Epigenetics and Primary Care

abstract

Epigenetics, the study of functionally relevant chemical modifications to DNA that do not involve a change in the DNA nucleotide sequence, is at the interface between research and clinical medicine. Research on epigenetic marks, which regulate gene expression independently of the underlying genetic code, has dramatically changed our understanding of the interplay between genes and the environment. This interplay alters human biology and developmental trajectories, and can lead to programmed human disease years after the environmental exposure. In addition, epigenetic marks are potentially heritable. In this article, we discuss the underlying concepts of epigenetics and address its current and potential applicability for primary care providers. *Pediatrics* 2013;132:S216–S223

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KEY WORDS

DNA methylation epigenetics, histone modification, imprinting, noncoding RNA, pediatrics, primary care

ABBREVIATIONS

CpG—cytosine-phosphate-guanine
lncRNA—long noncoding RNA
mRNA—messenger RNA
PCP—primary care provider

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The term "epigenotype" was coined in 1942 by the developmental biologist Conrad Waddington to refer to the whole complex of developmental processes connecting the genotype and the phenotype.[1] Epigenetic changes (referred to as epigenetic marks) can be transmitted through mitosis, meiosis, or both. Furthermore, epigenetic marks represent a form of acquired cellular memory because they respond to changes in the cellular environment (in contrast to the DNA sequence, which is static). All cells in the human body contain the same DNA sequence, and epigenetic marks have become recognized as an additional set of codes that regulate the expression of the genes encoded by the DNA sequence. These marks bring about stem cell differentiation by determining the expression of genes in various cell types and at different life stages. Furthermore, these marks are by necessity dynamic, because cells must adapt to changes in their chemical and physical environment. The cellular capacity to adaptively respond to the environment by turning on or off specific genes may vary with developmental stage. This is known as "cellular plasticity."

EPIGENETIC HYPOTHESES

It is widely believed that epigenetic responsiveness to the environment varies by life stage, with the fetal stage and childhood being periods of epigenetic sensitivity, in which adaptive (or maladaptive) epigenetic marks are set.[2] These marks later stabilize and effectively program cells to respond in a particular way to the environment. An example of epigenetic programming has been postulated by David Barker.[3,4] The Barker hypothesis states that a harsh fetal environment, for example, famine experienced through the mother during pregnancy, programs an individual toward hyperabsorption of nutrients after birth. If, during that individual's adult life, nutrients become more plentiful, this predisposition increases the risk of obesity and metabolic syndrome over time.[5] This hypothesis differs from the thrifty genotype hypothesis, another proposed explanation for the increasing levels of obesity in Western society. The thrifty genotype hypothesis holds that populations that evolved over generations to survive in harsh environments cannot adapt to the modern environment because the change was too dramatic to allow for evolutionary adaptation over a short time frame.[6] That is, populations have evolved genetic traits that were adaptive in the past environment but cause them to hyperabsorb nutrients in today's world, where high-calorie foods are plentiful. In this genetic theory, populations are predisposed to obesity by their genetics and a changed nutritional environment at the population level, and phenotype is determined by genetics not by fetal environment. Note that the Barker hypothesis works at the individual level over a single lifetime, whereas the thrifty genotype hypothesis works at the population level over multiple generations. The 2 hypotheses are not mutually exclusive; both can occur simultaneously within a population, given that famine can occur at the individual or population level.[7]

Epigenetic systems should not be considered to be independent from genetic systems. The 2 systems are so tightly intertwined that they generally work in tandem to produce a given phenotype. For example, if an environmental factor, such as famine, induces a change in gene expression by altering DNA methylation patterns, the gene expressed will include any genetic variant that changes the amino acid sequence of the protein encoded by that gene. In other words, epigenetics will turn off or on the products of gene mutations.

