Chapter 16
Asthma Epigenetics: Emergence of a New Paradigm?

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Abstract Asthma is a disease that is influenced by environmental exposures, including those that occur prenatally. Recently, epigenetic regulation has been posited as an explanation for how environmental toxicants may induce asthma-related immune responses. However, our knowledge of the epigenetic regulation of asthma lags substantially behind our understanding of the epigenetic regulation of other complex diseases such as cancer. Fortunately new data are beginning to emerge. These include translational data from molecular experiments that implicate epigenetic regulation in T helper differentiation and/or the development of T regulatory cells, important in allergic immune responses. They also include a growing collection of cohort studies that associate epigenetic regulation with several components of the asthma clinical phenotype. So far these clinical studies are small, often
unconfirmed, and only have started to address key issues relating to tissue specificity. Nonetheless, these studies provide a preview of what future research may reveal and raise the possibility that previously held paradigms for asthma pathogenesis may, and perhaps should, be changing.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACSL3</td>
<td>Acyl-CoA synthetase long-chain family member 3</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
<tr>
<td>CCCEH</td>
<td>Columbia Center for Children’s Environmental Health</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CpG nucleotides</td>
<td>C–phosphate–G nucleotides</td>
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<td>GRs</td>
<td>Glucocorticoid receptors</td>
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<td>GSTM1</td>
<td>Glutathione S-transferase mu 1</td>
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<tr>
<td>HDAC</td>
<td>Histone deacetylases</td>
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<tr>
<td>HAT</td>
<td>Histone acetyltransferases</td>
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<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<td>iNOS</td>
<td>Inducible nitric oxide synthases</td>
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<tr>
<td>IGF</td>
<td>Insulin-like growth factor</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>LINE-1</td>
<td>Long interspersed nucleotide elements</td>
</tr>
<tr>
<td>MS4A2</td>
<td>Membrane-spanning 4-domains, subfamily A, member 2 gene</td>
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<tr>
<td>miRNAs</td>
<td>MicroRNAs</td>
</tr>
<tr>
<td>MyD88</td>
<td>Myeloid differentiation primary response gene (88)</td>
</tr>
<tr>
<td>nfkB</td>
<td>Nuclear factor kappa B</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PM</td>
<td>Particulate matter</td>
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<tr>
<td>PAHs</td>
<td>Polycyclic aromatic hydrocarbons</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>Runx3</td>
<td>Runt-related transcription factor 3</td>
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<tr>
<td>Th</td>
<td>T helper</td>
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<tr>
<td>TLR</td>
<td>Toll like receptor</td>
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<td>Treg</td>
<td>T regulatory</td>
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**16.1 Introduction**

Our understanding of epigenetic regulation in asthma lags substantially behind our understanding of epigenetic regulation in other complex diseases such as cancer [1, 2]. But experimental work discovering new potential roles for epigenetic regulation in asthma-related immune pathways has grown exponentially in recent years, as
reviewed recently [3–5]. New epidemiological data that link molecular mechanisms or epigenetic biomarkers with asthma-related clinical outcomes are beginning to emerge.

Asthma is a disease that is influenced by environmental exposures, including those that occur prenatally [6, 7]. The longstanding presumption is that the development of asthma is plastic, i.e., not a foregone conclusion based on genetic makeup, and hence modifiable. Asthma also is a disease that exhibits a notoriously variable phenotype [8]. Epigenetic marks that occur prenatally or during other susceptible time periods may modify the clinical manifestations and variable nature of this complex disease. In this chapter, significant advances in the knowledge of epigenetic regulation in response to environmental exposures implicated in asthma will be reviewed. Emerging translational basic science that implicates epigenetic regulation associated with T helper differentiation and/or the development of T regulatory cells that may underlie clinical manifestations of asthma will be mentioned. The last several years have produced many molecular epidemiological reports that associate epigenetic regulation and several components of the clinical asthma phenotype. These studies provide a preview of what future research may reveal and raise the possibility that previously held paradigms for asthma pathogenesis may, and perhaps should, be changing.

