Current Allergy and Asthma Reports (2019) 19:56
https://doi.org/10.1007/s11882-019-0886-y

ASTHMA (WJ CALHOUN AND V ORTEGA, SECTION EDITORS)

Epigenetics in Asthma

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Abstract

Purpose of Review Asthma is one of the most common chronic respiratory diseases linked with increased morbidity and healthcare utilization. The underlying pathophysiological processes and causal relationships of asthma with epigenetic mechanisms are partially understood. Here we review human studies of epigenetic mechanisms in asthma, with a special focus on DNA methylation.

Recent Findings Epigenetic studies of childhood asthma have identified specific methylation signatures associated with allergic inflammation in the airway and immune cells, demonstrating a regulatory role for methylation in asthma pathogenesis. Despite these novel findings, additional research in the role of epigenetic mechanisms underlying asthma endotypes is needed. Similarly, studies of histone modifications are also lacking in asthma. Future studies of epigenetic mechanisms in asthma will benefit from data integration in well phenotyped cohorts.

Summary This review provides an overview of the current literature on epigenetic studies in human asthma, with special emphasis on methylation and childhood asthma.

Keywords Asthma · Epigenetics · Childhood asthma · Methylation · Endotype · Asthma risk

Introduction

The term epigenetics, derived from the Greek epi and genome, was introduced by Waddington to describe changes in phenotype without changes in genotype. Although these mechanisms were not known at the time the term was originated, advances in genetics and genomics have unveiled key epigenetic processes involved in cell function. These essential mechanisms maintain homeostasis in normal cells and are also involved in disease pathogenesis.

In asthma, multiple studies have demonstrated how epigenetic mechanisms affect different aspects of the disease ranging from childhood to adult asthma. The significant heterogeneity of asthma can be explained partially by epigenetic control mechanisms that are dysregulated either primarily, in association with inflammation and control of airway function, or secondary to pharmacologic therapies or environmental influences. This review will focus on recent advances in our understanding of the epigenetics of asthma in human studies and will use classic examples of epigenetic mechanisms in asthma to frame the discussion.

Overview of Epigenetic Mechanisms

DNA Methylation The transfer of a methyl group onto the C5 position of cytosine to form 5-methylcytosine (5mC) is one of the best-characterized epigenetic mechanisms. The presence of 5mC in distinct areas of the genome is associated with changes in gene expression through the control of transcription factor binding [1]. CpG islands (CGI) are DNA segments enriched for CG sequences; these CG-rich segments are often located at or near the transcription start site (TSS) of genes. Thus, methylation changes in CGIs are associated with either activation or inhibition of gene expression. Typically methylation of CGIs is associated with gene repression [2]. However, the role of DNA methylation is more complex and extends beyond CGIs to methylation in the gene body, where it has demonstrated other roles in transcription elongation, splicing, chromosomal stability, and expression of transposable elements [2]. An additional feature of DNA methylation is its

This article is part of the Topical Collection on *Asthma*

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Published online: 27 November 2019

heritability over cell division cycles and also across generations [2]. The term "epimutation" has been used to describe heritable changes in gene activity due to DNA modifications [3]. DNA methylation is a complex mechanism of gene regulation that can be inherited after mitotic and/or meiotic division.

Histone Modifications Histones are the main proteins forming the DNA-protein complex chromatin. This close association with DNA is essential for packaging, providing genomic stability, and regulation of gene expression. Regulation of histone function through post-translational modifications is a key epigenetic mechanism. Multiple enzymes are involved in histone modifications; however, they can be divided into two main categories, histone acetyltransferases (HATs) and histone deacetylases (HDACs). Both HATs and HDACs are subdivided based on their location and specificity [4]. A simple model for understanding the role of HATs and HDACs in histone modifications is their opposing effect on lysine acetylation. Due to their stabilizing effect on chromatin architecture following reversal of lysine acetylation, HDACs act as transcriptional repressors [4].

In addition to acetylation, histone phosphorylation and methylation are complementary mechanisms involved in the regulation of gene expression. Histone core phosphorylation regulates DNA accessibility through nucleosome unwrapping [5]; and histone methylation, controlled by multiple methyltransferases and demethylases, results in the addition and removal of methyl groups leading to dynamic changes in these proteins affecting their role in the regulation of gene function. Importantly, DNA methylation affects histone methylation and vice-versa [6, 7].