Epigenetics and Heredity

The genetic component of complex childhood diseases, such as obesity,[8] diabetes,[9,10] and pubertal delay,[11,12] appears to account for little of the variation in their prevalence. Interest has grown in understanding other molecular biomarkers that might explain the rise in these disorders. Epigenetics offers an additional mechanism that blends together genetics and the environment to explain the etiology of complex diseases. Epigenetic marks regulate gene expression, just as DNA sequence variants can, but unlike DNA sequence, epigenetic marks respond to environmental factors. Epigenetic marks form the basis of a large proportion of gene-environment interactions and may offer a complementary mechanism for heredity variance that can operate outside changes in DNA sequence. Note, however, that true epigenetic inheritance requires that changes in epigenetic marks take place in germ cells and in turn be passed on to progeny. Most research in epigenetics is conducted with somatic cells and hence can explain heritability in mitosis but not in meiosis. Whether epigenetic changes are truly heritable is still unclear; however, the heritability of epigenetic marks is less important than the role they play in programming an individual's response to changing environmental stimuli.

It should also be emphasized that in epigenetics research, the tissue being studied must be relevant to the disease. For example, studying changes in the methylation of dopamine receptor genes in children with attention-deficit/hyperactivity disorder may sound enticing, but if the DNA for such a study were collected from white blood cells, the relevance of the work would be questionable. A neuron is a neuron precisely because of its epigenetic marks; likewise, a white blood cell. Each cell type has a distinct epigenome;

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changes in DNA methylation or histone modification in one cell type do not necessarily reflect changes in other cell types. This is yet another manner in which epigenetics is distinct from genetics; the source of DNA for genotyping is irrelevant because the sequence is the same in all cells, whereas in epigenetics, the source of the DNA is a critical component of the study.

BASIC PRINCIPLES OF EPIGENETICS

Epigenetic regulatory processes involve epigenetic marks that are added to either DNA or chromatin (DNA bound to histones), leading to transient or persistent changes in gene transcription. Each cell has a unique epigenetic signature that is inherited via mitosis but can be modified over time, even into adult life, by changes in the cellular environment. Epigenetic marks arise as part of normal development. At every life stage, our DNA is modified to turn off or turn on specific genes, and some of these modifications are programmed to occur based on our current life stage. The degree to which a gene is turned on or off will vary, and this variation represents modification of epigenetic marks in response to various environmental factors. There are 3 main categories of epigenetic marks: (1) histone modification, (2) DNA methylation, and (3) noncoding RNA.

Histone Modification

Histones, which were first discovered in the 19th century, are DNA-binding proteins that package DNA into tight coils known as nucleosomes. Nucleosomes consist of ∼150 bp and are the repeating subunits of chromatin, which in turn make up the chromosomes. Our understanding of the primary function of histones has evolved over the years: histones were originally thought to simply package DNA, but today they are known to play a key role in regulating gene expression. Posttranslational modification of specific histone amino acids changes their 3-dimensional configuration. This configuration change in turn alters the 3-dimensional structure of their bound DNA. Posttranslational histone modifications include the addition or subtraction of methyl groups, acetyl groups, ubiquitin molecules, or phosphate groups. The addition or subtraction of these groups changes the coiled DNA to an open configuration (euchromatin) or a closed configuration (heterochromatin). When the DNA adopts an open configuration at a gene promoter region proximal to the histone modification, the nuclear transcription machinery (transcription factors and RNA polymerase) can bind to the DNA in the promoter region, and local genes can then be expressed. In contrast, in the closed configuration, DNA is tightly coiled, inaccessible to transcription factors and RNA polymerase, and therefore local genes cannot be expressed. Perhaps the simplest way to think of histones is as dynamic mediators of the 3-dimensional structure of DNA, mediators that can turn gene expression on or off.

Enzymatic modifications of histones that alter DNA conformations include acetylation and methylation of lysine residues in the amino terminus. Acetylation leads to a more open configuration and increases DNA accessibility. Histone methylation can either increase or decrease DNA accessibility, depending on the amino acid and subclass of histone protein affected. Histones can also be ubiquitinated and phosphorylated, and each of these modifications can change the conformation of DNA at specific loci, thus increasing or decreasing local gene transcription.

