

Recent advances in the epigenetics and genomics of asthma

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Purpose of review

Epigenetics is the study of heritable changes in gene expression that occur without direct changes in the DNA sequence. Epigenetic mechanisms may explain important observations in asthma, such as the effect of the environment during certain periods in life, transgenerational, and maternal effects and account for some of the missing heritability in asthma. Here, we review recent evidence for the role of epigenetics and genomics in asthma.

Recent findings

Environmental factors known to increase asthma risk affect methylation patterns in the genome, yet the link to subsequent asthma development is not yet established. Posttranslational histone modifications and chromatin remodeling are important in establishing T-helper-2 cell differentiation. MicroRNAs have been shown to regulate experimental asthma in mice. Integration of genomic methods leads to increased understanding on how variation at the DNA levels affects mRNA transcription or chromatin remodeling.

Summary

Epigenetic mechanisms regulate gene expression at the DNA, mRNA, and the chromatin level and more studies are needed to establish its role in human asthma. Integration of genomic methods will provide more insight into the complex pathophysiology of asthma.

Keywords

epigenetics, expression quantitative trait loci, histone modification, methylation, microRNA

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Introduction

Asthma is a common chronic disease, characterized by respiratory symptoms, variable airflow obstruction, and airway hyperresponsiveness. Most of asthma has its origins in childhood, yet its initiation is incompletely understood. Asthma results from genetic factors, environmental effects, and their interactions. According to twin studies, on average 50–60% of liability to develop asthma is heritable [1].

Since completion of the draft version of the human genome project in 2000, tremendous progress has been made in the dissection of monogenic and multifactorial diseases. The number of loci identified by genome-wide association studies (GWASs) for any complex disease increased from 12 in 2000 to over 1100 loci in 165 diseases in 2010 [2]. This trend can also be observed for asthma. Since 2007, 13 genome wide significant asthma loci have been found by eight GWASs and meta-analysis [3]. However, the proportion of genetic variance (heritability) explained by single nucleotide polymorphisms

(SNPs) varies between different diseases, ranging from 60% for type I diabetes to 20–25% for type II diabetes and Crohn's disease [2]. For asthma, SNPs explain less than 5% of its heritability, as estimated from the largest GWAS in asthma [4••]. It may be anticipated that larger GWAS will reveal more SNPs for asthma and, thus, explain more of the heritability. However, it becomes increasingly clear that a large proportion of heritability cannot be explained by common SNPs with small effects that are typically found in GWAS, a phenomenon commonly referred to as 'hidden heritability'. Sources of this hidden heritability include rare DNA variants, large deletions, gene–gene and gene–environment interactions, copy number variants, and epigenetics [5].

In this review, we will focus on recent progress made in epigenetic and genomic research in human and animal studies in asthma. We first provide an outline of epigenetics, summarize observations in asthma that could be explained by epigenetics, discuss recently published studies in this field, and provide some directions for future research.

Epigenetics

Epigenetics refers to heritable changes in gene expression that occur without directly changing the DNA sequence. These changes can occur at the DNA level through DNA methylation at CpG residues; at the level of chromatin by posttranslational modifications of histones and chromatin remodeling that regulate accessibility of the DNA; and at the mRNA level by small noncoding RNAs, including microRNAs (miRNAs), that interfere with translation (Fig. 1). Epigenetic changes result in altered gene transcription and translation. Epigenetics is important in biological processes such as embryogenesis, but also in disease such as cancers and immune disease [6]. Epigenetic regulation may be dynamic throughout the lifespan, is cell-specific and tissue-specific, and is used to selectively inactivate genes depending on the parental origin, such as paternal or maternal imprinting. Epigenetics may be affected by the environment and contribute strongly to phenotypic variation [6].

