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Epigenetics, Asthma, and Allergic Diseases: A Review of the Latest Advancements

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Abstract

Environmental epigenetic regulation in asthma and allergic disease is an exciting area that has gained a great deal of scientific momentum in recent years. Environmental exposures, including prenatal maternal smoking, have been associated with asthma-related outcomes that may be explained by epigenetic regulation. In addition, several known allergy and asthma genes have been found to be susceptible to epigenetic regulation. We review the latest experimental and translational studies that have been published this past year in several areas, including 1) characterization of environmental asthma triggers that induce epigenetic changes, 2) characterization of allergic immune and regulatory pathways important to asthma that undergo epigenetic regulation, 3) evidence of active epigenetic regulation in asthma experimental models and the production of asthma biomarkers, 4) evidence of transmission of an asthma-related phenotype across multiple generations, and 5) “pharmaco-epigenetics.” The field has certainly advanced significantly in the past year.

Keywords

Epigenetics; Asthma; Allergy; Environment; DNA methylation; Histone modification; microRNA; T-helper cell; Regulatory T cell; Transgenerational; Pharmaco-epigenetics

Introduction

Recently, there have been numerous publications addressing the role of epigenetic regulation in complex diseases, and how environmental exposures may induce these molecular events. The most common epigenetic mechanisms include DNA methylation, histone modifications, and noncoding RNAs, all of which can affect gene transcription through effects on DNA structure and induction of gene silencing (Table 1). They may explain immune modulation induced by the environment even when we cannot measure the inciting environmental exposure itself. Epigenetic regulation also provides an attractive mechanism for explaining known associations of several prenatal exposures on the later development of various disorders in children and adults.

All these explanations fit well with why epigenetic regulation may be an important mechanism in asthma and allergic disease. Several prenatal exposures, with maternal

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smoking being the most described, have been associated with asthma-related outcomes in children [1, 2]. Allergies and asthma are more likely to develop in children if the mother has allergies or asthma compared with the father, suggesting the possibility of intrauterine programming [3, 4]. Moreover, the atopic phenotype characteristically is heterogeneous, in part related to varying individual environmental exposures, and can remit or be induced at various times in a person's lifetime [5–7]. Furthermore, several known atopy and asthma genes have been found to be susceptible to epigenetic regulation, including genes important to T-effector pathways (interferon (IFN)-γ, interleukin (IL)4, IL13, IL17) [8–13], T-regulatory pathways (forkhead box P3 [FoxP3]) [14], and airway inflammation (arginase [ARG], inducible nitric oxide synthase [iNOS]) [15, 16]. Hence, the investigation into epigenetic regulation and allergic disease continues.

The scientific literature in recent years has benefited from the publication of numerous comprehensive review articles and call for more studies on epigenetic regulation in allergic disease and asthma [17–19]. Nonetheless, it has been apparent that these raised many more questions than provided answers. The published experimental work, with few exceptions [15, 16, 20], mostly has comprised small observational studies and models in cell systems and animals [21–23]. However, in the past year, exciting and elegant experimental studies and novel translational research works were published. Advances were made in many areas, including 1) better characterization of how several environmental asthma triggers induce epigenetic changes, 2) better characterization of how allergic immune pathways and regulatory pathways important to asthma undergo epigenetic regulation, 3) growing evidence of active epigenetic regulation in asthma experimental models and the production of asthma biomarkers, 4) experimental evidence of transmission of an asthma-related phenotype across multiple generations, and 5) "pharmaco-epigenetics.: This review discusses such key papers.

Environmental Asthma Triggers

Among the airborne pollutants, the one most associated with the induction of epigenetic changes is tobacco smoke. Exposure to cigarette smoke was shown to inhibit the expression of histone deacetylase (HDAC) in alveolar macrophages. Blocking deacetylation or removal of acetyl groups on the histone presumably permitted greater access of the DNA to RNA polymerases and transcription factors, augmented the inflammatory cytokine gene transcription, and thereby reduced the efficacy of anti-inflammatory therapy such as glucocorticoids in chronic obstructive lung disease [24]. More recently, experimental models and epidemiologic studies have demonstrated the ability of exposure to cigarette smoke to change patterns of DNA methylation and microRNA (miRNA) expression important to the transcription of genes implicated in apoptosis, proliferation, and cancer [25, 26]. Liu and colleagues [27•], in an informative experimental model using primary and immortalized human airway epithelial cells chronically exposed to cigarette smoke condensate, found that smoke condensate induced dose- and time-dependent histone alterations that were associated with decreased expression of DNA methyltransferase (DNMT)1 and increased expression of DNMT3b, enzymes that catalyze the transfer of methyl groups to DNA. They also found time-dependent demethylation of several specific genes implicated in carcinogenesis (eg, *D4Z4*, *NBL2*) and globally that were variably associated with changes in gene expression, suggesting a large array of possible epigenetic targets of cigarette smoke exposure [27•]. In addition, prenatal exposure to cigarette smoke in a pediatric cohort was associated with decreased DNA methylation globally, as indicated by reduced methylation of Alu sequences (the short interspersed nucleotide elements) and in CpG regions in the promoter of receptor tyrosine kinase (*AXL*), protein tyrosine phosphatase, receptor type (*PTPRO*), and other genes [28•].