16.2 Common Epigenetic Mechanisms

DNA methylation, histone modifications, and production of noncoding RNAs are epigenetic molecular changes that can alter gene transcription without changing the DNA coding sequence. As a result, the host response to environmental exposures, the downstream proinflammatory reaction, or even the therapeutic efficacy of pharmacological agents may be changed if epigenetic modifications ensue. Several animal studies have provided some evidence that the epigenetic state induced by environmental exposures may occur prenatally and influence the phenotype in the offspring [9, 10]. Alternatively, epigenetic modifications may occur postnatally, leading to sustained effects on gene transcription. Another feature of epigenetic regulation is that it may be modifiable [11–13]. There are specific time periods when asthma may be more susceptible to the effects of exposure to environmental toxicants (i.e., gestation, early childhood, adolescence). It has been postulated, but not yet demonstrated, that epigenetic modifications may be contributing to the greater susceptibility that seems to occur during these time periods [3] (Fig. 16.1).

DNA methylation refers to the process whereby methyl groups are added to the fifth carbon of the nucleotide cytosine. This process can suppress gene transcription by either inhibiting transcription factor binding to the recognition sites on CpG nucleotides or by aiding transcription inhibiting protein binding [14]. Importantly, DNA methylation may not be stable and exhibit variation over time [11, 13, 15]. In comparison, post-translational modifications of histones, key elements in the chromatin packaging of DNA, occur by means of acetylation, methylation, and
phosphorylation. During acetylation by histone acetyltransferases (HAT), the DNA tightly packaged around the histone core unwinds, activators of transcription obtain access to DNA, and gene expression can then proceed. Histone deacetylases (HDAC), of which there are at least 11 isoenzymes, reverse acetylation and turn off transcription. In general, the extent of histone acetylation is a result of the amount of HAT compared to HDAC activity. The third prominent epigenetic mechanism involves the activity of microRNAs (miRNAs) that function as endogenous inhibitors of translation and thereby regulate protein production. They consist of single-stranded RNA molecules 21–23 nucleotides in length that induce the degradation of target mRNA. The activity of microRNAs’ role in asthma or any complex disease is perhaps one of the least understood epigenetic mechanisms. But one exciting study by Mattes and colleagues found that inhaled dust mite allergens increased the expression of specific miRNAs in the airways through TLR4- or MyD88-dependent mechanisms in mouse models. The associated allergic phenotype was inhibited by selective blockade of microRNA (miR)-126.

