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A REVIEW

Epigenetics: new relation of health and nutrition

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The development and maintenance of an organism is orchestrated by a set of chemical reactions that switch parts of the genome off and on at strategic times and locations. Epigenetics is the study of these reactions and the factors that influence them. The nutrients we extract from food enter metabolic pathways where they are manipulated, modified and molded into molecules, the body can use. One such pathway is responsible for making methyl groups - important epigenetic tags that silence genes. Familiar nutrients like folic acid, B vitamins and SAM-e (S-Adenosyl methionine) are key components of this methyl-making pathway. Diets high in these methyl-donating nutrients can rapidly alter gene expression, especially during early development when the epigenome is first being established. Nutrients can reverse or change epigenetic phenomena such as DNA methylation and histone modifications, thereby modifying the expression of critical genes associated with physiologic and pathologic processes, including embryonic development, aging, and carcinogenesis. It appears that nutrients and bioactive food components can influence epigenetic phenomena either by directly inhibiting enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for those enzymatic reactions. As we better understand the connections between diet and the epigenome, the opportunity arises for clinical applications. Enter the future field of nutrigenomics, where nutritionists take a look at your methylation pattern and design a personalized nutrition plan. While we're not quite to that point yet, your doctor can already tell a lot about your disease risk by looking at your family health history. In this regard, nutritional epigenetics has been viewed as an attractive tool to prevent pediatric developmental diseases and cancer as well as to delay aging-associated processes. In recent years, epigenetics has become an emerging issue in a broad range of diseases such as type 2 diabetes mellitus, obesity, inflammation and neurocognitive disorders.

Key words : Epigenetics, Nutrients, Gene expression, DNA methylation, Histone modifications, Epigenome

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INTRODUCTION

Epigenetics is the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence – hence the name *epi-* (Greek: £®í- over, above, outer) *-genetics*. It refers to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Examples of such changes are DNA methylation and histone modification, both of which serve to regulate gene expression without altering the underlying DNA sequence. Conclusive evidence supporting epigenetics show that these mechanisms can enable the effects of parents' experiences to be passed down to subsequent generations. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism (Bird, 2007) instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently (Philip, 2008). In 2011, it was demonstrated that the methylation of mRNA has a critical role in human energy homeostasis. The obesity associated FTO gene is shown to be able to demethylate N6-methyladenosine in RNA. This opened the related field of RNA epigenetics (Jia *et al.,* 2011).

Epigenetics involves genetic control by factors other than an individual's DNA sequence. Epigenetic changes can switch genes on or off and determine which proteins are transcribed. Epigenetics is involved in many normal cellular processes. Consider the fact that our cells all have the same DNA, but our bodies contain many different types of cells: neurons, liver cells, pancreatic cells, inflammatory cells, and others. In short, cells, tissues and organs differ because they have certain sets

of genes that are "turned on" or expressed, as well as other sets that are "turned off" or inhibited. Epigenetic silencing is one way to turn genes off, and it can contribute to differential expression. Silencing might also explain, in part, why genetic twins are not phenotypically identical. In addition, epigenetics is important for X-chromosome inactivation in female mammals, which is necessary so that females do not have twice the number of X-chromosome gene products as males (Egger *et al.,* 2004). Thus, the significance of turning genes off via epigenetic changes is readily apparent.

Three systems that can interact with each other to genes :

Within cells, there are three systems that can interact with each other to silence genes: DNA methylation, histone modifications, and RNA-associated silencing (Egger *et al.,* 2004).

DNA methylation :

DNA methylation is a chemical process that adds a methyl group to DNA. It is highly specific and always happens in a region in which a cytosine nucleotide is located next to a guanine nucleotide that is linked by a phosphate; this is called a CpG site (Egger *et al.,* 2004; Jones and Baylin, 2002; Robertson, 2002) CpG sites are methylated by one of three enzymes called DNA methyltransferases (DNMTs) (Egger *et al.,* 2004; Robertson, 2002). Inserting methyl groups changes the appearance and structure of DNA, modifying a gene's interactions with the machinery within a cell's nucleus that is needed for transcription. DNA methylation is used in some genes to differentiate which gene copy is inherited from the father and which gene copy is inherited from the mother, a phenomenon known as imprinting.

Histone modifications :

Histones are proteins that are the primary components of chromatin, which is the complex of DNA and proteins that makes up chromosomes. Histones act as a spool around which DNA can wind. When histones are modified after they are translated into protein (*i.e.,* post-translation modification), they can influence how chromatin is arranged, which, in turn, can determine whether the associated chromosomal DNA will be transcribed. If chromatin is not in a compact form, it is active, and the associated DNA can be transcribed. Conversely, if chromatin is condensed (creating a complex called heterochromatin), then it is inactive, and DNA transcription does not occur.