Exposure to traffic-related pollutants, known triggers of allergies and asthma [29, 30], also has emerged as a potentially important inducer of epigenetic changes since Baccarelli and colleagues [20] found that measured levels of fine particulate matter and black carbon/soot were associated with time-dependent reductions in global methylation in a cohort of older adult participants in the Boston area Normative Aging Study. Ambient levels of another combustion traffic emission, namely polycyclic aromatic hydrocarbons (PAH), measured from backpacks worn by pregnant women were associated with asthma and allergy candidate gene-specific changes in DNA methylation [31]. In even more recent studies of PAH exposure, administration of benzo(a)pyrene (BaP), one of the PAHs measured in this last study, to cultures of immortalized HeLa cells, induced the early recruitment of several histone activation markers, followed by decreased DNMT1 protein levels, and globally reduced DNA methylation at CpG islands [32]. Nadeau and colleagues [33•] found while studying asthmatic children living in either the relatively polluted Fresno area (ie, airborne fine particulate matter concentrations that exceeded federal annual standards) versus cleaner Stanford areas of California that children with greater exposure to air pollution were more likely to have evidence of increased DNA methylation of the forkhead box P3 (FoxP3) transcription factor and impaired T-regulatory (Treg) function. Annual average PAH levels, estimated based on land use regression analyses that used actual PAH measures from a subset of homes, were correlated with the number of methylated CpG islands in the FoxP3 gene [33•]. Moreover, changes in the expression of several miRNAs have been reported in association with exposure to particulate matter. In one such study, Bollati and colleagues examined individual exposure to fine particulate matter and metals including chromium, lead, cadmium, arsenic, nickel, manganese, many of which have been implicated in allergies and asthma [34, 35]. They found in foundry workers from an electrical furnace steel plant that estimated individual levels of exposure to fine particulate matter and metals were associated with both upregulation and downregulation of an array of miRNAs important in inflammation and oxidative stress [36••].

Questions about the effect of diet during pregnancy on the subsequent risk of allergies or asthma in the offspring have been raised for years, with some data supporting the ability of Mediterranean diets, and supplemental fish oil and vitamin E, to provide some protection from risk [37, 38]. Given the presumption that folic acid supplementation is a source of methyl donors that could alter DNA methylation and thereby gene expression, its use has become the focus of several studies. This question, in part, was fueled by elegant murine models that demonstrated that a diet high in methyl donors during pregnancy was associated with a more pronounced allergic phenotype in the offspring. The allergic phenotype was associated with altered DNA methylation of several genes, including the T-cell suppressor runt related transcription factor 3 (*RUNX3*) [39]. Of course, this issue is of great public health concern given the established importance of folic acid supplementation in the prevention of neural tube defects in infants [40]. However, data on folic acid supplementation in humans and associated allergic disease have been mixed. While some found that prenatal folic acid supplementation was associated with more asthma, wheeze, and other respiratory problems in early-childhood [41, 42], these findings have been difficult to replicate [43]. This debate arguably continued this past year, when Haberg and colleagues [44], in follow-up studies now looking at nonfasting plasma folate levels in their cohort of pregnant mothers, reported a trend of increasing risk of asthma in children across quintiles of plasma folate levels during pregnancy. In contrast, Magdelijns et al. [45••] found that folic acid use during pregnancy was not associated with a greater risk of wheeze, asthma, or eczema. Intracellular folic acid measured in later pregnancy was associated with a reduced risk of childhood asthma. Therefore, the weight of current evidence is insufficient to recommend any change from the current practice of periconceptional folic acid supplementation to protect children from neural tube defects.

