Epigenetic Considerations in Medicine

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Epigenetic modifications are gene regulatory mechanisms that allow rapid adaptation to the environment. These mitotically stable and meiotically heritable changes are sensitive to environmental conditions especially during developmental periods, and they are essential to understanding how information in the DNA sequence is utilized. Recent research in this area has led to excitement and questions about medical applications of epigenetics.

Most common pathologies are complex, with multiple genetic and environmental factors contributing to disease etiology. Epigenetics is one mechanism through which gene-environment interactions occur. The term epigenetics—a combination of epigenesis (the study of embryological development) and genetics—was coined by Conrad Waddington in the 1940s to refer to gene-environment interactions during development that produce certain phenotypes [1]. The definition of epigenetics has changed as our understanding of genetics and molecular mechanisms has evolved, and today the term is commonly defined as the study of mitotically and/or meiotically heritable changes in gene expression without changes in DNA sequence [2]. Epigenetics arose to explain non-Mendelian inheritance and has sometimes been viewed as being in conflict with genetics, but epigenetics is actually complementary to genetics. Epigenetic modifications allow rapid adaptation to the environment and fine-tuning of genomic expression; thus epigenetics is essential to understanding how information in the DNA sequence is utilized.

Epigenetic Mechanisms

The most extensively studied epigenetic modification is DNA methylation, in which methyl groups are added to a region of DNA where cytosine nucleotides (C) are found adjacent to guanine nucleotides (G); such regions are known as CpG sites. Methylation is enzymatically mediated by several distinct DNA methyltransferases, which act to maintain existing marks through mitotic cell division, to preserve parental imprinting of genes, and to generate de novo methylation during development and in response to environmental conditions. CpG-rich regions, called CpG islands, are found in regulatory regions of approximately 70% of human genes, and methylation of these sites has traditionally been associated with silencing of gene expression [3] either through recruitment of histone deacetylases by methyl-CpG-binding proteins and chromatin compaction [4, 5], or by steric hindrance of transcription factor binding to promoter recognition sites [6]. Interestingly, the CpG density of gene promoters seems to inversely correlate with methylation status; in general, transcriptionally active genes have high-CpG-content promoters that are unmethylated and vice versa [3, 7], although some genes with methylated low-CpG-content promoters may still be activated by transcription factor binding in a tissue-specific manner [7]. This mode of regulation is thought to be important for somatic cell differentiation during development, so that specific genes are activated only during critical developmental periods. Unlike promoter methylation, CpG methylation within the body of genes correlates with a high level of gene expression, although the precise role of intragenic DNA methylation is incompletely understood.

Gene expression is also influenced by a number of chromatin structural modifications. The basic chromatin unit consists of 147 base pairs of DNA wrapped around a histone octamer; this unit is called a nucleosome. Nucleosome structure allows the entire genome to be compacted into the nucleus of a cell and regulates the extent to which transcription machinery has access to the DNA. This mode of transcriptional regulation involves post-translational covalent modification of the histone tails by specific enzymes. The most common modifications are acetylation and methylation, although numerous other modifications have been identified, including phosphorylation, ubiquitination, SUMOylation, citrullination, and adenosine diphosphate ribosylation. In general, acetylation is associated with DNA accessibility and transcriptional activity, whereas deacetylation is associated with transcriptional repression; histone methylation may be related to either activation or repression. These modifications alter the charge of the histone tail and therefore alter interactions with the DNA to allow nucleosome mobility and changes in DNA accessibility. Histone modifications can also affect higher-order folding.

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of the chromatin through internucleosome interactions.

Another epigenetic mechanism involves noncoding ribonucleic acids (ncRNAs), which are key regulators of many cellular processes, including proliferation, differentiation, and apoptosis. The best-studied ncRNAs are microRNAs (miRNAs), which are 22-nucleotide sequences that bind the 3’ untranslated region of target mRNA. Binding of miRNA to its target leads to mRNA degradation or translational repression. Although mRNA silencing through this mechanism does not directly inhibit gene transcription, miRNAs prevent protein expression and are considered by many to be an epigenetic mechanism. Expression of miRNA is itself regulated by DNA methylation, in much the same way that methylation alters the expression of protein-coding genes. Alteration of DNA methylation patterns can thus be responsible for deregulation of miRNAs and can consequently alter the expression of target genes.

These epigenetic marks together compose the epigenome and work in combination to regulate genome-wide expression patterns throughout life. Epigenetics is critically important during the earliest stages of development and during differentiation of distinct cells and tissues. Epigenetic marks are replicated during mitotic cell division, with the result that cells of the same lineage will have the same epigenome and will express the same phenotype. Factors that alter the epigenome can therefore have lasting effects.

