# A translational perspective on epigenetics in allergic diseases



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**Overall Purpose/Goal:** To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

**Target Audience:** Physicians and researchers within the field of allergic disease.

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**Activity Objectives:**

1. To understand the concept of epigenetics and the role of epigenetic modifications in shaping the incidence and phenotype of allergic diseases.
2. To know the cellular and molecular processes involved in modification of the epigenome.
3. To understand the ways by which the environment, nutrients, and the microbiome can affect the development and course of allergic diseases through alterations in the epigenetic code.

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**The analysis of epigenetic modifications in allergic diseases has recently attracted substantial interest because epigenetic modifications can mediate the effects of the environment on the development of or protection from allergic diseases. Furthermore, recent research has provided evidence for an altered epigenomic landscape in disease-relevant cell populations. Although still in the early phase, epigenetic modifications, particularly DNA methylation and microRNAs, might have potential for assisting in the stratification of patients for treatment and complement or replace in the future biochemical or clinical tests. The first epigenetic biomarkers correlating with the successful outcome of immunotherapy have been reported, and with personalized treatment options being rolled out, epigenetic modifications might well play a role in monitoring or even predicting the response to tailored therapy. However, further studies in larger cohorts with well-defined phenotypes in specific cell populations need to be performed before their implementation. Furthermore, the epigenome provides an interesting target for therapeutic intervention, with microRNA mimics, inhibitors, and antisense oligonucleotides being evaluated in clinical trials in patients with other diseases. Selection or engineering of populations of extracellular vesicles and epigenetic editing represent novel tools for modulation of the cellular phenotype and responses, although further technological improvements are required. Moreover, interactions between the host epigenome and the microbiome are increasingly recognized, and interventions of the microbiome could contribute to modulation of the epigenome with a potential effect on the overall goal of prevention of allergic diseases. (J Allergy Clin Immunol 2018;142:715-26.)**

***Key words:*** *Epigenetics, DNA methylation, microRNA, biomarker, allergy, asthma, forkhead protein 3, epigenetic editing, antagomirs, antisense molecules, oligonucleotide therapy*

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*Abbreviations used*
EV: Extracellular vesicle
EWAS: Epigenome-wide association study
FOXP3: Forkhead protein 3
HDAC: Histone deacetylase
ICS: Inhaled corticosteroid
miRNA: MicroRNA
Treg: Regulatory T
TSDR: Regulatory T cell–specific demethylated region

There has been a rapid increase in the prevalence of allergic diseases, including IgE-related asthma, in the Western world. For example, severe asthma is now reaching a prevalence of 8%, and challenge-proven food allergy has reached a prevalence of up to 10% in Australia and 2% to 4% in the United States and European countries.[1-4] Allergic diseases are nowadays a major cost factor for the health care system, with estimated worldwide costs for asthma close to 100 billion US dollars per year and 25 billion US dollars for food allergy in the United States only.[5,6]

Epigenetics is "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" or, as defined more recently, "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states."[7] Epigenetics determines which regions of the genome will be accessible and expressed with changes or altered plasticity leading to potentially disease-predisposing physiologic states. Recently, the analysis of epigenetic modifications, including DNA methylation, posttranslational histone modifications, nucleosome occupancy, and small and long noncoding RNAs, has attracted much interest in the field of allergic disease. Epigenetics might indeed hold the key to explaining the high degree of plasticity of the immune response throughout life. Epigenetics can also mediate the effects of environmental protective and risk factors on the development and course of asthma and allergic diseases.[8]

Although still under debate, a number of explanations for the increased prevalence of allergic diseases have been proposed, including increased hygiene, insufficient exposure to microbes, and Western diet.[8] Of note, many of these factors can exert their effects on cellular homeostasis through alteration of the epigenetic code. In this review I will briefly describe the potential applications using epigenetic modifications, including DNA methylation, histone modifications, and small noncoding RNAs (microRNAs [miRNAs]) for asthma and allergic diseases (Fig 1).

## DNA METHYLATION

A number of epigenome-wide association studies (EWASs) have been performed and have identified, at least in asthmatic patients, common themes, such as the importance of eosinophils and regulatory T (Treg) cells and probably an altered epigenetic state of these cells.[9-11] Large-scale EWASs have also shown that disease-predisposing environmental factors, such as prenatal maternal smoking or prenatal or postnatal air pollution, lead to DNA methylation changes at genes with relevance for asthma and allergic diseases.[12-15] Although most studies have focused on analysis of blood-based immune cells (reviewed by Potaczek et al[8]), it has also been shown that respiratory epithelial cells from the nose or the bronchium show differential methylation between asthmatic patients and control subjects, with differences in DNA methylation levels exceeding those normally observed in blood cells.[16,17] In addition, nasal epithelial cells might represent a good proxy for upper airway epithelial cells.[18] However, a number of challenges remain for the biological interpretation and clinical implementation of EWAS-identified DNA methylation changes, such as the choice of the best tissue and cell type for analysis, the lack of reproducibility of identified changes between studies, and concerns on the functional relevance caused by the small magnitude of the detected changes. Furthermore, coverage of the human methylome is still limited in most studies because epigenotyping arrays, the most commonly used tools for genome-wide DNA methylation analysis, cover only between 450,000 and 840,000 CpG positions of the 29 million CpGs present in the human genome, corresponding to only 1.6% to 2.9% of all CpGs. Although a major criticism of DNA methylation analyses has been that changes will only reflect variations in proportions of the analyzed cell populations, recent results have also shown that not only are cell proportions changed but also the epigenomic landscape is modified in specific cell populations.[10,19]

Nonetheless, EWASs have great potential for explaining phenotypic variability, as exemplified by a study on DNA methylation levels associated with serum IgE levels, which showed a 10-fold greater capacity of genome-wide DNA methylation patterns to explain the observed variability in IgE concentrations compared with genetic variation.[20] EWASs might not only deepen our understanding of the underlying disease etiology by pointing to disease-relevant pathways, such as the $T_H1/T_H2$ pathway[21] and other immunologically relevant pathways in patients with cow's milk allergy[22] but could also provide a multitude of other target genes that need to be further investigated in functional studies, including transcription factors, mitochondrial proteins, and proteins involved in T-cell maturation or oxidative stress. However, despite common themes, there is currently a lack of consistency between the findings from different studies, which might be due to differences in the analyzed populations, the definition of the underlying phenotype, and statistical methods used for analysis. Signatures of differentially methylated positions are in some cases already present at birth and predict future onset of the allergic disease.[23] However, in a recent large-scale study on childhood asthma, none of the asthma-associated CpGs were found to be differentially methylated at birth, pointing rather to the postnatal environment as the critical period. However, heterogeneity of the different analyzed populations, as well as unknown confounders, might limit the ability to replicate the findings of the discovery cohorts in the birth cohort.[10]

### DNA methylation changes as potential biomarkers for allergic disease

Different allergic diseases manifesting at the same epithelial barrier organ do not show a homogeneous phenotype but constitute a highly heterogeneous group of diseases with different molecular endotypes. Phenotyping of inflammatory profiles has allowed for patient stratification and promoted the idea of personalized management of allergic diseases. However, there is currently a lack of robust, easy-to-measure, and preferentially nucleic acid–based biomarkers to tailor therapies to individual patients. The analysis of epigenetic changes has the potential to assist in the detection, management, and possibly prevention of allergic diseases as diagnostic tools; to assess tolerance after