16.3 Environmental Exposures Implicated in Both Asthma and Epigenetic Regulation

One environmental exposure implicated in both asthma and epigenetic regulation is diet. In the former case, a number of cohort studies have implicated various dietary modifications with greater or reduced risk for asthma, such as supplementation with vitamin D, E, soy, and Mediterranean diet. However, the dietary supplement most implicated for inducing epigenetic changes relevant to asthma is folic acid, a source of methyl donors. Hollingsworth and colleagues suggested such an association using elegant mouse models. In their experiments, folic acid supplementation administered during gestation and weaning was associated with greater airway hyperactivity and eosinophilic inflammation, as well as chemokines and immunoglobulin...
(Ig) E production in the offspring. They argued that this association occurred due to folic acid’s ability to hypermethylate DNA and hence suppress the expression of several genes including Runx3, a gene involved in CD4 silencing during T cell lineage decisions [21]. In human cohort work, Whitrow and colleagues assessed the use of supplemental folic acid in women during pregnancy, determined retrospectively by food frequency questionnaire, and found associations with a greater risk of reported physician-diagnosed asthma in children [22]. The strongest association occurred when women took supplemental folic acid later in their pregnancy (30–34 weeks; relative risk (RR) 1.26, confidence interval (CI) 1.08, 1.43), suggesting a possible time window during pregnancy when supplemental folic acid ingestion may induce more extensive epigenetic alterations associated with pediatric asthma. The association between prenatal folic acid supplementation and asthma in children was examined as well in the Norwegian Mother and Child Cohort Study. In Norway, it is recommended the women take supplemental 400 mg of folic acid daily around the time of conception and during the first 3 months of pregnancy. Because the food is not fortified, the authors argued that their assessment of folic acid intake by questionnaire may be relatively accurate. In this cohort, folic acid supplementation only in the first trimester was associated with a slightly greater relative risk of lower respiratory infections (LRTI) (adjusted RR 1.10, 95% CI 1.01–1.20) and hospitalizations for LRTIs (RR 1.28, CI 1.07–1.53) in the child through 18 months of age. Folic acid supplementation anytime during pregnancy was associated with more wheeze at ages 6–18 months (RR 1.07, CI 1.02–1.12). In other models, they adjusted the effects of exposure in the first trimester to exposure both later in pregnancy and in infancy, and the associations with exposure in the first trimester on LRTIs remained significant. In the follow-up nested study within the same cohort, the group reported on maternal folate levels obtained on nonfasting specimens collected during the second trimester of pregnancy (median 18 weeks) and reported that levels were higher among women who reported supplemental folic acid use. An increased risk of asthma at age 3 years for children with maternal plasma folate levels in pregnancy in the highest compared with the lowest quintile, and a trend of increasing risk across quintiles of folate levels also was reported. The authors acknowledged that exposure to folic acid supplements in pregnancy was associated as well with several other characteristics presumed to lower the risk of LTRI, including higher maternal educational level, longer duration of breast feeding, and less smoking, so residual confounding (that for these covariates could lead to a negative bias) could not be ruled out. They also acknowledged that nonfasting plasma samples may be influenced heavily by the most recent intake of folic acid and could have added preanalytical variation [23]. In contrast, Matsui and Matsui determined that folic acid supplementation, indicated by serum levels measured by the 2006–2006 National Health and Nutrition Examination Survey, was associated with a reduced risk for seroatopy and wheeze in individuals age 2 years and older [24]. It is unclear whether the apparent discrepancies among the three cohort studies may be related to exposure misclassification (i.e., from retrospective questionnaires vs measured sera folate levels) or timing of exposure (i.e., prenatal vs postnatal, adult), but some links between folic acid intake and asthma are suggested.
Furthermore, another group determined that periconceptional folic acid administration (400 μg/day) was associated with hypermethylation of the insulin-like growth factor (IGF)2 gene. In this cohort study, 17-month-old children of mothers who used folic acid had a 4.5% higher relative methylation level of the differentially methylated region of IGF2 compared to children who were not exposed to folic acid \( (p=0.014) \). Higher levels of methylation were observed for individual CpG dinucleotides comprising the area, but they were not always statistically significant. IGF2 methylation of the child also was associated with the maternal (but not child) S-adenosylmethionine blood levels \( (+1.7\% \text{ methylation per SD S-adenosylmethionine}; p=0.037) \) \[25\]. Higher methylation levels were associated with decreased birth weight. However, the authors acknowledged that even the statistically significant differences were very small, suggesting that other genes or mechanisms may be involved as well. They also proposed that the extraction of DNA from whole blood composed of multiple cell types may have diluted some of the biological outcomes measured. Still, the paper remains one of the first studies to link periconceptional folic acid supplementation with DNA methylation and a clinically relevant phenotype in the child.

Another environmental exposure long considered a risk factor for the development of asthma in children is maternal smoking \[7, 26–28\]. One intriguing study by Li and colleagues suggested the mechanism of action on childhood asthma could be transmitted across generations. As part of a case-control study nested within the Children’s Health Study, detailed maternal and household smoking histories and histories of other asthma risk factors were obtained by telephone interview. The authors found that a reported history of prenatal smoking was associated with increased risk for asthma diagnosed in the first 5 years of life (odds ratio [OR] 1.5; CI 1.0–2.3), and for persistent asthma (OR 1.5; 95% CI 1.0–2.3). The associations did not differ in children with early transient asthma compared to those with early persistent asthma. Interestingly, grandmaternal smoking during pregnancy was associated with a greater risk of asthma in grandchildren (OR 2.1; 95% CI 1.4–3.2) that remained borderline significant even if there was no report of maternal smoking during pregnancy (OR 1.8; 95% CI 1.0–3.3) \[29\]. The study was retrospective and did not test epigenetic regulation specifically. Yet this first report of a grandparental effect on asthma may lead to speculation about a contribution of epigenetic regulation to inheritance that would need to be tested rigorously.