Non-Coding RNA and Transcriptional Gene Silencing Non-protein-coding RNAs are transcripts involved in the regulation of cellular functions. Non-coding RNAs (ncRNAs) can be classified by size into long ncRNAs (> 200 nucleotides) and small RNAs (≤ 200 nucleotides) [8]. Studies of ncRNAs have revealed their role in organ development and cell differentiation. Despite their classification under the ncRNA label, small and large ncRNAs are diverse and exhibit specific behaviors that characterize their function.

1. Small ncRNAs: Under this category, we can include microRNAs, piwi-interacting RNA (piRNA), small interfering RNA (siRNA), small nucleolar RNA (snoRNAs), tRNA-derived small RNA (tsRNA), small rDNA-derived RNA (srRNA), and small nuclear RNA (U-RNA). These small RNAs perform diverse functions in the regulation of cellular functions.
2. Long ncRNAs are often involved in the regulation of neighboring protein-coding genes [8]. Additionally, lncRNAs are involved in the targeting of histone methyltransferases and demethylases, increasing the complexity of their role in the epigenetic regulation of cell function [9].

This review will be organized by sections on childhood asthma, adult asthma, and asthma risk. The majority of high-quality human studies in asthma to date have focused on DNA methylation; consequently, this review will emphasize this epigenetic mechanism and include a summary of microRNAs and histone modifications.

Childhood Asthma

The majority of human studies of epigenetic mechanisms in asthma have concentrated in DNA methylation using both genome-wide and candidate-gene approaches and sampling different biologic compartments (i.e., epithelial vs. immune). These studies have revealed how methylation patterns in the blood are associated with distinct mechanisms and characteristics of childhood asthma.

Candidate-gene studies have revealed that intermediate and high methylation of the beta-2-adrenergic receptor (*ADRB2*) in the blood is associated with severe asthma, and how this association is modified by nitrogen dioxide (NO_2), a known air pollutant [10]. However, a similar study showed that *ARDB2* methylation was associated with decreased dyspnea in children with asthma [11]. Cohort-specific characteristics may underlie these discrepancies, and this observation requires additional studies.

Genome-wide methylation studies have demonstrated that hypomethylation at arachidonate 12-lipoxygenase (*ALOX12*) CGIs in blood samples was associated with increased risk of persistent wheezing [12]. Hypomethylation of *IL13*, *RUNX3*, and *TIGIT* in blood was associated with asthma [13•]. Similarly, hypomethylation of CGIs associated with *IL5RA* was associated with asthma in teens [14]. An additional observation from Arathimos et al. [14] was the demonstration of cell-specific effect in the strength of the association between methylation and asthma, suggesting that methylation analysis of pooled cells may affect these observations. The impact of cell-specific methylation in childhood asthma was confirmed by Xu et al. by demonstrating that hypomethylation of 14 CpG sites in eosinophils was associated with childhood asthma [15•]. Thus, blood methylation studies must be subject to cell-specific analyses, and cell-specific methylation patterns may affect the interpretation of previous studies.

Analyses of cord blood and blood spots have been used to evaluate associations with allergic disease and asthma. Hypermethylation of the *GATA3* transcription factor at birth was associated with a decreased risk of asthma [16]. Methylation differences between cord blood and mid-childhood peripheral blood have also identified an association

between IgE levels, *C7orf50*, and *ZAR1* [17]. Analysis of blood spots demonstrated that hypermethylation of the *AXL* receptor at birth was associated with increased risk of wheezing, an association stronger in girls than boys [18], suggesting sex-specific effects of methylation. Thus, methylation profiles at birth identified in cord blood and blood spots are associated with the risk of wheezing, asthma, and IgE levels in children.

Methylation on buccal DNA has demonstrated that increased methylation of arginase 2 (*ARG2*) was associated with decreased fractional exhaled nitric oxide (FeNO) in children with asthma [19]. Similarly, decreasing mouse allergen exposure led to decreased *FOXP3* promoter methylation [20]. Together these observations suggest a role for methylation in the control of airway inflammation and immune signaling.