DNA Methylation

Methylation of DNA occurs only at the 5-carbon of cytosine. Methylation anywhere else is interpreted by the cell as DNA damage and elicits the expression of DNA repair enzymes. In addition, DNA methylation typically occurs at positions where a cytosine is next to a guanine, that is, at cytosine-phosphate-guanine (CpG) dinucleotides (where "p" stands for the phosphate groups that link nucleotides in DNA). (Note that several exceptions to this "rule" have recently been reported in embryonic stem cells.[13]) Genomic regions that are dense in CpG dinucleotides are termed "CpG islands." CpG islands are overrepresented at gene promoters, demonstrating their role in regulating gene expression.[14] Regions with lower CpG density bordering the CpG islands are termed "CpG shores" and are more frequent in regulatory sites critical to tissue differentiation.[15]

Methylation of CpG dinucleotides is mediated by several DNA methyltransferases.[16,17] Like histone modifications, DNA methylation is best thought of as a regulator of the 3-dimensional structure of DNA. Methylation leads to gene silencing because it tightens coiled DNA at loci corresponding to specific gene promoter regions, and transcription factors cannot be recruited to their DNA-binding sites within the tightened coil. In addition, methyl-binding proteins interact with methylated CpGs and actively repress gene transcription.[18]

DNA methylation and histone modification work in tandem. There is evidence that methyl-binding proteins recruited by DNA methylation exert their effects through recruitment of histone deacetylases, which remove acetyl groups from histones. The resulting loss of acetylation within histones, in tandem with DNA methylation, produces heterochromatin (DNA in a closed configuration) and results in transcriptional inactivation.[19,20]

Noncoding RNA

One of the most exciting new discoveries in the field of epigenetics is the

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role of noncoding RNA (RNA that is not translated into protein) in regulating gene expression. Noncoding RNA comes in at least 2 classes: long and short. An example of the latter is microRNA. MicroRNAs, small strands of RNA ~22 nucleotides long, interfere with gene expression at the level of translation; that is, they regulate the translation of RNA transcripts into amino acid chains. MicroRNAs form active ribonuclear complexes with cytoplasmic proteins. These complexes have RNAase activity.[21] Each microRNA has a base sequence that is complementary to a specific messenger RNA (mRNA) sequence, meaning that each microRNA degrades a specific mRNA.[21,22] Because the complementary RNA sequence is short, 1 microRNA can degrade multiple mRNAs corresponding to several different genes, often with similar functions. Thus, microRNAs differ from RNAase enzymes in that the former are a targeted regulatory mechanism to reduce gene expression. MicroRNAs work posttranscriptionally by binding to the 3′-untranslated regions of their target mRNAs, thereby inducing enzymatic degradation and preventing translation.

Long noncoding RNAs (lncRNAs) represent another class of epigenetic marks. These transcripts are ~200 bp long and are thought to form ribonucleoprotein complexes that interact with chromatin, regulating histone modifications and the structural transformations that distinguish heterochromatin (transcriptionally inactive DNA) from euchromatin (transcriptionally active DNA).[23,24] Previously, lncRNA was thought to be a byproduct of normal gene transcription, but we now know that lncRNAs show cell type–specific expression and also respond to diverse environmental stimuli, suggesting that their expression is both regulated by and responsive to the environment.[24]

EPIGENETICS IN GENETIC DISORDERS

The expression of every gene is regulated to some extent by epigenetics, but a small subset of genes are subject to regulation by an epigenetic phenomenon called imprinting, in which areas of DNA methylation differentially affect the paternal and maternal chromosomes of a chromosome pair. The experimental evidence for imprinting is often indirect. Imprinting leads to silencing of 1 of the 2 alleles of an imprinted gene. About 1% of all genes are imprinted. In some cases, the allele of paternal origin is silenced, and in other cases the allele of maternal origin is silenced. The specific evolutionary advantage of imprinting is unknown, but imprinted genes are believed to encode proteins that, if overexpressed, would have deleterious results. Therefore, 1 of the 2 alleles is silenced to protect the cell. Intriguingly, most important genes code for proteins that regulate either growth or human behavior.