### 16.4 Environmental Exposures Implicated in Asthma Are Susceptible to Epigenetic Regulation

Several environmental exposures implicated in asthma have been shown to induce epigenetic alterations, but perhaps the exposures best characterized in ex vivo or cohort studies are air pollutants. For example, Cao and colleagues documented that diesel exhaust particles induced chromatin modifications in an assay involving exposure of human bronchial epithelial cell lines. Increased histone H4 acetylation
and posttranslation degradation of histone deacetylase (HDAC1) was found. These events in turn were associated with activation of the cyclooxygenase (COX)-2 promoter [30]. Baccarelli and colleagues recently compared exposure to traffic-related air pollution at multiple time points with repeated analyses for global methylation among a cohort of elderly males as part of the longitudinal Normative Aging Study. Ambient particulate matter (PM)\textsubscript{2.5}, black carbon, and sulfate were measured by stationary site monitoring, and average pollutant concentrations 4 h to 7 days were calculated (moving averages) prior to phlebotomy. DNA methylation in long interspersed nucleotide elements (LINE-1), an indicator of global methylation, decreased in relation to higher black carbon and PM\textsubscript{2.5} levels, especially during the longer time windows (2–7 days) [13]. Tarantini and colleagues examined two indicators of DNA methylation, Alu and LINE-1, and one measure of asthma candidate gene-specific (iNOS) DNA methylation, after short- (after 2 consecutive days off from work in a steel production plant) and long-term (after 3 consecutive days of work) exposure to PM\textsubscript{10} exposure among electric furnace steel plant workers (n=63). They reported that ambient PM\textsubscript{10} levels at work sites may be associated with the extent of DNA demethylation of the iNOS promoter. Also, PM\textsubscript{10} levels correlated with global DNA demethylation as estimated in Alu repeated elements and LINE-1 [15].

The relative expression of several candidate miRNAs implicated in oxidative stress and inflammation (miR-222, miR-21, and miR-146a) also were measured in the blood prior to and following 3 days of work among the electric furnace steel plant workers. Levels were compared to individual exposures to fine and course PM and PM metal components (chromium, lead, cadmium, arsenic, nickel, manganese). Among the post-exposure samples, miR-222 expression was correlated positively with lead exposure (beta=0.41, p=0.02), but miR-21 expression was not associated with individual PM or metals. Some negative correlations between miRNA levels and measures of metals exposure were found [31]. At minimum, the study suggests that changes in miRNA expression may occur, albeit inconsistently, in association with exposure to PM and its metal components, pollutants associated with asthma and other respiratory diseases [32]. Our group at the Columbia Center for Children’s Environmental Health (CCCEH) showed that higher levels of polycyclic aromatic hydrocarbons (PAHs), measured prenatally using personal monitors worn by pregnant women, was associated with greater DNA methylation of Acyl-CoA synthetase long-chain family member 3 (ACSL3) and other genes (see below) [33]. Finally, Breton and colleagues reported that a history of prenatal tobacco smoke exposure was associated with lower levels of DNA methylation for short interspersed nucleotide element (AluYb8; but not LINE-1) from buccal cells collected from children. Ilumina GoldenGate Bead Array DNA methylation assay of 1,031 gene-specific loci of similar samples yielded 9 candidate genes whose expression differed by prenatal tobacco smoke exposure. Furthermore, when children’s data were stratified by the absence or presence of the common GSTM1 null genotype, prenatal tobacco smoke exposure was associated with lower LINE1 methylation in the GSTM1 null children but higher methylation in the GSTM1-present children. This work suggests a novel interaction between genotype and environmental exposure on DNA methylation [34].
16.5 Epigenetic Regulation and Clinical Allergic Disease