The role of vitamin D as an immunoregulatory agent has gained wide recognition in recent years. Indeed, higher intake of vitamin D during pregnancy has been associated with some protection from wheeze in children at age 5 years [46]. Modification of T-helper effector cell cytokine production and Treg cell function are some of the suggested mechanisms [47]. Evidence of epigenetic regulation of these processes thus far is limited, though in one recent study, the active metabolite, 1,25-dihydroxyvitamin D3, upregulated histone H4 acetylation and participated in other chromatin remodeling events important to the expression of proinflammatory genes [48].

Food allergens themselves have been found to be susceptible to epigenetic regulation. In one paper, the promoter of the peanut allergen Ara h 3 underwent changes in histone acetylation influencing its gene expression in early- and late-maturation embryos [49]. Clearly the implication of this research in relation to susceptibility to allergy is unclear but does suggest the potential wide scope of some of these processes.

Allergic Immune and Regulatory Pathways Important to Asthma

Growing fundamental cellular and experimental work continues to provide strong biological support for the premise that key pathways important to the allergic immune response, such as T-cell differentiation and Treg function, are susceptible to distinct epigenetic modifications. This includes DNA methylation and histone modifications that direct immune programming related to pro-allergic IL-4, IL-13 [9, 22, 50, 51], and counterregulatory IFN-γ production [8, 10–12]. For example, we now are learning that pro-allergic T-helper type 2 (Th2) or counterregulatory Th1 cytokine production such as IFN-γ by human effector T cells can be flexible or plastic [52]. In many experimental settings, the induction of IFN-γ transcription is regulated primarily by DNA demethylation of CpG sites within the IFN-γ gene [8, 10–12, 53]. New findings also have emerged detailing the induction of FoxP3, a Treg-specific transcription factor, and its dependence on DNA methylation and histone modifications [14, 54, 55]. As described below and in Table 2, major advances in the past year have been made in the further refinement/description of the role of DNA methylation, histone changes, and miRNA in these pathways, as well as better localization of the sites involved.

For example, Janson and colleagues [54] used the high-resolution Epigenetic Immune Lineage Analysis (EILA) in combination with several probes as a method to evaluate simultaneously Th1, Th2, Th17, and Treg commitment. The method involves profiling each lineage in an isolated population of human $CD4^+$ T cells based on the specific CpG methylation status of signature cytokine and transcription factor loci. In examples described in the paper, they were able to apply the method to $CD4^+$ cells from patients with two autoimmune diseases associated with imbalances of the Th1 and the Treg cell responses [56••], rheumatoid arthritis, and multiple sclerosis, and demonstrate specific CpG methylation patterns compatible with their Th effector populations. Their technique holds some interesting promise for future studies in the ability to define epigenomes relevant to a cell population and possibly many clinical diseases, including allergy and asthma [57].

One informative paper by Koh and colleagues [58] demonstrated the importance of chromatin remodeling of the Th2 cytokine locus (clustered on human chromosome 5, mouse chromosome 11) in murine models deficient for the conserved regulatory regions within the locus. These cLCR knockout mice experienced a loss of general H3 acetylation and histone H3-K4 methylation and demethylation of the DNA in the Th2 cytokine locus. This led to a marked reduction in the recruitment of eosinophils and lymphocytes in the airways, as well as decreased IgE levels and airway hyperreactivity [58]. Grausenburger et al. [59] showed in conditional T-cell–specific HDAC1 knockout mice that HDAC was important to the

development of Th2 cytokine production and allergic airway inflammation. Using ChIP assays in nonactivated naïve $CD4^+$ T cells, they also showed that HDAC was bound to the IL-4 gene locus, suggesting HDAC may be particularly important during early T-cell differentiation [59].

Interesting work was done on the function of miRNA expression on lesional and healthy skin of patients with atopic dermatitis. miR-155 was one of the most upregulated miRNA in atopic dermatitis lesions and was most expressed in the infiltrating immune cells. Additional experiments by the group showed that the miRNA may induce the dermatitis via inhibition of the negative T-cell regulator cytotoxic T lymphocyte–associated antigen (CTLA)-4 [60].