In certain situations, disruption of normal imprinting (referred to as loss of imprinting) can lead to the manifestation of specific disease states; that is, the manifestation of certain disorders depends on the methylation statuses of the paternal and maternal chromosomes. For example, differential methylation of regions of chromosome 15 in a diploid cell can lead to 2 related but distinctly different conditions: Prader-Willi syndrome and Angelman syndrome. Prader-Willi syndrome occurs when there is a paternally inherited deletion of the imprinted region and the corresponding maternal region is imprinted normally (ie, silenced). These deletions are large and involve multiple imprinted genes, some expressed from the maternal allele, and some expressed from the paternal allele. Its sister syndrome, Angelman syndrome, occurs when there is maternal deletion of the imprinted region with normal imprinting of the region inherited from the father (unmethylated and active). Angelman syndrome and Prader-Willi syndrome result from a combination of gene deletions and imprinting.

Loss of imprinting explains most cases of Beckwith-Wiedemann syndrome, which is characterized by macroglossia, omphalocele, macrosomia, abnormal ear creases, and neonatal hypoglycemia. In this syndrome, imprinting-control regions of the insulinlike growth factor 2 gene that are normally methylated, and thus suppressed, are not methylated (ie, they demonstrate loss of imprinting). Both the maternal and the paternal alleles are therefore expressed. This leads to an overgrowth syndrome, presumably secondary to the loss of regulation of insulinlike growth factor 2 expression. The syndrome can occur with loss of imprinting alone, in the absence of a gene mutation. The fact that 2 of these 3 genetic syndromes have been ascribed to an epigenetic mechanism in addition to gene mutations suggests that an epigenetic basis will be delineated for many more conditions. Other conditions with known or suspected epigenetic etiology are shown in Table 1.

Evidence suggests that artificial reproductive technologies, which theoretically can be associated with early methylation changes in zygotes around the time of fertilization and implantation, will lead to an increased occurrence of certain disorders. Table 2 lists some of the conditions with epigenetic factors that may be associated with these technologies.

EPIGENETIC INFLUENCES IN PREGNANCY AND SUBSEQUENT HEALTH IMPACT

There is an increasing body of evidence suggesting that epigenetic changes can occur in utero and affect postnatal development, with the effects being

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TABLE 1 Genetic Syndromes With Known or Putative Epigenetic Etiology[25]

Angelman syndrome[a]
Autism spectrum disorders
Beckwith-Wiedemann syndrome[a]
CHARGE association
Fragile X syndrome
Maternal duplication 15q11-13
Metabolic syndrome
Prader-Willi syndrome[a]
Rett syndrome
Russell-Silver syndrome[a]
Turner syndrome

CHARGE, coloboma, congenital heart disease, choanal atresia, mental and growth retardation, genital anomalies, and ear malformations and hearing loss.
[a] Presumed to be due to imprinting.

dormant for several decades. Studies of people who were born during the Dutch famine during World War II[28] and the Chinese famine in the 20th century[29] have revealed the presumed effects of environmental factors occurring during pregnancy on the health of the same people many years after birth. These 2 studies showed that children who suffered from intrauterine nutritional deficiency because they were conceived during severe famine had a twofold increased risk of schizophrenia, demonstrating a connection between mental illness and the maternal intrauterine environment. Schizophrenia does not typically present until adolescence, meaning that the impact of the intrauterine environment on this disease lies dormant for more than a decade.

The persistence of the effects of the Dutch famine is even more intriguing. Demonstrable consequences have been documented more than 6 decades later.[28] A group of 60 individuals conceived during the famine had less DNA methylation of an imprinted gene (*IGF-2*) than did their same-gender unexposed siblings, and a group of 62 individuals exposed to intrauterine nutritional deficiency late in gestation had no difference in methylation as compared with their same-gender unexposed siblings.[30] Therefore, these epigenetic differences were specific for periconceptional exposure, suggesting that very early development is a crucial time for the establishment and maintenance of epigenetic marks.