Reviewing the epigenetic epidemiology of asthma is plagued by the lack of cohort studies. But significant advances in basic molecular work that provide the biological support for several translational and clinical studies have been made in this area. These include mounting evidence suggesting that immune programming associated with the development of proallergic T helper (Th) 2 cytokine responses (e.g., interleukin (IL)-4) or the counterregulatory Th1 cytokine responses (e.g., interferon (IFN)γ) may be susceptible to epigenetic regulation [35–39]. The most progress to date has been made in determining how DNA methylation of CpG sites within the counterregulatory IFN-γ promoter may confer protection from proallergic immune activation [39]. The IFN γ promoter also has been shown to be susceptible to chromatin remodeling [40]. Susceptibility to proallergic Th2 immune activation in association with demethylation occurs at the IL-4 locus [36, 41] and at the proximal IL-13 promoter [42]. Moreover, epigenetic mechanisms controlling T regulatory (Treg) development are just beginning to be explored. Early results suggest that Treg suppressive function important to allergic sensitization may be dependent on demethylation of Foxp3 [43, 44].

More clinical studies of epigenetic regulation in clinical asthma now test the etiology of the observed “maternal effect” of atopy. This paradigm refers to the greater predominance of asthma or allergy if the mother, as opposed to the father, is afflicted with the disease. Indeed this pattern has been observed for both asthma and production of proallergic IgE antibodies [5, 8]. To date, one cohort study by Ferreira and colleagues tried to associate such patterns with altered DNA methylation of either AluSp repeat or membrane-spanning 4-domains, subfamily A, member 2 gene (MS4A2) (β-chain of the IgE high-affinity receptor), a key gene in the allergic cascade. Their small study was essentially negative, failing to find differences in AuSp DNA methylation between cases and controls or according to atopic status of the mother or father [45].

As mentioned earlier, our group at CCCEH conducted one of the first proof of concept papers that tried to discover candidate asthma genes that may be susceptible to altered DNA methylation following air pollution exposure. In this case, the approach was to study cord blood DNA derived from high versus low prenatal PAH exposure groups. Genomic DNA was digested with methylation sensitive restriction enzymes, amplified, and aberrantly methylated bands on a gel eluted, reamplified, cloned, and sequenced. Using BLAST search or silicon database analysis of sequenced DNA that focused on promoter and CpG island searches, candidate clones were selected to undergo more intensive evaluations. These validation experiments included bisulﬁte conversion of DNA and methylation-speciﬁc PCR that revealed the 59-CpG island methylation status of ACSL3 as associated with prenatal PAH exposure. In addition, methylation of ACSL3 was associated signiﬁcantly with a parental report of asthma symptoms in children prior to age 5 years [33]. This study is the first to associate a measured prenatal environmental exposure with
altered gene-specific DNA methylation in cord blood and then associate such alterations with the later development of disease. Subsequently, Nadeau and colleagues using a cross-sectional design of age and sex-matched participants, recruited children in Fresno and Stanford California. They compared regional levels of ambient air pollution exposure with peripheral blood DNA methylation of Forkhead box transcription factor 3 (Foxp3), a key transcription factor in Treg suppressive activity and asthma symptom scores. They found that asthmatics living in Fresno where levels of polycyclic aromatic hydrocarbons (PAH), fine particulate matter, and ozone are higher than in Stanford had worse asthma symptoms and higher levels of methylation in the CpG islands in the Foxp3 promoter and one intronic region compared to nonasthmatics from Fresno and participants from Stanford. An association between the subject-specific estimated annual average PAH exposure in Fresno and the number of methylated CpG islands among Fresno asthmatics was detected as well [46]. While interesting, it should be noted that the study did not adjust the analyses levels for seasonal variation in PAH measures nor control for levels of other pollutants [47].