Major advances describing epigenetic regulation of the pro-allergic cytokine IL-13 were made this year as well. For example, Lim and colleagues [61] examined cAMP-responsive element binding protein (CBP) and chromatin remodeling in IL-13 pro-allergic chemokine regulation. Inhibition of HDAC (using culture of primary esophageal epithelial cells with trichostatin A) and induction of acetylated histone 3 increased IL-13–induced, and CBP-mediated, eotaxin-3 gene expression. Interestingly, in a sample of patients with eosinophilic esophagitis, they were able to document a greater level of acetylated histone 3 staining in the nuclei of the epithelial cells in their esophageal tissue [61]. The critical IL-4 signaling transcription factor STAT6 also appears susceptible to DNA methylation. This work was delineated in experiments by Kim and colleagues [62••], who treated activated human primary T cells isolated from healthy donors with a DNMT inhibitor (5-Aza-2-DC) and found that expression of STAT6 mRNA and protein were increased. In a recent study by Tanaka and colleagues [63••], a greater understanding was gained regarding chromosome modification of the IL-4 locus during Th2 differentiation. Their study demonstrated that GATA protein binding-3 (GATA-3) chromosomal modification of IL-4's second intron is regulated by the DNase I-hypersensitive site (HS) 2 element. Targeted deletion of a series of HS sites in the IL4–IL13 locus led to functional impairment of epigenetic regulation of the IL4 locus in mice. Specifically, the deletion impaired acetylation and the onset of methylation by histone H3, resulting in failure to activate GATA-3 and abrogation of the allergic response [63••].

Th17 cells comprise a relatively recently discovered subset of T-helper cells producing IL-17 that provide host defense against extracellular bacteria, especially at the mucosa. Histone H3 acetylation and Lys-4 tri-methylation have been associated specifically with IL-17 and IL-17f gene promoters in Th17 cells [64]. More recent work this year by Mukasa and colleagues [65] focused on the stability versus plasticity of IL-17 epigenetic changes. They performed experiments of the DNase I HS and histone modifications of the clustered IL-17a–IL-17f and IFN-γ loci in naive Th1 and Th17 cells, as well as in Th17 cell precursors both prior to and following IL-12 versus transforming growth factor (TGF)-β stimulation. The experiments were intended to shift toward a Th1 phenotype (after IL-12) versus maintain the Th17 phenotype (after TGF-β). They observed permissive modifications across the IL-17a–IL-17f locus when cells were stimulated with TGF-β. However, STAT4- and Th1-specific T box transcription factor (T-bet) silenced the pro-IL17 RAR-related orphan receptor gamma (*RORC*) gene when the cells were stimulated with IL-12. The experiments suggest that Th17 cell lineage is plastic, and this instability is mediated epigenetically through reversal and remodeling of the chromatin structure [65].

In recent studies, Treg cell function and regulation of FoxP3 transcription have emerged as targets of epigenetic modifications. Some of the experimental work may have been inspired by the reported role of Tregs in the protection from atopy found in association with being born to a mother who farms [66]. Since then, the FoxP3 promoter has been shown to undergo both histone acetylation and DNA methylation affecting gene transcription

(reviewed in [14]). The expression of the FoxP3 gene in the Treg promoter, and differentiation of naive T cells into Tregs, has been shown to be dependent on epigenetic regulation. FoxP3 methylation also distinguished natural Treg (nTregs), found in the thymus, from TGF-β–induced Tregs, found in the periphery [67−]. Most recently, Kim and colleagues [68], in elegant experiments, found that antigen-specific memory Th2 cells were able to redifferentiate into functional $FoxP3^+$ T cells by TGF-β in the presence of all-trans retinoic acid and rapamycin. These new Tregs functioned as usual Tregs and were able to downregulate key transcription factors such as GATA-3 and IRF-4, suppress T-cell proliferation, and suppress pro-allergic cytokine production. Also, Th2 memory-derived converted Tregs adoptively transferred into Th2 memory-bearing recipient mice suppressed ongoing airway hyperreactivity, airway eosinophilia, and antigen-specific IgE responses. Also, they were able to home very efficiently to the airways [68].

In addition to advances in epigenetic regulation of T-cell lineage, new studies have examined dendritic cell (DC) immune responses. In attempt to identify epigenome-wide DNA methylation, Fedulov and Kobzik [69] isolated splenic DCs from their neonatal asthma–susceptible murine model. The splenic DCs were isolated from 14-day-old naïve neonatal mice that were from mothers who previously were sensitized to ovalbumin, and transferred these cells to healthy, nonsensitized mice. They found an increase in the overall methylation and increased allergen presentation in the sensitized DCs compared with DCs isolated from control mice that were not sensitized but were otherwise genetically and environmentally identical. These findings suggest that allergen induction in mothers can be passed along to offspring by epigenetic mechanisms [69].