TABLE 2 Conditions With Epigenetic Factors and Presumptive Association With Artificial Reproductive Technologies[26,27]

Angelman syndrome
Beckwith-Wiedemann syndrome
Maternal hypomethylation syndrome
Retinoblastoma
Russell-Silver syndrome

Similar findings have been demonstrated in rural Gambia.[31] DNA methylation at metastable epialleles (epigenotypes established in the early embryo and maintained in different cellular lineages) was found to be representative of periconceptional nutrition as manifested by changes in seasonal fluctuations in nutrition. Rainy season changes decreased the availability of food, and interestingly DNA methylation was increased at the tested metastable epialleles. These data and those of the Dutch famine confirm that developmental establishment of DNA methylation is sensitive to the maternal environment.

Swedish harvest data provide compelling evidence for the transgenerational effects of diet.[32,33] If a group of young boys in the slow-growth period (9–12 years of age) had access to an abundance of food (as indicated by harvesting information dating back to the 19th century), their grandchildren had an increased risk of developing cardiovascular disease or diabetes. In contrast, if a group of young boys experienced a shortage of food (as indicated by harvesting information), their grandchildren had a decreased risk of developing cardiovascular disease or diabetes. A related study also demonstrated a similar effect for life span: the grandchildren of young boys who experienced an abundance of food during the slow-growth period had a shorter life span than the grandchildren of boys who experienced a food shortage during the slow-growth period.[32] These studies have remarkable implications for the impact of diet and the environment on transgenerational health. The results are consistent with the presumption that sperm can carry information about ancestral nutrition to subsequent generations.

Epigenetic differences in monozygotic twins have been demonstrated to increase over the lifetimes of the twins.[34] These differences are negligible at birth, but approximately one-third of adult monozygotic twins have differences in methylation or histone modification. These changes might have a significant impact on susceptibility to disease.

Even more provocative is evidence that environmental factors can affect epigenetic processes in the human brain. For example, there is strong evidence that epigenetic changes in the glucocorticoid receptor *NR3C1* gene in the hippocampus are correlated with child abuse.[35] This finding provides compelling reasons why primary care providers (PCPs) need to be strong advocates for young children. In addition, information about DNA methylation profiles in specific brain-derived genes (eg, the brain-derived neurotrophic factor gene) might serve as a biomarker for depression.[36]

A whole host of additional factors have been demonstrated to have the potential to produce epigenetic changes associated with various disorders; a preliminary list of such factors is shown in Table 3. Note, however, that the cause-and-effect relationships are still uncertain for all these disorders; we cannot state with 100% certainty whether the factors listed in Table 3 cause the epigenetic changes and subsequently the disease phenotype or

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whether the factors cause the disease phenotype, which then leads to subsequent epigenetic changes. Additional research is certainly warranted. We can expect this list to expand, and hopefully the relevance of the associations between these factors and common complex diseases, such as heart disease, cancer, mental illness, and other adult-onset diseases, will be delineated. These factors will also need to be analyzed in terms of potential gender differences. For example, a girl has all her ova in utero, whereas in boys, there is continued turnover in sperm after birth. Such differences can lead to differential expression in subsequent offspring.

WHAT'S NEXT FOR EPIGENETICS?

Perhaps the greatest potential for the use of epigenetics as a clinical tool lies in the flexibility of epigenetic information. DNA sequence is static, and although risk of disease may be inferred from the presence of DNA variants, interventions that change DNA sequence are not likely in the foreseeable future. Epigenetic marks, on the other hand, can be modified. Although we are a long way from targeting specific marks in specific cells for modification, we will likely be able to do so eventually. Many existing treatments work via modification of epigenetic marks (eg, zidovudine for treating HIV, bromodomain inhibitors in cancer therapy).[50]

TABLE 3 Factors Leading to Epigenetic Changes[26,27,37–49]