Observations in asthma potentially explained by epigenetics

Several observations in asthma could be consistent with epigenetic effects, such as the effect of environmental factors during specific periods in life, maternal effect on asthma, and transgenerational transmission of asthma. This has caused considerable enthusiasm for the role of epigenetics in the field of asthma [7,8,9].

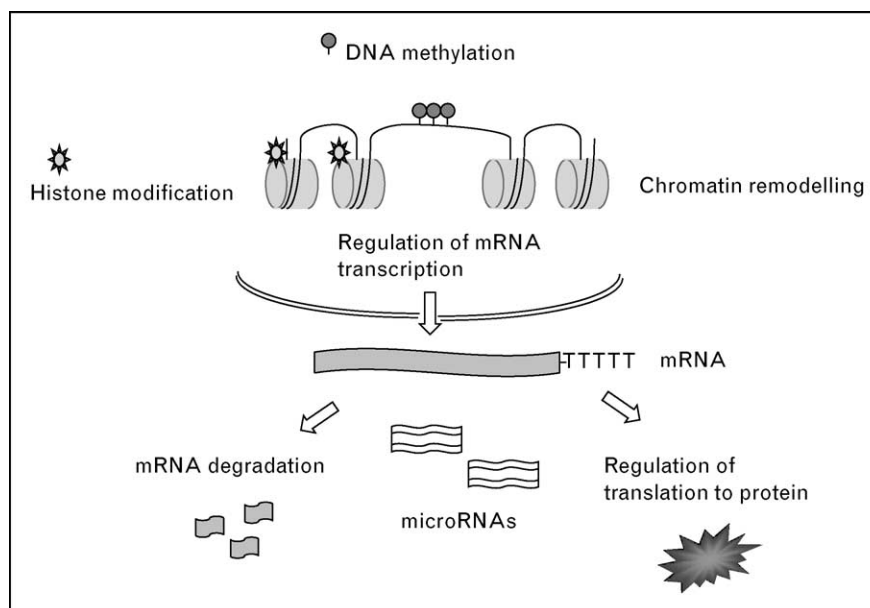
Key points

- Epigenetics may explain environmental, parent of origin and transgenerational effects in asthma.
- Epigenetic mechanisms regulate tissue-specific expression of asthma genes.
- T-helper cell differentiation is under strong epigenetic regulation.
- Micro RNA let-7 family members are involved in regulating experimental asthma in mice.
- Integration of genomic methods will provide more information on the complex pathogenesis of asthma.

Environmental exposures such as traffic-related air pollution, cigarette exposure *in utero*, dietary factors such as folic acid intake in pregnancy, and endotoxin or farm exposure during early life are associated with altered risk of asthma, as well as changes in epigenetic signatures in the genome (reviewed in Kabesch *et al.* [9]). However, very little data actually link these changes in epigenetic patterns to asthma in a longitudinal fashion.

Maternal effects in asthma and atopy have been described in several cohort and family studies [10]. Frequently, maternal atopy confers a greater risk for atopy development in the offspring than paternal atopy. In fact, some genetic studies indicate that inheritance from maternal, but not paternal alleles is linked to atopy or asthma in the children. This has, for example, been variably shown for a locus on 3q21 [11] and for the gene

Figure 1 Epigenetic regulation of gene expression



DNA methylation refers to the addition of a methyl group to the 5' position of the cytosine ring to create a 5-methylcytosine. Posttranslational histone modifications and chromatin remodeling regulate accessibility of the DNA for transcription. MicroRNAs are encoded by the DNA and may degrade target mRNA or inhibit translation.

encoding the beta chain of the high affinity IgE receptor (*MS4A2*) on chromosome 11q [12]. However, a recent study [13•] showed that methylation patterns of an Alu repeat in this latter gene were not consistent with classical imprinting and did not relate to the atopic status. Examples of specific patterns of CpG methylation depending on maternal or paternal inheritance have also been reported [14] and we, thus, suggest to direct future studies at imprinting effects in asthma.

