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Update on epigenetics in allergic disease

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Chronic inflammatory diseases, including allergies and asthma, are the result of complex gene-environment interactions. One of the most challenging questions in this regard relates to the biochemical mechanism of how exogenous environmental trigger factors modulate and modify gene expression, subsequently leading to the development of chronic inflammatory conditions. Epigenetics comprises the umbrella of biochemical reactions and mechanisms, such as DNA methylation and chromatin modifications on histones and other structures. Recently, several lifestyle and environmental factors have been investigated in terms of such biochemical interactions with the gene expression–regulating machinery: allergens; microbes and microbial compounds; dietary factors, including vitamin B12, folic acid, and fish oil; obesity; and stress. This article aims to update recent developments in this context with an emphasis on allergy and asthma research. (J Allergy Clin Immunol 2015;135:15-24.)

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Chronic inflammatory diseases, including allergies and asthma, are the result of complex interactions between genetic predisposition and environmental factors. Based on the individual genetic makeup, life-long exposures to various environmental, nutritional, and lifestyle factors contribute to either disease development or protection. Many of these external events directly or indirectly affect immune regulation. From a mechanistic point of view, one of the challenging questions is how such environmental components mechanistically affect immune functions.

In this regard the concept of ***epigenetic regulation*** has gained great interest in recent years.[1-3] Based on the given DNA sequence, epigenetic modifications comprise biochemical reactions that modulate and modify the accessibility of the gene transcription machinery. One such mechanism is CpG methylation directly occurring on the DNA sequence. Other mechanisms operate on the ***chromatin*** structure, such as biochemically modified ***histone*** protein tails that then subsequently allow or deny access of ***transcription factors*** to ***gene promoter regions***.

Such epigenetic modifications play an important role in cell differentiation but also in cell activation. Although each person's cells express the identical DNA sequence (with the exception of cancer cells and some others), the epigenetic makeup differs dramatically from tissue to tissue and cell type to cell type and also in a longitudinal fashion over time. Therefore it is of great importance to delineate the biochemical processes through which external environmental exposures and "hits" have a direct effect on the epigenetic program and therefore the development of tissue and organ functions to understand the development of chronic inflammatory diseases. In this regard prenatal and postnatal life events seem to play a pivotal role in which the susceptibility of environmental hits has an especially strong effect on immune development and functions.[4]

In this article we will focus on the following environmental factors and components, which have recently gained great interest in terms of epigenetic modifications in the field of allergy and asthma: allergen exposure; bacterial microbes and microbial components; dietary factors, such as folic acid, vitamin B12, and fish oil; obesity; and stress.

Abbreviations used

ADCYAP1R1:	Membrane receptor for pituitary adenylate cyclase–activating peptide
AluYb8:	DNA repetitive short interspersed nucleotide element
DNMT:	DNA methyltransferase
GPR15:	G protein–coupled receptor 15
GSTM-1:	Glutathione-S-transferase M1
HAT:	Histone acetyltransferase
HDAC:	Histone deacetylase
HDM:	House dust mite
FOXP3:	Forkhead box protein P3
OVA:	Ovalbumin
Th-POK:	Th inducing POZ-Kruppel factor
Treg:	Regulatory T
ZFP57:	Zinc finger protein 57

SOME PRINCIPLES OF EPIGENETIC MODIFICATION

There are many examples showing that epigenetic modifications are neither permanent nor transient. Some of them are implemented into the epigenome for a short time to open or close the chromatin or to change the methylation status of a certain gene.[5] Furthermore, epigenetic modifications are in most cases reversible. With the appropriate enzymatic machinery, the whole

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Terms in boldface and italics are defined in the glossary on page 16.

epigenome can be modified and changed.[6] In this review we will focus on some principles of DNA methylation and histone modifications and update the knowledge about the different environmental factors and their epigenetic effects in allergic disease. There are many different epigenetic modifications affecting the status of the transcription of genes.