Asthma Experimental Models and Asthma Biomarkers

The recent literature, using animal models for asthma and biomarkers as surrogates of the human disease processes, has brought us exciting new support for epigenetic regulation in asthma. Kumar and colleagues [70] first found that transfection of primary cultured T cells with let-7 (a highly conserved group of at least nine miRNAs known to be involved in Toll-like receptor 4 signaling) reduced IL-13 levels. Intranasal administration of let-7 reduced the allergic phenotype (airway inflammation, airway hyperresponsiveness, mucus metaplasia, and subepithelial brosis) in sensitized mice [70]. Let-7 miRNAs were tested further in a murine model for asthma by Polikepahad and colleagues [71]. Short RNAs and miRNAs were very enriched in both naïve and allergen-sensitized and challenged mouse lungs, with the most abundant ones belonging to the let-7 family. However, targeted inhibition of let-7 miRNA suppressed Th2 cytokine production, eosinophil recruitment to the lung, and airway hyperresponsiveness, suggesting that under some circumstances, and in this in vivo model, let-7 miRNAs may exert a proinflammatory role. The authors attributed these unexpected findings to the large (>800) repertoire of targets of let-7 miRNAs and possible secondary effects [71•].

As another example, Collision and colleagues [72] applied a murine model of allergic airway disease induced by house dust mite (HDM) allergen to new work on the contribution of several miRNAs. Interestingly, the authors identified significantly elevated levels of miR-145, miR-21, and let-7b in the HDM-induced allergic airways. All these specific miRNAs previously had been implicated in airway smooth muscle function, allergic inflammation, and airway epithelial cell function. Of the miRNAs identified, they found that the most significant proinflammatory role was played by miR-145 that, when specifically inhibited, suppressed allergic inflammation and airway remodeling. In additional experiments, both the suppression of miR-145 as well as treatment with the known anti-inflammatory dexamethasone significantly reduced the production of IL-5 and IL-13 from Th2 cells, though the effect of dexamethasone appeared to be more potent. These

informative studies are among the few to identify altered regulation of specific miRNAs in allergic-mediated inflamed airways and point to potential future therapeutic targets directed at airway inflammation [72].

The first paper to look at DNA methylation of specific asthma genes and biomarkers of airway inflammation was published by Breton and colleagues [16] in 2011. Under the auspices of the Children's Health Study, methylation levels of several CpG loci located in the promoter regions of the *iNOS* and *ARG* genes were compared with levels of fractional exhaled nitric oxide (FENO), an established asthma biomarker associated with airway inflammation and lung function decrements, among their asthmatic children. DNA methylation in the *ARG,* but not the *iNOS* gene, was associated inversely with FENO, suggesting a possible role of DNA methylation in the regulation of nitric oxide production [16].

In comparison, Isidoro-Garcia and colleagues [73] compared CpG methylation levels in a small cohort of allergic asthmatic patients with that of controls for the D prostanoid receptor (*PTGDR*) gene that mediates the production of PGD_2. Indeed, *PTGDR* methylation levels were decreased at multiple CpG sites among patients compared with controls. One site of differential methylation was located at the same site as a recognized 613C>T single nucleotide polymorphism, possibly implicating genetic and epigenetic factors in the association with allergic asthma [73].

Transmission of an Asthma-Related Phenotype Across Multiple Generations

The idea that environmental exposures early in life may impact clinical outcomes is a fascinating concept. However, also intriguing is the notion that these epigenetically regulated genes may be passed from parent to offspring. Previously it was thought that epigenetic marks were erased upon passage through the germline. However, there was a huge paradigm shift more than 10 years ago that disproved that previously held belief in pivotal work involving agouti mice performed by Morgan et al. [74] and Waterland and Jirtle [75]. Since their discoveries, there is now emerging evidence that environmental factors may alter the germline of the epigenome, leading to transgenerational epigenetic inheritance [76]. A recent meta-analysis illustrated the stronger inheritance pattern of asthma in children of mothers versus fathers with history of asthma [4]. This work suggests that intrauterine events yield sustained effects on the child's phenotype, possibly via passage of epigenetic marks through the germline. Recent studies have sought to delineate further these mechanisms.