There are two main ways histones can be modified: acetylation and methylation. These are chemical processes that add either an acetyl or methyl group, respectively, to the amino acid lysine that is located in the histone. Acetylation is usually associated with active chromatin, while deacetylation is generally associated with heterochromatin. On the other hand, histone methylation can be a marker for both active and inactive regions of chromatin. For example, methylation of a particular lysine (K9) on a specific histone (H3) that marks silent DNA is widely distributed throughout heterochromatin. This is the type of epigenetic change that is responsible for the inactivated X chromosome of females. In contrast, methylation of a different lysine (K4) on the same histone (H3) is a marker for active genes (Egger *et al.,* 2004).

RNA-associated silencing :

Genes can also be turned off by RNA when it is in the form of antisense transcripts, noncoding RNAs, or RNA interference. RNA might affect gene expression by causing heterochromatin to form, or by triggering histone modifications and DNA methylation (Egger *et al.,* 2004).

Nutriepigenomics :

Nutriepigenomics is the study of food nutrients and their effects on human health through epigenetic modifications. There is now considerable evidence that nutritional imbalances during gestation and lactation are linked to non-communicable diseases, such as obesity, cardiovascular disease, diabetes, hypertension, and cancer. If metabolic disturbances occur during critical time windows of development, the resulting epigenetic alterations can lead to permanent changes in tissue and organ structure or function and predispose individuals to disease (Gallou-Kabani *et al.,* 2007).

Epigenetics relates to heritable changes in gene function that occur independently of alterations in primary DNA sequence. Two major epigenetic mechanisms implicated in nutriepigenomics are DNA methylation and histone modification. DNA methylation in gene promoter regions usually results in gene silencing and influences gene expression. While this form of gene silencing is extremely important in development and cellular differentiation, aberrant DNA methylation can be detrimental and has been linked to various disease processes, such as cancer (Berdasco and Esteller, 2010). The methyl groups used in DNA methylation are often derived from dietary sources, such as folate and choline, and explains why diet can have a significant impact on methylation patterns and gene expression (Pozharny *et al*., 2010). Gene silencing can also be reinforced through the recruitment of histone deacetylases to decrease transcriptional activation. Conversely, histone acetylation induces transcriptional activation to increase gene expression. Dietary components can influence these epigenetic events, thereby altering gene expression and disturbing functions such as appetite control, metabolic balance and fuel utilization (Gallou-Kabani *et al.,* 2007).

Various genetic sequences can be targeted for epigenetic modification. A transcriptome-wide analysis in mice found

that a protein-restricted (PR) diet during gestation resulted in differential gene expression in approximately 1 per cent of the fetal genes analyzed (235/22,690). Specifically, increased expression was seen in genes involved in the p53 pathway, apoptosis, negative regulators of cell metabolism, and genes related to epigenetic control (Gheorghe, 2009). Additional studies have investigated the effect of a PR-diet in rats and found changes in promoter methylation of both the glucocorticoid receptor and peroxisome proliferator-activated receptor (PPAR) (Lillycrop *et al*.,2008; Lillycrop *et al*.,2007). Altered expression of these receptors can result in elevated blood glucose levels and affect lipid and carbohydrate metabolism (Pozharny *et al*., 2010). Feeding a PR-diet to pregnant and/or lactating mice also increased expression of glucokinase, acetyl-CoA carboxylase, PPARα, and acyl-CoA oxidase (Burdge and Lillycrop, 2010). Changes in expression were reportedly due to epigenetic regulation of either the gene promoter itself, or promoters of transcription factors that regulate gene expression. Additional genes that have been shown, either by *in vitro* or *in vivo* studies, to be regulated by epigenetic mechanisms include leptin, SOCS3, glucose transporter (GLUT)-4, POMC, 11-β-hydroxysteroid dehydrogenase type 2 and corticotrophin releasing hormone. Epigenetic modification of these genes may lead to "metabolic programming" of the fetus and result in long-term changes in metabolism and energy homeostasis (Tamashiro, 2010).

Epigenetic role of nutrition in physiologic and pathologic processes :

In the nutritional field, epegenetics is exceptionally important, because nutrients and bioactive food components can modify epigenetic phenomena and alter the expression of genes at the transcriptional level. Folate, vitamin B-12, methionine, choline, and betaine can affect DNA methylation and histone methylation through altering 1-carbon metabolism. Two metabolites of 1-carbon metabolism can affect methylation of DNA and histones: S-adenosylmethionine (AdoMet), which is a methyl donor for methylation reactions, and S-adenosylhomocysteine (AdoHcy), which is a product inhibitor of methyltransferases. Thus, theoretically, any nutrient, bioactive component, or condition that can affect AdoMet or AdoHcy levels in the tissue can alter the methylation of DNA and histones. Other water-soluble B vitamins like biotin, niacin, and pantothenic acid also play important role in histone modifications. (Kirkland, 2009).). Pantothenic acid is a part of Co A to form acetyl-CoA, which is the source of acetyl group in histone acetylation. Bioactive food components directly affect enzymes involved in epigenetic mechanisms. For instance, genistein and tea catechin affects DNA methyltransferases. Altered enzyme activity by these compounds may affect physiologic and pathologic processes during our lifetime by altering gene expression.