In airway epithelial cells (AECs) of asthmatics, CGIs were differentially methylated in the *STAT5A* transcription factor leading to downregulation of *STAT5A* expression [21]. This mechanism is relevant in the control of downstream signaling following stimulation of specific ligands that include IL-2, IL-3, IL-7, and GM-CSF. A similar study demonstrated that hypomethylation of *IL-6* and nitric oxide synthase 2 (*NOS2*) was associated with increased FeNO [22]. In African American children, arachidonate 15-lipoxygenase (*ALOX15*) and periostin (*POSTN*), two genes involved in Th2 (Type 2) immune responses, were differentially methylated in the nasal epithelium [23•]. More recently, a large study showed that methylation profiles in the airway epithelium of atopic children accumulated near genes involved in epithelial barrier function including cadherin related family member 3 (*CDHR3*) and cadherin 26 (*CDH26*). This study also demonstrated that a methylation-based classifier in nasal epithelium is able to discriminate atopy and atopic asthma in Hispanic, African American, and European children [24•]. The use of this methylation signature in the nasal epithelium has potential implications in the evaluation of children with atopy at risk for the development of wheezing and asthma [24•].

Table 1 summarizes studies of DNA methylation in childhood asthma. Gene methylation plays an essential role in childhood asthma through regulation of a substantial number of genes involved in allergic responses, demonstrating a strong association with the development of asthma and maintenance of inflammation via epigenetic control of IgE and FeNO, among other mechanisms.

Adult Asthma

Studies of DNA methylation in adult asthma are scarce. A study of asthmatics who smoke showed increased methylation of protocadherin-20 (*PCDH20*) in sputum cells. This association was robust despite adjustment for environmental factors [25]. Evaluation of methylation changes in airway epithelium demonstrated an association between CGIs and specific asthma endotypes [26••]. Specific methylation signatures were associated with inhaled corticosteroid (ICS) use, eosinophil counts and FENO, and IL-13 response modules [26••]. A separate study of methylation in blood identified methylation differences in gene networks associated with specific asthma subtypes, with enrichment of calcium signaling and purine metabolism genes in eosinophilic asthma, and wnt signaling pathway in neutrophilic asthma [27]. Together these studies support the role of distinct methylation patterns in association with asthma phenotypes and potentially endotypes.

Asthma Risk Environmental influences play a significant role in asthma and have an effect on DNA methylation. A study of prenatal exposure to traffic-related airborne polycyclic

Table 1 Methylation studies in childhood asthma, IgE, and wheezing

Phenotype	Tissue	Genes	Reference
Childhood asthma	Blood	*ADRB2*	[10]
Childhood asthma	Blood and buccal	*ADRB2*	[11]
Childhood wheezing	Blood	*ALOX12*	[12]
Childhood asthma	Blood	*IL13*, *RUNX3*, *TIGIT*	[13•]
Childhood asthma	Blood	*IL5RA*	[14]
Childhood asthma	Blood	14 sites	[15•]
Childhood asthma	Cord blood	*GATA3*	[16]
IgE levels	Cord blood	*C7orf50* and *ZAR1*	[17]
Wheezing	Blood spots	*AXL*	[18]
Childhood asthma	Buccal	*ARG2*	[19]
Childhood asthma	Buccal	*FOXP3*	[20]
Childhood asthma	Airway epithelium	*STAT5A*	[21]
Childhood asthma	Airway epithelium	*IL6*, *NOS2*	[22]
Childhood asthma	Airway epithelium	*ALOX15*, *POSTN*	[23•]
Childhood asthma	Airway epithelium	*CDHR3*,*CHD26*	[24•]

aromatic hydrocarbons demonstrated an association between methylation of acyl-CoA synthetase long-chain family member 3 (*ACSL3*) and asthma symptoms before the age of 5 [28]. A separate study identified increased methylation in the *FOXP3* locus of asthmatic children exposed to higher ambient pollution and an association with impaired regulatory T cells (Tregs) [29]. Further studies have demonstrated an interaction between air pollution and differential methylation of discs, large homolog 2 (DLG2) with concomitant changes in expression in the blood. Similarly, cigarette smoke also modulates DNA methylation, demonstrated by differential fetal lung tissue and placental methylation in association with cigarette smoke exposure [30], while two separate studies showed that prenatal tobacco exposure is associated with widespread differences in blood DNA methylation of children [31, 32]. It is unclear how these differentially methylated loci are associated with asthma but demonstrate the critical role of environmental influences in methylation profiles.