Brand and colleagues demonstrated a microbial protective effect from asthma that appears to be inherited transgenerationally in a murine model. They studied *Acinetobacter lwoffii*, a farm-derived gram negative bacteria, to test whether this particular microbial exposure may be responsible for some of the asthma-protective effects of early farm exposure. Female BALB/c mice sensitized to ovalbumin (vs negative controls) were exposed to *A. lwoffii* (5 exposures during the 1.5 weeks before mating and every other day during pregnancy) and studies were performed on their offspring (who were not exposed to *A. lwoffii)*. They found that stimulated T cells from the splenic mononuclear cells of these offspring had significantly decreased ability to produce Th2 cytokines such as IL-4, IL-5, and IL-13, while production of the counterregulatory IFN-γ remained intact, suggesting a blunted pro-allergic T-helper cell response. However, when the IFN-γ pathway was blocked selectively by treating the offspring with neutralizing anti–IFN-γ monoclonal antibody, Th2 cytokine production was restored [77]. These experiments suggest that prenatal *A. lwoffii* exposure

upregulated Th1 activity, suppressed Th2 activity, and protected against the allergic inflammatory phenotype in the offspring.

Furthermore, our group hypothesized that combined prenatal in vivo exposure to *Aspergillus fumigatus* allergen and diesel exhaust particles was associated with changes in the asthma phenotype in the mouse offspring as well. Following sensitization via the airway route to *A. fumigatus* and mating, pregnant BALB/c mice were exposed to additional *A. fumigatus* and/or diesel exhaust particles. At age 9 to 10 weeks, the offspring were sensitized and challenged with *A. fumigatus*. Adult offspring from mice that were exposed to *A. fumigatus* or diesel exhaust particles during pregnancy experienced decreased instead of the anticipated increased IgE production. Adult offspring of mice that were exposed to both *A. fumigatus* and diesel exhaust particles during pregnancy experienced decreases in airway eosinophilia [78•].

Transgenerational passages of phenotypes and differential DNA methylation also recently were published in *Arabidopsis thaliana* plants. Schmitz and colleagues [79] identified 114,289 CpG single methylation polymorphisms and 2,485 CpG differentially methylated regions in the plant's progeny that diverged over 30 generations from the ancestor to the descendent. Their findings suggest transgenerational methylation variation over multiple generations may affect gene transcription without changing the sequence of the genome [79]. Although we are closer in understanding that epigenetically modified genes may be differentially expressed by the offsprings, further studies are necessary to explore these relationships in human models.

Pharmaco-epigenetics

Epigenetic regulation also has emerged as a potential mechanism for the action of asthma-related pharmacologic therapies. For example, corticosteroids that have been used for decades to treat the inflammation present in acute and chronic asthma as well as chronic obstructive pulmonary disease (COPD) are now thought to act, at least in part, through histone acetylation. Corticosteroids bind intracellularly to glucocorticoid receptors, which become activated and bind to glucocorticoid response elements in the promoter regions of glucocorticoid-responsive genes. Corticosteroids exert their anti-inflammatory action by inducing histone acetylation of anti-inflammatory genes (eg, mitogen-activated protein kinase phosphatase-1 [MKP-1]), and by recruiting HDAC2 and inducing deacetylation of proinflammatory genes (eg, IL-8, NF-κB, activator protein-1 [AP-1]) [80]. Yet another proposed mechanism of corticosteroid action through induction of miRNA expression was studied in a recent paper by Williams and colleagues [81•] and found to be noncontributory. Five young adults with mild asthma underwent flexible bronchoscopy with bronchial biopsy before and after a 28-day course of inhaled corticosteroids. Although there was significant improvement in methacholine challenge following treatment, there was no change in the miRNA pattern following treatment with inhaled corticosteroids [81•]. Moreover, low concentrations of theophylline, another drug used for asthma and COPD, has been shown to reverse the effects of corticosteroid resistance by restoring HDAC2 activity, possibly via selective inhibition of phosphoinositide-3-kinase (PI3K)-δ and the phosphylation of downstream kinases [80].

Finally, PGI_2 analogues have emerged as potential new asthma therapies because of their anti-inflammatory effects. Kou and colleagues [82], in a recent study, found that iloprost, a PGI_2 analogue, enhanced H3 acetylation in the pro-allergic Th2 macrophage-derived chemokine promoter area and suppressed H3 acetylation, H3K4, and H3K36 trimethylation (addition of three methyl groups) in the counterregulatory Th1 I prostanoid-10 chemokine promoter area. These findings suggest that the PGI_2 analogues in fact may increase Th2 pro-

allergic inflammation via histone modifications of chemokines [82]. They also raise the possibility that epigenetic regulation of airway inflammation via histone modification of PGI_2 analogues may have benefit in patients with steroid-nonresponsive diseases such as COPD or refractory asthma.