Transgenerational transmission of asthma was evidenced by a nested case–control analysis performed in the Children’s Health Study in California, USA. The risk of parental-reported asthma in the first 5 years of life was analyzed in relation to maternal and grandmaternal smoking patterns. *In utero* smoke exposure by the mother was associated with an increased risk of asthma at age 5. Interestingly, grandmaternal smoking was also associated with increased asthma risk, independent of maternal smoking [15]. These data might indicate epigenetic effects of cigarette smoke exposure *in utero*. However, these effects are not necessarily inherited transgenerationally, as cigarette smoking during pregnancy will not only expose the fetus, but also the oocytes of a female fetus, as oogenesis takes place in the first 3 months of gestation. Further studies using a four-generation design are needed to assess the relative contribution of direct environmental effects on *in utero* development versus inheritable epigenetic changes induced by cigarette smoke exposure.

DNA methylation in asthma

DNA methylation is the best studied epigenetic mechanism and refers to the covalent binding of a methyl group to the 5’ position of the cytosine ring to create a 5’ methylcytosine. DNA methylation is typically, but not exclusively, found at CpG sites in the mammalian genome. These CpG sites tend to cluster at the 5’ site of the majority of genes, often at transcription initiation sites. Methylation of these CpG sites results in loss of transcription, whereas demethylation increases gene transcription. Methylation is used to regulate gene transcription in a cell-specific manner. For example, *ADAM33*, the first asthma gene identified by positional cloning [16], is expressed in airway fibroblasts and smooth muscle cells, but not in airway epithelium due to methylation of the *ADAM33* promoter [17].

One of the first indications of the relevance of methylation in experimental asthma came from a mouse model, in which mice were given a diet supplemented with methyl donors, known to increase DNA methylation. Offspring of these mice were fed on a normal diet and showed more severe features of ovalbumin-induced experimental asthma, including more severe airway

hyperresponsiveness and higher numbers of eosinophils in bronchoalveolar lavage than control mice. A high methyl donor diet of the mother was also associated with differential methylation at 82 gene-associated loci [18]. Human data from a birth cohort study [19] in Norway on perinatal maternal folic acid supplementation, a methyl donor, indicate the relevance of the observations in this mouse model. Folic acid supplements were associated with children’s wheezing symptoms at 18 months of age. Children from this birth cohort with maternal plasma folate levels in pregnancy in the highest compared with the lowest quintile had a higher risk of reporting asthma at age 3 [20•]. A longitudinal study [21] in Australia identified a significantly increased risk of asthma at age 3.5 years, but not at 5.5 years in children of mother taking folic acid supplements in late pregnancy. Still, longer follow-up and investigations of objective measures of asthma in relation to folic acid use are needed.

The possible link between traffic-related air pollution-exposed pregnant women, methylation patterns of their offspring, and subsequent asthma development was investigated in a study [22] of an inner city birth cohort in New York. Specifically, individual maternal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) was assessed. In 20 children, methylation-sensitive restriction fragment length polymorphisms of cord blood leukocytes revealed that methylation status of 31 loci were related to maternal PAH exposure, and with gene expression for *ACSL3* (*Acyl co-A synthetase long-chain family member 3*). In 56 children, methylation of *ACSL3* was associated with asthma at age 5. Although this is a small pilot study that needs replication, it represents one of the first attempts to relate antenatal exposures, offspring methylation patterns, and subsequent asthma development.

Finally, genes known to be involved in the production of nitric oxide were investigated in buccal mucosal cells in a US study [23]. Methylation of *ARG1* and *ARG2* was associated with exhaled nitric oxide levels. This association was stronger in asthmatic individuals compared with healthy controls. Moreover, this effect of methylation on exhaled nitric oxide levels was independent of *ARG1* and *ARG2* SNPs.

