Epigenetics and Environmental Diseases

Introduction

This document highlights basic concepts in Epigenetics and Environmental Diseases, the topic of the Office of Environmental Health Hazard Assessment (OEHHA) Distinguished Lecture Series: Advances in Toxicology and Risk Assessment in 2008.*

Many human diseases are caused in whole or in part by environmental factors. It has long been accepted that environmental chemicals can cause many of these diseases through changes in the genome (i.e., genetic effects). However, environmental chemicals can also cause effects in a variety of other ways. One of the fastest advancing areas of research in toxicological sciences is the study of epigenetic pathways that are involved in chemical-induced alterations in the development and function of biological systems. The purpose of the OEHHA lecture series in 2008 will be to explore this new direction in research as it affects how we evaluate the cause and effect relationships between environmental factors and disease endpoints.

Epigenetics

Epigenetics literally means "on top of or in addition to genetics." It is defined as the study of mechanisms or pathways that initiate and maintain heritable patterns of gene expression and gene function without changing the DNA sequence. In parallel to the term "genome" that defines the complete set of genetic information contained in the DNA of an organism, "epigenome" generally refers to the complete set of characteristics of epigenetic pathways in an organism. Researchers have identified a number of epigenetic pathways, such as DNA methylation, and histone modifications (see below). The epigenome can be thought of as a second code overlaid on top of the DNA sequence code of the genome. While each organism has but a single genome, the same individual has multiple epigenomes, which may differ by cell and tissue type, and which may change over the lifetime of the organism.

Epigenetic Mechanisms

Researchers have identified four types of epigenetic pathways: DNA methylation, histone modification, nucleosome remodeling, and non-coding RNA-mediated pathways. These epigenetic pathways intertwine with each other to regulate expression of genes,

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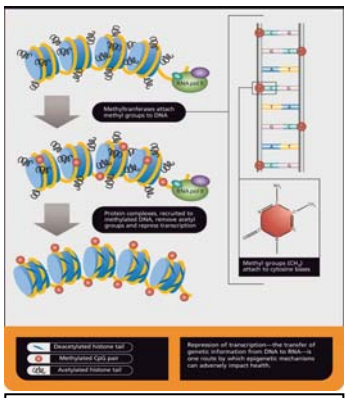
and it is likely that other pathways beyond these four known ones will be discovered in the future. To date, DNA methylation and histone modification are the most studied pathways. The general concepts of these two pathways are briefly outlined below.

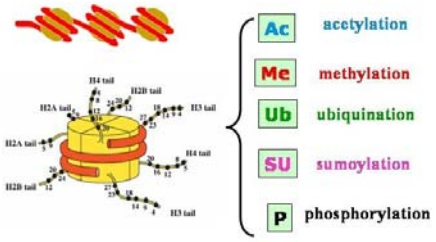
DNA Methylation



Source: Weinhold B (2006). Environ Health Persp 114 :A160.

In DNA methylation, a methyl group is covalently added to the fifth carbon of the cytosine ring to form 5-methyl cytosine. Cytosine is one of the five nucleotides in the nucleic acids of DNA and RNA. Along the linear DNA chain, there are sites of DNA where a cytosine is followed by and linked via a phosphate to guanine, another nucleotide. These sites are called CpG sites. Regions of DNA that have a high density of CpG sites are called CpG islands. DNA methylation occurs predominately on the CpG islands. DNA methylation is actively involved in regulating cell differentiation and function. When too much or too little methylation occurs, it can often negate a gene's function and thus causes unwanted alterations in the cell and even result in diseases.

Histone Modification



Source: http://chemistry.gsu.edu/faculty/Zheng

Histones are globular proteins that, together with the DNA, make up the nucleosome ─ the structural unit of chromatin. Histones influence how tightly or loosely packed the chromatin is during the phase when gene transcription occurs. In this way histones influence whether genes can be transcribed. Modification of histones occur through enzyme-catalyzed addition to or removal of certain molecules, such as, methyl or acetyl groups, phosphate, or ubiquitin. Improper modifications of histones cause genes to not be expressed when they normally would be, or vice versa. Inappropriate levels of gene expression can lead to diseases.

Epigenetics and Human Disease

Alterations in epigenetic pathways have been shown to be implicated in common human diseases. A few examples are given below to illustrate the importance of epigenetic pathways in disease development.

Cancer Epigenetic changes have been observed in virtually every step of tumor development and progression. Too little DNA methylation (hypomethylation) is believed to initiate chromosome instability and activate oncogenes. A malignant cell can have 20-60% less genomic methylation than its normal counterpart. Conversely, too much DNA methylation (hypermethylation) may initiate the silencing of tumor suppressor genes. Medical researchers are evaluating epigenetic markers as a means for early cancer diagnosis and prediction of clinical outcome. Therapeutics based on epigenetic strategies are also being considered for cancer treatment and prevention. How epigenetic changes may be a mechanism of environmental chemical-induced cancers is being researched as well.

Aging DNA methylation decreases as cells age. Identical twins are epigenetically indistinguishable early in life, but have substantial differences in epigenetic markers with age. This observation suggests an important role by the environment in shaping the epigenome. It has been shown that the process of aging involves some epigenetic pathways that have been identified in the process of carcinogenesis.

Other human diseases There is increasing evidence that epigenetic changes play a critical role in the development of certain human diseases, such as, neurodevelopmental disorders, cardiovascular diseases, type-2 diabetes, obesity and infertility.

Epigenetics and the Environment

Certain environmental and dietary factors have been linked to abnormal changes in epigenetic pathways in experimental and epidemiological studies. However, because these epigenetic changes are subtle and cumulative and they manifest over time, it is often difficult to establish clear-cut causal relationships between an environmental or dietary factor, the epigenetic change and the disease. Some examples of environmental factors have been shown to be related to changes in epigenetic pathways are:

- Heavy metals (e.g., cadmium) can disrupt DNA methylation.
- Vinclozolin, a widely used pesticide, can alter DNA methylation in exposed laboratory animals. These changes persist in unexposed offspring through several generations.
- Deficiencies in folate and methionine, both of which are involved in cellular processes that supply methyl groups needed for DNA methylation, can change the expression (imprinting) of growth factor genes (IGF1).
- Cigarette smoke can stimulate the demethylation of metastatic genes in lung cancer cells.

Websites

The Epigenome Network of Excellence (NoE): http://epigenome.eu/
Epigenetic Research: http://www.epidna.com/
The Human Epigenome Project: http://www.epigenome.org/
ScienceNOW on PBS Nova: http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html
Epigenetics Society: http://www.dnamethsoc.com/

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