Conclusions

Recent publications shed a great deal of light on several important epigenetic responses to environmental exposures, epigenetically regulated molecular pathways, and experimental models of allergy and asthma. These new insights open doors for new approaches toward prevention of disease by targeted improvements in the environment and by development of novel drugs. Questions remain regarding the time course of these epigenetic mechanisms in vivo as well as the sustainability of their effects. The emerging evidence that some of these epigenetic effects may be transferred across multiple generations highlights how far-reaching these effects and novel therapeutic approaches can be.

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Table 1

Mechanisms of epigenetic regulation

	Site(s) of action	Mechanism(s) of action	Effect(s)
DNA methylation	CpG islands (stretches of DNA >200 bp with >50% GC content) and other CpG regions (<200 bp)	Addition of methyl group to the 5′ position of cytosines by DNMTs	Turn off gene transcription
Histone modification	Histone proteins (H2A, H2B, H3, and H4) that form the nucleosome core	Chromatin remodeling by methylation, acetylation (via HAT, HDAC), phosphorylation, or ubiquitylation of histone tails	Regulate accessibility of DNA to RNA polymerase II and transcription factors
Noncoding RNAs	miRNAs (21–23 nucleotide long regulatory RNAs)	Regulatory transcripts: binding of miRNA to the 3′ untranslated regions of mRNA	Induce degradation of target mRNA

CpG, cytosine-phosphate-guanine, DNMT, DNA methyltransferase; HAT, histone acetyltransferases, HDAC, histone deacetylases; miRNA, microRNA

Table 2

Epigenetic T-cell regulation and asthma- and allergy-related outcomes

Th pathway responses		
Authors	**Gene(s)**	**Epigenetic finding(s)**
Koh et al. [58]	*Th2*	Chromatin remodeling of the Th2 cytokine locus critical to systemic and airway inflammation
Grausenburger et al. [59]	*Th2*	HDAC1 important to early Th2 cell differentiation and development of allergic airway inflammation
Sonkoly et al. [60]	*CTLA-4*	miR-155 upregulated in atopic dermatitis and its overexpression associated with decreased CTLA-4
Lim et al. [61]	*Eotaxin*	Inhibition of HDAC increased IL-13–induced and CBP-mediated eotaxin expression
Kumar et al. [70]	*IL-13*	Transfection of T cells with let-7 reduced IL-13 levels; intranasal administration of let-7 reduced airway allergic inflammation in mice
Polikepahad et al. [71•]	*Th2*	Inhibition of let-7 miRNAs reduced allergic inflammation in mouse lung
Kim et al. [62••]	*STAT6*	Inhibition of DNMT increased STAT6 expression
Tanaka et al. [63••]	*IL4, IL13*	Targeted deletion of HS sites in the IL-4–IL-13 locus inhibited GATA-3 activation
Mucasa et al. [65]	*IL17*	Th17 cell lineage is not stable and mediated epigenetically through chromatin remodeling
Treg pathway responses		
Authors	**Gene(s)**	**Epigenetic finding(s)**
Lal and Bromberg [67•]	*FoxP3*	Differential FoxP3 methylation in thymus derived nTreg versus peripheral TGF-β–induced Treg
Th and Treg pathway responses		
Authors	**Gene(s)**	**Epigenetic finding(s)**
Janson et al. [57]	*Th1, Th2, Th17, Treg*	Epigenetic immune lineage analysis profiled $CD4^+$ cells in rheumatoid arthritis, multiple sclerosis
Kim et al. [68]	*Th2, Treg*	Memory antigen-specific Th2 cells can redifferentiate into functional Tregs

CBP, cAMP-responsive element binding protein; CTLA, cytotoxic T-lymphocyte antigen; DNMT, DNA methyltransferases; FoxP3, forkhead box P3; GATA-3, trans-acting T-cell–specific transcription factor 3; HDAC, histone deacetylases; HS, DNase I-hypersensitive site; IL, interleukin; miRNA, microRNA; nTreg, natural Treg; STAT6, signal transducer and activator of transcription 6; Th, T helper; Treg, regulatory T cell