Higher-level gene regulation by microRNAs in asthma

miRNAs are small, noncoding RNA molecules that mediate gene silencing through translation repression or mRNA degradation. miRNAs are expressed in a tissue-specific fashion and are thought to orchestrate higher-order gene regulation by binding to multiple mRNA transcripts, resulting in coordinated repression of translation [24]. Expression of miRNAs is highly regulated

during development and organogenesis, including lung development, such as a maternally imprinted miRNA cluster containing the miR-154 and miR-335 families that was found to be upregulated in mouse and human fetal lung [25].

Dysregulated expression of miRNAs has been shown to contribute to lung disease such as lung cancer and experimental asthma in mice. The role for miRNAs in lung cancer was established by a groundbreaking study [26] that indicated miRNA let-7 as a critical negative regulator of the Ras oncogene and showed strongly reduced expression of let-7 family members in lung cancer compared with normal lung tissue. Further studies in mice found that let-7 family members also contributed to experimental asthma. In mouse lung, more than 50% of all miRNAs were found to belong to the let-7 family [27]. Expression of let-7 family members did not change with allergen exposure, although other miRNAs (miR-147, miR-135, miR-715, and miR-712) did. Let-7 family members were predicted to bind the 3'untranslated region (UTR) of the IL-13 mRNA transcript, and expression levels of let-7 and IL-13 were inversely correlated in Th2 cells, but not in lung [27]. Also in human T cells, IL-13 and let-7 levels were found to be inversely correlated, and ectopic expression of let-7 was shown to reduce IL-13 protein production [28^{••}]. These authors observed a decreased expression of let-7 family members in the lungs of allergen-challenged mice compared with naive animals. Remarkably, IL-13 protein levels in lung were fully suppressed by in-vivo delivery of let-7 miRNA by inhalation. This was accompanied by reduced airway hyperresponsiveness, airway inflammation, and mucous cell metaplasia [28^{••}]. Moreover, inhibition of miR-145 [29^{••}] or miR-126 [30] inhibited eosinophilic inflammation, mucus hypersecretion, Th2 cytokine production, and airway hyperresponsiveness in a house dust mite (HDM)-driven mouse model of experimental asthma and was as effective as treatment with dexamethasone in the case of miR-145 [29^{••}]. This indicates that interference with miRNA-mediated target gene repression might allow interesting novel therapeutic opportunities in asthma.

Only one miRNA profiling study [31] is available in human participants, comparing the expression levels of 227 miRNAs in airway wall biopsies of eight mild asthmatic individuals and eight healthy controls, and analyzing the effect of corticosteroid treatment. No significant differences in miRNA expression profiles were observed in relation to asthma status or corticosteroid treatment. These results in human asthma might be partly due to the selection of miRNAs studied, the low number of participants, or the choice to include only mild, but not more severe asthmatic individuals. Clearly, more studies are needed.

Finally, SNPs located in the 3'UTR of *HLA-G*, an asthma susceptibility gene [32], corresponded to an altered miRNA-binding site, which suggests that allele-specific binding of miRNAs to the 3'UTR of *HLA-G* might contribute to the association of *HLA-G* polymorphisms and asthma [33].

Histone modification and chromatin remodeling

Chromatin exists of DNA stretches of 147 base pairs in length, wrapped around an octamer of eight histone proteins, a structure known as the nucleosome. Each histone protein has an amino-terminal tail that protrudes from the nucleosome and is subject to posttranslational modification [34[•]]. Histone tails can encode both permissive epigenetic marks (associated with enhanced gene transcription) such as histone acetylation and trimethylation on histone H3 lysine 4 (H3K4), H3K36, or H3K79, and repressive epigenetic marks (associated with reduced gene transcription) such as dimethylated or trimethylated H3K27, H3K9, or H4K20 [35].

