Epigenetics and the environment

Recent studies revealed that epigenetic changes may be associated with aging and exposure to various environmental, dietary and lifestyle risk factors. Therefore, epigenetic changes that are risk factor-specific ("fingerprints") may be instrumental in the discovery of new biomarkers for early diagnosis, prognosis and risk stratification, but also new targets for epigenetics-based therapies and prevention

DOI 10.12910/EAI2017-056

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If our genome would be solely a static combination of four nucleotide bases, we could not explain the diversity of cell types that characterize our tissues/organs but share an almost identical genome sequence.

What is epigenetics

This is because the fate of cell development and therefore the cell status is not only a matter of sequence but epigenetic modifications will contribute significantly to cell diversity by regulating global gene expression. These modifications occur on DNA and histones without involving a change in DNA sequence but creating "tags" that alter DNA accessibility and chromatin structure, thereby leading to a sophisticated level of genetic control. The principal epigenetic tag found in DNA is methylation at the 5'-position of cytosine in CpG dinucleotide sequences. CpG methylation can suppress transcription by blocking DNA recognition and binding by some transcription factors. The N-terminal tails of histone proteins are subject to a wide range of different post-translational modifications (PTMs), including acetylation, methylation, phosphorylation and ubiquitylation. The PTMs made to histones can have a substantial influence on chromatin structure and gene function determining what is known as the histone code. DNA methylation tags also promote the persistence of certain histone states thus providing a mechanism for perpetuating histone PTMs. These epigenetic mechanisms regulate also the expression of short non-coding RNA, micro RNAs (miRNAs), of which a subset can in turn control the expression of important epigenetic regulators such as DNA methyltransferases and histone deacetylases. This creates a complicated chromatin-miRNA regulatory circuit able to organize the whole gene expression profile.

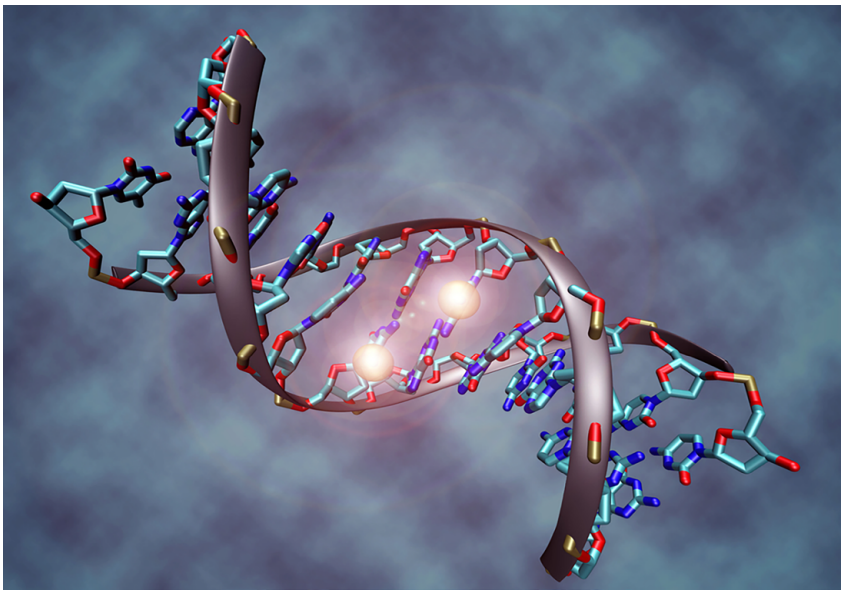
DNA methylation is both an effector and a biomarker of exposure

Epigenetic inheritance includes three distinct self-reinforcing

mechanisms: DNA methylation, histone modifications and RNA-mediated gene silencing DNA methylation at CpG dinucleotides is carried out by a family of enzymes known as DNA methyltransferases (DNMTs). Methylcytosine is often referred to as the fifth base that forms the "DNA methylation code" and is recognized as a principal mechanism for propagating transcriptional repression and participation in the maintenance of specific chromatin states. DNA methylation plays multiple roles in cellular processes including regulation of gene expression and cellular defense against parasitic DNA sequences such as viruses. In normal cells, DNA methylation marks are concentrated in transposons and repetitive sequences but are virtually absent at gene promoter regions. However, CpG islands that are typically unmethylated in normal cells are often hypermethylated in tumor cells, a finding associated with abnormal silencing of tumor suppressor genes and other cancer-associated genes. Recent studies have provided a wealth of evidence that DNA methylation plays an important role in the development and progression of virtually all types of cancer.

DNA methylation patterns are thus becoming increasingly attractive targets for biomarker discovery in diagnostics.