Diet during the slow-growth period
Hypoxia
Chemical exposures (eg, prenatal exposure to valproate)
Psychological trauma (posttraumatic stress disorder, depression)
Asthma (including allergic diseases)
Maternal diabetes
Endocrine-disrupting compounds (eg, bisphenol A)
Psychosocial stress
Maternal smoking
Maternal habitus, maternal age, and placenta size

As our understanding of epigenetics deepens, and additional knowledge is generated on how the environment (diet, chemicals, even social environment) impacts gene expression, we may one day be able to develop therapies to reprogram the genome away from disease phenotypes toward healthier developmental phenotypes. Epigenetic marks could provide even stronger scientific evidence to back recommendations regarding early childhood development and programs needed to bolster sound child-rearing practices.

Epigenetics is a genomic factor to be recognized and considered from the standpoints of personal health and public health. Although the ultimate impact of epigenetics in medicine may be unclear, and how behavior can be adjusted to diminish the likelihood of harm is uncertain, PCPs should nevertheless remain mindful of the fact that the actions and behaviors of one generation can affect subsequent generations. It is naïve to think that this influence will be only positive. For example, the obesity epidemic affecting today's children may be detrimental to future generations. Will communities burdened by a disproportionate incidence of obesity require generations to recover? What effects will the field of epigenetics have on other health disparities in society? What is apparent is that epigenetic factors affect the structure and future of the communities themselves.

Prevention

There is excellent evidence that multiple factors early in life affect the onset and severity of adult diseases, such as cancer, autoimmune diseases, cardiovascular diseases, mental disorders, diabetes, and hypertension. The list of such factors can be expected to grow substantially as the various influences on DNA methylation, histone modification, and noncoding RNA are delineated. Because multiple factors that affect adult-onset diseases occur in the prenatal, perinatal, and early infancy periods, it would behoove PCPs to have information about childhood exposure to such factors available as adolescents transition to adulthood. Historically, such information was thought to be unimportant unless a pediatric patient had a severe disease that required management into adulthood. One solution would be to set up a system for recording this type of information so that it could be included, along with immunization records, in an individual's health care record. Table 4 contains a list of suggested information to be considered for inclusion. A collaborative effort of obstetrics-gynecology, pediatric, and adult-medicine providers will be needed to establish a comprehensive catalog of necessary information, and such an effort should be encouraged because of its potential to contribute substantially to health care decisions made by individuals and by public health officials concerned with the allocation of resources and health care dollars.

Diagnosis

The applicability of epigenetics to primary care also depends on clinicians' ability to use its associated tools to aid in diagnosis. Precise diagnoses allow PCPs and their subspecialty

TABLE 4 Checklist of Factors to Acquire in Early Infancy and Maintain for Adult Health Management[26,39]

Size for gestational age
Maternal weight gain
Maternal height and weight (BMI)
Placenta size and shape
Birth weight and length
Prenatal exposures
Maternal diseases
Hypertension
Preeclampsia
Diabetes mellitus
HELLP syndrome (H, hemolysis; EL, elevated liver enzymes; LP, low platelet count)

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consultants to provide patients with appropriate care, anticipatory guidance, and reproductive counseling. The list of current disorders with known epigenetic factors (Table 1) is limited, so the tools necessary for diagnosing these disorders (eg, methylation assays for imprinting) must continue to improve.

We are beginning to understand methylation changes associated with disorders such as autism, and this understanding might eventually lead to methods for diagnosis and intervention. As the number of known associations between disease states and epigenetic changes increases, our diagnostic acumen should improve and enhance potential therapeutic interventions.

Treatment

There are currently no clinical treatments based on epigenetic changes, and various dietary intervention studies carried out to date have not shown significant results. Methods for altering epigenetic marks (and, thus, gene expression, protein expression, and ultimately the phenotype) have not been developed. As we learn more about the known epigenetic mechanisms (DNA methylation, histone modification, noncoding RNAs, and their variations), and discover new ones, additional modalities may be developed. The identification of epigenetic changes promises the possibility of therapeutic interventions that will add to the armamentarium of PCPs in the not-too-distant future.

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