Other groups have reported provocative experimental results from small human studies, particularly in genes associated with Th polarization associated with allergic airway disease. As an example, ex vivo IFN-γ promoter methylation was reduced in CD8+ T cells, but not CD4+ T cells from atopic, but not healthy, children [48]. Kwon and colleagues measured the extent of DNA methylation of IFNγ and IL-4 gene promoters following ex vivo stimulation of peripheral blood mononuclear cells with Dermatophagoides pteronissinus/Dermatophagoides farinae dust mite antigens. Among asthmatics, methylation at the IL-4 promoter (CpG −80) increased following antigen stimulation and was strongly correlated with IL-4 production. In contrast, demethylation at the IFNγ promoter increased following ex vivo stimulation with phytohemagglutinin [49].

Su and colleagues reported on the importance of endogenous HDAC activity in regulating Th1 versus Th2 differentiation. Their approach was to block endogenous HDAC activity with trichostatin A following ex vivo polyclonal stimulation of peripheral blood mononuclear cells derived from children. Not only did trichostatin markedly reduce endogenous HDAC activity, but this result was associated with greater Th2 polarization and increased expression of GATA-3, suggesting that endogenous HDAC activity is necessary for preserving Th1 versus Th2 balance. Finally, the same group compared levels of HAT activity and endogenous HDAC in atopic nonasthmatic (n = 27) versus atopic asthmatic (n = 18) children with the extent of bronchial hyperresponsiveness, an indicator of asthma severity. They found significant elevations of HAT activity and reductions in the level of HDAC activity (determined in nuclear peripheral blood mononuclear cell lysates) among asthmatic children compared to atopic nonasthmatic controls. Moreover, these changes were associated progressively with the degree of bronchial hyperreactivity becoming the first study to compare the extent of epigenetic alteration with clinically relevant physiological outcomes [50].
16.6 Pharmacoepigenetics

Given that epigenetic alterations may be reversible, at least in theory, it stands to reason that there may be substantial potential to develop or take advantage of epigenetically-based therapies in asthma. DNA methyltransferases and histone deacetylases have shown promising anti-tumorigenic effects for some malignancies (reviewed in [51, 52]). Inhibitors of enzymes controlling epigenetic modifications associated with inflammation or other immune processes that result in airway disease, specifically DNA methyltransferases, histone deacetylases, and inhibitory RNAs, have therapeutic potential.

One way to consider the therapeutic potential of epigenetic regulation is to consider mechanisms that underlie the efficacy of glucocorticoids. Steroids exert some of their anti-inflammatory properties by inducing the acetylation of anti-inflammatory genes important for the production of cytokines, chemokines, or adhesion molecules. Specifically, glucocorticoid receptors (GRs) bind to their DNA binding site following acetylation [53]. Under other circumstances, such as during suppression of Nfkβ activation, steroids may recruit histone deacetylase-2 (HDAC-2) to activated inflammatory gene complexes [53]. Indeed, alveolar macrophages have been shown to express elevated levels of HAT activity and reduced levels of HDAC activity [54, 55]. One could speculate that therapeutics that modify the relative HAT, HDAC levels or target miRNA expression levels in the airways or their alveolar macrophages may hold promise as novel anti-inflammatory treatments for allergic asthma [17].

16.7 Conclusion

Recent advances have been made in the last few years, particularly in the molecular epidemiological work that associates epigenetic regulation with asthma phenotypes. However, there are several areas where this field has barely begun to tackle important questions. These include translational studies that examine the differential effects of epigenetic regulation according to specific cell types. For example, HDAC activity sampled from human alveolar macrophages was lower than levels sampled from those measured simultaneously in peripheral blood mononuclear cells [54]. Promoter methylation of leukotriene B4 receptor and its associated gene expression also has been shown to vary according to cell type [56]. In addition, the cohort studies conducted to date have been small and possess limited statistical power to adjust for covariates or to measure small effect sizes associated with epigenetic changes. Large prospective cohort studies are needed to examine all of these issues and how they may apply to the complex disease of asthma. Despite these limitations, there is exciting promise that the “bench” will communicate with the “bedside” and direct appropriate translational studies in the molecular epidemiology of asthma epigenetics.
References

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