Recent studies revealed that DNA methylation changes may be associated with aging and exposure to various environmental risk factors. Therefore, epigenetic changes that are risk factor-specific ("fingerprints") should prove instrumental in the discovery of new biomarkers of exposure in molecular epidemiology and population based study.



The epigenetic response to physiological and environmental factors

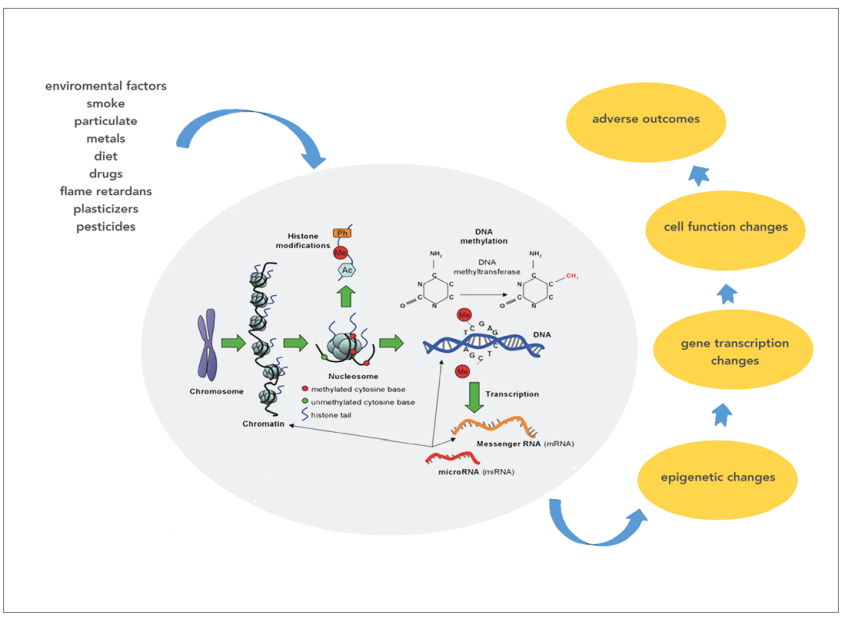
The interplay between transcription factors, nuclear receptors, chromatin remodeling factors (like histone acetyltransferases, histone acetylases, DNA methyltransferases and a growing number of cofactors) and the transcription machinery determines what has been described as the epigenetic landscape of a cell, corresponding to a specific transcriptional profile. Even few changes to the higher order chromatin structures can determine transcriptional changes to large sets of correlated genes. In this way, very different epigenetic landscapes can be achieved that have allowed the evolution of pluricellular organisms with cell type, tissue, and stage specific genetic information. During every biological process, like embryogenesis, myogenesis, or even carcinogenesis, epigenetic changes will allow a unique genotype to give rise to different stable phenotypes, accounting for different cell identities, functions and morphology.

The epigenetic changes responsible for this diversity are not embedded in the cell's genetic program. They are usually induced by the local or distal production of molecules like morphogens, hormones, cytokines or growth factors to which they respond through cellular receptors starting a signaling cascade ending in chromatin conformation changes in the nucleus.

Even many external factors like diet, nutrition and lifestyle can induce epigenetic changes. Lack or excess food, nutrients and natural hormones in our diet, hypoxia during altitude adaptation, temperature switches, sun light exposure, can induce changes to our epigenome. These changes can be reversible or inherited and responsible for cell type specificity, adaptation or the onset of pathological conditions. High fat diet, obesity, but even food shortage and famine have been linked to persistent epigenetic changes.

In summary, epigenetic changes are

a way to convert external stimuli to internal changes at the cellular and molecular levels in terms of gene regulation and gene expression profile.
This responsiveness to external factors is the key to predict and understand the effects on the epigenome by contaminants present in our environment, food, drinking water even in very small concentrations, given they have the ability to determine a cellular response or to mimic cellular effectors.