**Epigenetic Gene-Environment Interactions**

Epigenetic regulation is important from conception through adulthood; it first regulates gene expression in the generation of specific cell types, and it then ensures that cells maintain their differentiated state through cell division. The mitotic stability of epigenetic marks enables proliferating cells to maintain the same phenotype and function during growth, renewal, or healing processes. However, it also means that detrimental epigenetic marks will be carried to successive cell divisions. Because the epigenome can be altered by environmental factors, epigenetics is emerging as an etiological factor in a number of chronic conditions, including cancer, obesity, type 2 diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, chronic inflammatory diseases, and immune diseases.

The environment during embryogenesis is particularly important in establishing epigenetic marks, because reprogramming occurs shortly after fertilization and during germ cell differentiation. Although the mechanisms of methyl erasure and restoration are an active area of research, it is clear that several factors—including availability of methyl groups, exposure to environmental toxicants, and/or other stresses—can impact this process and can have effects well beyond the developmental period. The hypothesis that adult-onset diseases may have developmental origins is supported by studies of gestational exposures in both animals and humans. A number of environmental factors—including nutrition, toxicants, and stress—have been shown to have epigenetic effects [8]. In humans, prenatal exposure to famine was found to increase the incidence in adulthood of impaired glucose tolerance, obesity, coronary heart disease, lipid profile, hypertension, and schizophrenia, depending on gestational timing and the sex of the individual [9].

Although certain developmental stages represent particularly sensitive periods, epigenomic plasticity occurs in somatic cells throughout life. Epigenetic marks acquired over time may contribute to adult-onset diseases, especially age-related conditions, for which lifelong accumulation of epigenetic marks would be expected to increase risk. Most environmental epigenetic effects involve exposure of somatic cells, and these mitotically stable marks are passed down within a cell line. However, epigenetic states may be meiotically inherited from one generation to the next; this occurs when epigenetic marks are acquired during germline formation. Transgenerational inheritance of epigenetic marks is dependent on DNA methylation patterns that become programmed into the germline. Epigenetic inheritance occurs under normal circumstances in imprinted genes that express parent-specific methylation patterns. These genes are protected from reprogramming in the developing embryo. However, DNA methylation is erased and reestablished for most genes during primordial germ cell migration and gonadal sex determination. Thus, sex determination represents an exceptionally sensitive time period for epigenetic modification by environmental factors. One study uncovered evidence of transgenerational environmental effects in humans when preadolescent paternal smoking was found to be associated with greater body mass index in sons only, and paternal grandfathers’ food supply was found to be correlated with grandsons’ mortality risk [10].

**Implications for Health Care**

Recent research has improved our understanding of epigenetic mechanisms and has fostered both excitement and questions about the application of epigenetics to medicine. Epigenetic information has many potential applications in health care, including both therapeutic and diagnostic uses. Because the epigenome is responsive to environmental influences such as diet, prevention strategies are well recognized. Public health could also benefit from greater awareness of the effects of diet and lifestyle on chronic diseases such as obesity and type 2 diabetes, not only in the present generation but also in future generations. In addition, gene-specific alterations can potentially be used as biomarkers for diagnosis, classification, and prognosis; many studies are being carried out to explore possible uses of gene-specific alterations in cancer. Moreover, identification of developmental epigenetic changes that predispose an individual to late-onset diseases could facilitate early diagnosis, and preventive or therapeutic strategies could be implemented before these diseases present clinically. Since epigenetic changes tend to be reversible, there are also opportunities...
for epigenetic drug development to restore healthy epigenetic states. However, safety and efficacy testing of such drugs may be complicated, because epigenetic modifications are tissue-specific.

Because epigenetics has the potential for medical applications, it raises a number of ethical issues [11], many of which are similar to the ethical issues associated with genetic information. Epigenetic analysis could generate a vast amount of sensitive information concerning the risk of developing chronic disease and the possible transmission of that risk to offspring, leading to privacy and confidentiality issues. There is also the potential for discrimination based on an individual’s epigenetic information, both in employment and insurance settings. This is especially important for women of childbearing age, given the early developmental sensitivity of the epigenome to environmental exposures. Epigenetics also highlights the effects of inequality in living and working conditions; harmful exposures are associated with socioeconomic status, so certain populations may be at greater risk of epigenetic alterations. These and many other questions will need to be addressed as epigenetics becomes integrated into our health care system and medical knowledge base. Although the discipline of epigenetics is still in its infancy, advances in the field hold promise for improved human health. NCMJ

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