In children born to asthmatic mothers, *SMAD3* methylation at birth was associated with childhood asthma risk and was more prominent in asthmatic mothers [33]. A separate study demonstrated a similar effect of maternal asthma in the blood methylome of children [34]. *MAPK8IP3* methylation in children was negatively correlated with maternal blood eosinophils, FeNO, and total IgE [34]. These studies suggest that in utero exposure to an asthmatic mother affect DNA methylation in offspring and may have implications in the development of asthma.

Role of microRNAs in Asthma MiRNAs are deeply involved in the regulation of normal and pathologic cellular responses [35]. The *let-7* family of miRNAs in human, animal, and in vitro studies has been associated with modulation of Th2 inflammation [36–38]. IL-12, a molecule involved in Th1 cell polarization, is regulated by *miR-21* [39]. Studies on the impact of genetic variation on miRNA function and their association with asthma have identified *miR-146a* as a candidate molecule in asthma [40]; in addition, variation on HLA-G in children affects asthma risk through interaction with *miR-152* [41]. Two miRNAs, *miR-155* and *miR-221*, have been associated with Th2 responses and several cellular components of the allergic response, including eosinophils [42], macrophages [43], and mast cells [44] in both asthma and allergic rhinitis. Several miRNAs, *miR-26* [45], *-133a* [46], *-140* [47], *-206* [48], and *-221* [49], have been associated with an effect on smooth muscle cell function and proliferation. Despite this important role, few studies have been focused on the role played by miRNAs on severe asthma [49–51]. These studies in severe asthma demonstrated that *miR-221* controls the increased proliferation in the airway smooth muscle cells from patients with severe asthma [49]; downregulation of *miR-28-5p* and *miR-146a/b* led to the activation of circulating CD8+ T cells in severe asthma [50]; and *miR-223-3p*, *miR-142-3p*, and *miR-629-3p* were associated with severe neutrophilic asthma[51]. Eight serum microRNAs, including *miR-296-5p*, were associated with PC20 in the Childhood Asthma Management Program (CAMP) cohort [52]. Budesonide, an inhaled corticosteroid used to treat asthma, showed a modest effect on the miRNA profile in bronchial epithelium of steroid-naïve asthmatics after treatment [53•]. Together, these observations on the role played by multiple miRNAs in asthma highlight their effect on the control of inflammatory responses, Th1/Th2 polarization, cell function, disease severity, and response to therapy.

Role of Histone Modifications in Asthma Epigenetic changes in histones are an understudied mechanism in asthma. In children, the ratio of HDAC/HAT activity was skewed toward increased histone acetylation in allergic asthmatic subjects, and the degree of cellular acetylation activity was associated with increased severity of bronchial hyperresponsiveness [54]. In mononuclear cells of adults with asthma, nuclear HDAC and HAT activities were reduced in patients with severe asthma compared with patients with nonsevere disease [55]. A study characterizing genome-wide histone modifications in T cell subsets from patients with asthma and healthy controls demonstrated asthma-specific differences in cell enhancers involved in T cell differentiation [56]. Finally, human bronchial epithelial cells (HBECs) of adult asthmatics demonstrated decreased tight junction integrity compared with cells from healthy subjects. Expression of *HDACs* -1 and -9 and *Sirtuins* -6 and -7 were higher in HBECs from asthmatic patients. HDAC inhibition was associated with improvement of tight junction molecules to levels comparable with those seen in healthy controls [57]. Together, these observations identify a cell- and asthma-specific overlap resulting from distinct histone modifications.

Conclusions

Data integration of omics data (genome-wide variation, transcriptome, methylome, and microRNAs) in well-characterized cohorts can potentially improve our understanding of these associations. A significant limitation to our current understanding of asthma is the lack of studies in adults, the effect of histone modifications in asthma, environmental data, and the extent of associations with specific asthma endotypes. These observations need to be translated into better prediction models, as well as the development of biomarkers and therapies targeting dysregulated pathways.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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