Exposure and epigenetics

As the epigenome can be considered a way to integrate and adapt to external physiological stimuli, the same applies to non-physiological factors such as many environmental contaminants. Many of these compounds have been shown or suspected to be able to induce changes to the epigenetic landscape of a cell thus altering its regulation and functions. There are many possible ways in which environmental contaminants can induce changes to the epigenome at different levels.
Global and unspecific modifications have been linked to exposure related metabolic changes, like the arsenic induced shortage of the methyl donor S-adenosyl methionine (SAM) used to methylate and detoxify arsenic, leading to global hypomethylation. Other mechanisms inducing global hypomethylation include the inhibition of epigenetic factors like the DNA methyltransferases (DNMT) by arsenic and cadmium.
Global epigenetic changes like DNA hypomethylation can in turn contribute to genetic changes like genetic instability and participate to cancer transformation. Even the dysregulated expression of oncogenes and tumor suppressor genes by changing their methylation status are a consequence of global changes to the epigenome. These events should be considered mechanisms of non-genotoxic carcinogenicity (NGC).
A completely different and very specific mechanism of action is the binding of hormone-like environmental contaminants like Bisphenol A (BPA), Bisphenol AF (PBAF), Polybrominated diphenyl ethers (PBDEs) to nuclear hormone receptors instead of their physiological ligands. Many of these compounds have been shown to bind with sufficient affinity to nuclear receptors in an agonist manner thus exerting an inappropriate biological function affecting the epigenome. The ligand bound hormone receptor will enter the nucleus and bind to accessible hormone responsive elements (HRE), or switch its conformation status and change its associated cofactor set from corepressors to coactivators if already bound to the regulative regions of hormone-controlled genes. Either way the bound contaminant will disrupt the finely tuned action of hormones known to be produced or active at very low concentration and in narrow windows of sensitivity possibly deregulating the transcription status of critical genes involved in sensitive biological processes. For instance, the activity of some HOX genes during embryo development has been shown to be dysregulated by *in utero* exposure to estrogen-like compounds in a strict tissue specific manner. This results both in altered morphogenic processes and increased predisposition to hormone driven cancers later in life. Other mechanisms of toxicity for hormone-like compounds include increased signaling in hormone responsive cancer patients, or indirect mechanisms like the binding of some polybrominated flame retardants to the sulfotransferase SULT1E1 with consequent interference in the elimination of 17β-estradiol and enhancing a non-

physiological estrogenic signaling. Being active at very low concentrations, in a tissue and cell mediated manner and causing associable effects mainly at later stages in life are all relevant factors to understand the importance and the difficulties of assessing hormone-like substances toxicity mediated by epigenetic mechanisms.
Cigarette smoke is a further worthwhile example of environmental contaminant able to induce epigenetic changes, for different reasons.
It is not a substance but it is a complex mix of substances, each one with its own mechanism of action like direct damage to DNA, enhanced cellular signaling, hypoxia, just to name a few.
Besides, it is a good model for the concept that environmental contaminants induced changes to the epigenome should be considered in their dual role of biomarkers of effect but even of potent effectors as, just like cigarette smoke, they can in turn determine or enhance the onset of pathological conditions like respiratory and cardiovascular diseases and cancer. Metabolic and neurological diseases are other examples

Major outcomes of of epigenetic deregulation. Cancer, metabolic diseases and inflammation

Accumulating evidence points to the key role of epigenetic changes in mediating gene-environment interactions and their effect on many complex human diseases. Deregulation of the epigenome is a nearly universal phenomenon in human cancers and a key driver of many cancers. It is also increasingly recognized that nutrients, and their metabolites, may have a major impact on the epigenome, and be involved in the development of metabolic diseases, potentially leading to transgenerational alterations in the phenotype. Several important discoveries have led to growing interest in understanding the potential role of the epigenome deregulation in the mechanism underlying the development of obesity and its associated comorbidities. Furthermore, suboptimal maternal nutrition during pregnancy may have a marked effect on the fetal epigenome, which may constitute a risk for disorders in childhood and adulthood. New evidence from functional studies in model organisms and humans have implicated the deregulation of epigenetic mechanisms in different human neurodegenerative disorders. Many studies, including those on population-based cohorts revealed that epigenetic changes have a striking impact on the aging process. Finally, although there is little understanding of the role of epigenetic mechanisms in inflammation process, the molecular links between the epigenome states and various chronic inflammatory diseases have been established.

Conclusions

Almost spectacular progresses in epigenetics and epigenomics have contributed to a better understanding of the etiology of human complex diseases, notably cancer. These advances have revealed that epigenetic changes have causal role in the development and progression of cancer and other diseases as well as in linking environmental exposure to the mechanisms underlying the disease. Many conceptual breakthroughs in epigenetics and the advent of powerful technological advances in epigenomics allowing the analysis of the epigenetic changes with high resolution in both genome-wide and high-throughput settings, have been fueling investigation of cancer research but also other related fields. Recent population based studies contributed to the identification of epigenetic alterations caused by specific environmental, dietary and lifestyle exposures, supporting the notion that the epigenome may function as an interface between the environment and the genome. Accumulating evidence that environmental exposures can induce specific changes in the epigenome provides the rationale that such epigenetic "fingerprints" may be instrumental in the discovery of new biomarkers for early diagnosis, prognosis and risk stratification, but also new targets for epigenetics-based therapies and prevention. Progress in studies of epigenetic alterations during cancer development and different complex human disease should open opportunities for the development of efficient epigenetics-based therapies for these diseases.