



Epigenetics of allergy

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SUMMARY

Epigenetics has recently been considered as a potential mechanism involved in the development of many disorders, including allergic diseases. Animal models have shown that environmental factors such as maternal tobacco smoke or mechanical ventilation can alter gene transcription and consequently the structure and function of lungs. Moreover, asthma and other allergic diseases (atopic dermatitis and food allergy) are influenced by epigenetics. In fact, the exposure to environmental factors during early childhood may induce a long-lasting altered genetic state adapting to a persistent “Th2 state” thus influencing the development of asthma or atopic dermatitis and food allergy if alterations involve the filaggrin gene.

In conclusion, progresses have been made linking environmental pollution, environmental tobacco smoke (ETS) and diet exposure with atopy through epigenetic mechanisms. Furthermore, considerable advances have been made implicating epigenetic mechanisms in T cell differentiation. However, much more research is still needed, in particular to define the clinical consequences of such epigenetic alterations.

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1. Introduction

Epigenetics can be defined as the study of “heritable changes of a phenotype that are not caused by changes in the nucleotide sequence of the genetic code itself but are due to a different gene expression pattern of a specific cell type” [1]. These epigenetic changes involve methylation of DNA by the covalent addition of a methyl group to a cytosine residue in a CpG, posttranslational modification of the amino-acid tails of histones (proteins which help the two meter strand of human DNA fold into a tiny ball that will fit in the nucleus in each and every cell in the body) by means of acetylation, phosphorylation, methylation, sumoylation, or ubiquitylation. Other epigenetic mechanisms are related to the aberrant expression of microRNAs (miRNAs are small non-coding RNA molecules involved in translational repression and gene silencing). Each of these mechanisms is involved in posttranscriptional regulation of target gene expression [2]. Transcriptionally active chromatin is associated with acetylated histones, whereas inactive chromatin has methylated DNA and de-acetylated histones. DNA methylation, executed by methyltransferases, allows recruitment of methyl-binding domain proteins (MBD), which then recruit histone

deacetylases (HDAC, transcriptional co-repressors and other chromatin modifying enzymes) [3].

2. Epigenetics of infants' lung diseases

Epigenetics has recently been considered as a potential mechanism involved in the early origins of lung disease, particularly early events that alter lung development. In fact, animal models of intrauterine growth restriction (IUGR), preterm birth with the need for prolonged mechanical ventilation, and maternal tobacco smoke (MTS) or nicotine exposure display impaired alveolarization with alveolar simplification. Both IUGR and MTS often involve hypoxia. In contrast, mechanical ventilation is associated with recurring hypoxia and hyperoxia and volume trauma. Interestingly, these conditions result in increased elastin expression and disordered and excessive lung elastin deposition [4] accompanied by decreased expression of vascular endothelial growth factor (VEGF) and its receptor in the lung (VEGFR2), also crucial for alveolar formation [5]. Another gene that is important for alveolar formation is IGF1, which is increased in the lung of infants who died from bronchopulmonary dysplasia (BPD). Notably, a characteristic of the BPD lung phenotype is increased thickness and cellularity of the mesenchyme, where IGF1 is located. These characteristics could be due to increased IGF1 mRNA transcript and protein abundance in the lung [6]. There are two long-term implications when epigenetics and gene transcription are disrupted developmentally: the first is

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that altered gene transcription can change the final structure and function of an organ, via changes in transcription from apoptotic or proliferative genes. Secondly, when epigenetics of a gene are altered during development, the “new” epigenetic code becomes the platform for future epigenetic modifications that would normally accompany development [4].

3. Epigenetics of asthma and other allergic diseases

Moreover, there is now significant evidence that early immune development is altered in children affected by asthma and allergic diseases. During pregnancy, the maternal cellular immune system adapts to a “Th2 state” to down-regulate Th1 IFN- γ cell mediated immune responses to fetal antigens. This is realised by the suppression of fetal IFN- γ production via hypermethylation (gene silencing) of the IFN- γ gene promoter in CD4+ T cells at the materno–fetal interface [7]. Exposure to environmental factors during early childhood may induce a long-lasting altered genetic state persisting during life which may be reversed by mechanisms still undefined. Besides, Th2 cytokines are self-perpetuating the atopic state once IgE against environmental allergens have been produced [8]. Furthermore, a study performed in asthmatic subjects showed an increased histone acetyltransferase (HAT) activity and decreased histone deacetylase (HDAC) activity in bronchial biopsies compared to normal subjects. This may underlie the increased expression of multiple inflammatory genes, that is reversed, at least in part, by treatment with inhaled steroids. In fact, those subjects treated with inhaled corticosteroids showed a reduction of HAT and HDAC activity reflecting, in part, the repression of inflammation seen with these drugs [9]. Therefore, no gene alone is enough to predict or explain asthma, and there is a high degree of heterogeneity in the association of these genotypes among affected subjects. Asthma genes interact in a complex manner to regulate the risk and severity of the disorder, and genetics alone is insufficient to fully explain intersubject or interpopulation variations of the disease. The missing explanation could reside in gene–environment interactions, which are now supposed to be mediated by epigenetic mechanisms [2].

Other allergic diseases, such as atopic dermatitis and food allergy, are caused by a complex interplay of multiple factors including gene–environment interaction thus resulting in epigenetic changes. The gene most convincingly associated with eczema is the filaggrin (filament-aggregating protein) gene (FLG). FLG is a good candidate for food allergy too, as mutation in genes predisposing to eczema may increase the risk of food allergy as the skin or the mucosal barrier is more permeable to food allergens. FLG has a strategic role in epidermal barrier function: it aggregates keratin filaments within the cytoskeleton of keratinocytes. The cornified cell envelope formed acts a permeability barrier to water, microbes and allergens and contributes in maintaining skin integrity [10]. Nevertheless, since the rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by population-based changes in genetic sequence, it is most likely due to environmental factors. Such environmental stimuli include diet and nutrition: dietary methyl donors and cofactors, such as folic acid, vitamins B12, B6, B2 and zinc are necessary for DNA methylation and can modify the heritable risk of allergic airway disease. Other factors influencing the risk of food allergy include exposure to xenobiotic chemicals, maternal

behaviour, tobacco smoke and psychosocial stress. In particular, the exposure to tobacco smoke prenatally has been linked to aberrant global methylation in the placenta and cord blood as well as in children. Moreover, exposure to tobacco smoke has been linked to reduced HDAC expression and activity, which may account for the enhanced expression of inflammatory mediators (IL-8 and TNF- α) [11].

4. Conclusions

In conclusion, there is increasing evidence that epigenetics mechanisms are involved in the development of asthma and allergic diseases (Fetal Programming – Developmental Origins of Health and Diseases). Progresses have been made linking air pollution, environmental tobacco smoke (ETS), diet exposure with atopy through epigenetic mechanisms. Furthermore, considerable advances have been made implicating epigenetic mechanisms in T cell differentiation, especially at the IFN- γ locus. However, much more research is still needed, particularly to delineate the role of epigenetics in the lineage commitment of Treg cells and also to define the clinical consequences of such epigenetic alterations. Longitudinal cohort studies are needed to examine the time course and time period of susceptibility to epigenetic regulation following environmental exposure and their contribution to allergic disease. Ultimately, an individual's epigenome early in life may be a helpful biomarker in determining later risk of asthma and atopy and initiating an early intervention. Emerging epigenetic paradigms in allergic disease are likely to offer further novel insights into the mechanisms and pathways through which the early environment can be used to modify immune development and prevent allergic disease.

Conflict of interest statement

The authors have no financial and personal conflict of interest to declare.

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