DNA methylation

DNA methylation is a biochemical process involving the addition of a methyl group to the DNA nucleotides cysteine or adenine. It is considered one of the epigenetic processes that lead mainly to ***gene silencing*** and subsequently to inhibition of the gene transcription.[7] In general, DNA methylation occurs on the different CpGs clustered as islands on the majority of the genes. There are several million potentially methylated CpG islands throughout the genome of a single cell. They are clustered through the gene body and play a critical role within the promoter regions. Once these islands are methylated, gene transcription might not occur.[8] On the other hand, once these CpG islands are unmethylated, an active promoter allows interaction with the various transcription factors controlling gene activation.[9]

In T cells DNA methylation plays an important role in the development, activation, and maintenance of T-cell effector function. For example, demethylation of the forkhead box protein P3 *(FOXP3)* region might favor the development of regulatory T (Treg) cells.[10] During the development of T cells toward different types of T_H or effector cells, they undergo extensive epigenetic editing. The ***zinc finger protein*** T_H inducing POZ-Kruppel Factor (Th-POK) regulates the development of $CD4^+$ T cells and inhibits the development of $CD8^+$ cells through different DNA methylation of CD8-associated genes.[11] Furthermore, displacement of the polycomb-group protein through signal transducer and activator of transcription 6 causes long-lasting maintenance of the transacting T cell–specific transcription factor (GATA3) transcription factor and, subsequently, maintenance of T_H2 cells.[12-14]

The major regulatory enzymes of DNA methylation are DNA methyltransferases (DNMTs). There are different DNMTs that play unique roles in the DNA methylation process.[15] DNMT1 is the major DNMT and is important for maintenance of the DNA methylation status of a gene. Most of the genes are silenced in their normal state. DNMT1 retains gene silencing in its usually normal state (Table I).[16] DNMT3a and DNMT3b are the main enzymes for *de novo* methylation and mediate methylation-independent gene repression. DNMT3a can colocalize with heterochromatin protein and methyl-CpG–binding protein (Table I).[17] They also interact with DNMT1, which might be a cooperative event during DNA methylation.[18-22]

Histone modifications

Histones are highly alkaline proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. DNA is usually wrapped around 2 copies of the core histones H2A, H2B, H3, and H4.[23] The main mechanism of regulating chromatin is through posttranslational modifications of various protein tails of these histones.[24] From a biochemical point of view, the major histone modifications are acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. The effects of such modifications range from gene activation[25] to gene silencing[26] and can have some DNA repair functions as well.[27]

Histone acetylation of different lysine residues represents one of the best studied examples in this regard, resulting in activation of transcription (Fig 1).[25] This activation is catalyzed by histone acetyltransferases (HATs). HATs transfer the acetyl group from the acetyl-CoA cofactor to the Nζ nitrogen of a lysine side chain within histones.[28]

There are 2 main families for HATs. Type A HATs are located in the nucleus and involved in the regulation of gene expression through acetylation of nucleosomal histones. Gcn5, p300/CpG-binding protein, and TAFII250 are some examples of type A HATs that cooperate with activators to enhance transcription.

GLOSSARY

ARACHIDONIC ACID: A polyunsaturated omega-6 fatty acid that is the counterpart to the saturated arachidonic acid found in peanut oil.

CHROMATIN: A complex of DNA, proteins, and RNA that tightly compact DNA to fit into the cell.

CPG SITES: Regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide separated by only 1 phosphate. CpG islands are regions with a high frequency of CpG sites. Methylation of the cytosine within a gene can turn the gene off.

EPIGENETIC REGULATION: Modifications of gene expression that are not caused by changes in the DNA sequence but by histone modification, DNA methylation, and other mechanisms.

GENE PROMOTER REGIONS: Specific regions of DNA that initiate the transcription of a particular gene.

GENE SILENCING: Epigenetic regulation that prevents the expression of a gene.

HISTONE: The protein component of chromatin responsible for compacting DNA.

LONG-CHAIN POLYUNSATURATED FATTY ACIDS: Lipids that are composed of omega-3 and omega-6 fatty acids, which are thought to be instrumental in the prevention of neurodegeneration and inflammation.

METHYLATION-SENSITIVE HIGH-RESOLUTION MELTING (MS-HRM): PCR products subjected to thermal denaturation show different melting profiles. MS-HRM compares melting profiles of PCR products from unknown samples with profiles specific for PCR products derived from methylated and unmethylated control DNAs.

MHC II: Presents processed antigen that is derived from extracellular proteins to T-cell receptors.

PHORBOL 12-MYSISTATE 13-ACETATE/IONOMYCIN: Can be used to stimulate T-cell activation, proliferation, and cytokine production.

T-CELL RECEPTOR: A molecule expressed on the surface of T cells that recognizes antigens bound to MHCs.

TRANSCRIPTION FACTORS: Proteins that bind to specific DNA sequences, which control the rate of transcription of genetic information from DNA to mRNA.

V(D)J RECOMBINATION: The somatic assembly of component gene segments that encode antigen recognition sites of receptors expressed on B and T lymphocytes.

ZINC FINGER PROTEINS: A variety of protein structures that use zinc to stabilize DNA folding.

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