contribution. The role of histone modification is manifested at least at two levels. One involves the regulation of cells participating in the allergic inflammatory reaction, namely the inflammatory cells, T cells and macrophages, and the local tissue cells, such as (myo-) fibroblasts, which contribute to remodeling of airways. The other is the direct relationships between histone modifications and allergic phenotypes.

Furthermore, experimental observations of effects of histone marks modifying substances, e.g., HDACis or HMTis, suggest the potential application of histone epi-genome editing in the treatment of allergies [35, 86–92]. Such therapies do not need to be simply restricted to histone-modifying enzyme inhibitors but may also include more targeted approaches based on e.g. CRISPR/dCas9 system [6, 92] or antisense molecules [6, 93–95]. Others include nutrients [71] or even bio-physical interventions [96]. Finally, also diagnostic/prognostic tools for allergic traits based on epigenetic patterns/signatures could possibly be developed in future, as suggested by several studies on DNA methylation [6, 97–99].

This review provides a systematic update of the current knowledge on the contribution of histone modifications to allergic inflammation and disorders.

Abbreviations
ADAM33: ADAM metallopeptidase domain 33 (ADAM33) gene; ASM: airway smooth muscle cell; BET (proteins): bromodomain and extra-terminal (proteins); CB: cord blood; CCL2/17/22: C–C motif chemokine ligand 2/17/22 gene; COX2: cytochrome c oxidase subunit II (COX2) gene; CXCL8: C–C motif chemokine ligand 8 (CXCL8) gene; DOT1L (human KMT): DOT1-like (human KMT); DUB: deubiquitinating enzyme; DUSP1: dual specificity phosphatase 1 (DUSP1) gene; EGF: epidermal growth factor receptor gene; EGFR: epidermal growth factor receptor (EGFR) gene; E1A binding protein p300: p300; FAM: folate; FCS: fetal calf serum; GATA3: GATA binding protein 3 (GATA3) gene; GATA3 (family): GCNS-related N-acetyltransferase (family); HAT: histone acetyltransferase; HDAC: histone deacetylase; HDAC inhibitor; HDM: histone demethylase; HMT: histone methyltransferase; HMTi: HMT inhibitor; IL6/9/13: interleukin 6/9/13 (IL-6/9/13) gene; IFNG: interferon gamma (IFNγ) gene; IPF: idiopathic pulmonary fibrosis; JUMIC (domain): Jumonjic (domain); KMT: lysine methyltransferase; LSD1/KDM1: (amine-oxidase type) lysine-specific demethylase; PRMT: arginine methyltransferase; PCAF: p300/CBP-associated factor; PRKCKZ: protein kinase C zeta (PKCζ) gene; PTGER2: prostaglandin E receptor 2 (EP2) gene; p300: E1A binding protein p300; SAM: S-adenosyl-l-methionine; STAT6: signal transducer and activator of transcription 6 gene; TBX21: T-box 21 (TBX21) gene; TGF-β: transforming growth factor beta; Th (cell): helper T-cells/T-helper (cell); TP63: tumor protein p63 gene; VEGFA: vascular endothelial growth factor A (VEGFA) gene.

Authors’ contributions
BAA, RK, and JW drafted the first version of the manuscript. VvB, HH, FA, CSH, and SLP contributed to the specific parts of the first draft. DPP, HG, BAA, and HR developed the design of this work. DPP and RK conducted the systematic search. DPP, HG, AF, and HR wrote the final version of the manuscript. All authors read and approved the final manuscript.

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For Abbreviations used in plain text, please refer to “Abbreviations” section; for histone modification code, please, refer to Table 1.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data is sharing not applicable to this article as no datasets were generated or analyzed during the current work.
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