One clear example of the relevance of histone modifications stems from T-helper cell differentiation. Asthma is characterized by skewed T-helper cell differentiation toward the Th2 phenotype, a process that is critically dependent on STAT6-driven activation of GATA3 expression and adaptation of the Th2 cell fate, characterized by the production of cytokines such as IL-4 and IL-13. Epigenetic mechanisms are critical for implementation of cell fate decisions during Th2 cell differentiation [35,36]. For instance, expression of STAT6 is regulated by methylation, rather than by SNPs in the promoter region [37]. STAT6 has been shown to regulate gene expression through inducing permissive chromatin signatures at Th2-expressed genes, while inducing repressive chromatin signatures at genes expressed in Th cells of alternative fates [35]. Th cell subset-specific effector cytokines carry repressive epigenetic marks in cells that have adopted another Th cell phenotype, such as methylation of the IFN γ locus, a Th1 cytokine, in Th2 cells [38] or methylation of the *IL4-IL13* locus in Th1 cells [39]. Mouse models have shown that conserved regulatory regions in the mouse *il4-il13* locus are critical for inducing and maintaining the permissive epigenetic marks in the Th2 locus such as histone methylation and acetylation, allowing Th2 cytokine expression and the development of an asthmatic phenotype *in vivo* [40[•],41[•]]. Thus, combined epigenetic effects regulate the differentiation and maintenance of T-helper subsets [9[•],42].

The level of histone acetylation, a posttranslational modification associated with enhanced gene expression, is dependent on the balance of histone deacetylase (HDAC) and histone acetyltransferase (HAT) activity.

The relevance of histone acetylation for asthma was established in mouse models showing that loss of histone acetylation in the *il4-il13* locus strongly reduced Th2 effector functions *in vivo* [41•], whereas T-cell specific loss of HDAC1 resulted in increased acetylation of this locus, strongly enhancing Th2 effector functions and asthma phenotype *in vivo* [43]. In human studies, inhibition of HDAC activity during ex-vivo stimulation of antigen-experienced T cells selectively enhanced Th2-associated responses while reducing Th1-associated responses [44]. Moreover, the ratio of HDAC over HAT activity in peripheral blood mononuclear cells isolated from atopic children was found to correlate to bronchial hyperresponsiveness [45]. These studies underscore the relevance of histone acetylation for Th2 effector activity in asthma. Of note, increasing HDAC activity represents an interesting therapeutic opportunity for regulating inflammation in asthma [46].

Conclusion

Although genomic methods are able to provide substantial information on one dimension of asthma (i.e. whole genomic SNP information, transcriptome, epigenome, and proteome), integration of these datasets using multi-dimensional approaches will provide an opportunity to fully appreciate the complexity of asthma [47]. A first step is the integration of SNP genotype and mRNA expression, called expression quantitative trait loci (eQTL) mapping. eQTL mapping asks whether SNPs regulate the expression of the gene in which the SNP is located (in cis) or an unrelated gene (in trans). One example in asthma was provided by the first asthma GWAS, showing that SNPs on 17q12–21 that are associated with childhood asthma regulate expression of *ORMDL3* [48]. Subsequent work showed that next to *ORMDL3*, the expression of other genes on 17q12–21 is also regulated by asthma-associated SNPs, and that one SNP affects a binding site for a nucleosome binding protein and thus regulates chromatin remodeling in this chromosomal region [49]. Recently, whole genome eQTL mapping in CD4⁺ T lymphocytes in 200 participants showed that significant associations were observed for 1585 loci, with a 63% overrepresentation of disease-associated genes, indicating the importance of these regulatory mechanisms in disease development [50•]. Future studies will likely provide more information on rare genetic variants in the genome as a result of the 1000 Genomes Project [51], as well as full sequence information of the RNAome. We expect that the integration of these datasets will provide more insight into complex regulatory mechanism in asthma.

Epigenetics may explain important observations in asthma. Future longitudinal studies are needed to understand how environmental factors may regulate

epigenetics and lead to asthma. The fact that epigenetic signatures are dynamic holds promise for new options to prevent or treat asthma.

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Conflicts of interest

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