During our life time, nutrients can modify physiologic and pathologic processes through epigenetic mechanism that are critical for gene expression. Modulation of these processes through diet or specific nutrients may prevent diseases and maintain health. However, it is very hard to delineate the precise effect of nutrients or bioactive food components on each epigenetic modulation and their associations with physiologic and pathologic processes in our body, because the nutrients also interact with genes, other nutrients, and other lifestyle factors. Furthermore, each epigenetic phenomenon also interacts with the others, adding to the complexity of the system.

Epigenetic effects in humans :

Genomic imprinting and related disorders :

Some human disorders are associated with genomic imprinting, a phenomenon in mammals where the father and mother contribute different epigenetic patterns for specific genomic loci in their germ cells (Cooney *et al.*, 2002). The best-known case of imprinting in human disorders is that of Angelman syndrome and Prader-Willi syndrome—both can be produced by the same genetic mutation, chromosome 15q partial deletion, and the particular syndrome that will develop depends on whether the mutation is inherited from the child's mother or from their father (Waterland and Jirtle, 2003). This is due to the presence of genomic imprinting in the region. Beckwith-Wiedemann syndrome is also associated with genomic imprinting, often caused by abnormalities in maternal genomic imprinting of a region on chromosome 11.

Transgenerational epigenetic observations :

In the Överkalix study, Marcus Pembrey and colleagues observed that the paternal (but not maternal) grandsons (Jablonka and Raz, 2009) of Swedish men who were exposed during preadolescence to famine in the 19th century were less likely to die of cardiovascular disease. If food was plentiful, then diabetes mortality in the grandchildren

Physiological /pathological conditions	Nutrient or diet	Epigenetic mechnaism	References
Embryonic development	Folate	DNA methylation	Regine *et al.*, 2009
	Choline	DNA methylation	Niculescu *et al.*, 2006
	Protein restriction	DNA methylation	Liilycrop *et al.*, 2008
cancer	Methyl-deficient diet	histone modifications, micro RNA	Pogribny *et al.*, 2006
Obesity, insulin resistance	Methyl-deficient diet	DNA methylation	Sinclair *et al.*, 2007
aging	Folate	DNA methylation	Keyes *et al.*, 2007

increased, suggesting that this was a transgenerational epigenetic inheritance (Wood and Oakey, 2006). The opposite effect was observed for females—the paternal (but not maternal) granddaughters of women who experienced famine while in the womb (and therefore while their eggs were being formed) lived shorter lives on average.

Cancer and developmental abnormalities :

A variety of compounds are considered as epigenetic carcinogens—they result in an increased incidence of tumors, but they do not show mutagen activity (toxic compounds or pathogens that cause tumors incident to increased regeneration should also be excluded). Examples include diethylstilbestrol, arsenite, hexachlorobenzene, and nickel compounds.

Many teratogens exert specific effects on the fetus by epigenetic mechanisms (Pembrey *et al.*, 2006). While epigenetic effects may preserve the effect of a teratogen such as diethylstilbestrol throughout the life of an affected child, the possibility of birth defects resulting from exposure of fathers or in second and succeeding generations of offspring has generally been rejected on theoretical grounds and for lack of evidence. However, a range of male-mediated abnormalities have been demonstrated, and more are likely to exist (Bishop *et al.*, 1997). Recent studies have shown that the mixed-lineage leukemia (MLL) gene causes leukemia by rearranging and fusing with other genes in different chromosomes, which is a process under epigenetic control (Bishop *et al.*, 1997).

Other investigations have concluded that alterations in histone acetylation and DNA methylation occur in various genes influencing prostate cancer (Bishop *et al.*, 1997). Gene expression in the prostate can be modulated by nutrition and lifestyle changes (Cicero *et al.*, 1991).

DNA methylation in cancer :

DNA methylation is an important regulator of gene transcription and a large body of evidence has demonstrated that aberrant DNA methylation is associated with unscheduled gene silencing, and the genes with high levels of 5-methylcytosine in their promoter region are transcriptionally silent. DNA methylation is essential during embryonic development, and in somatic cells, patterns of DNA methylation are in general transmitted to daughter cells with a high fidelity. Aberrant DNA methylation patterns have been associated with a large number of human malignancies and found in two distinct forms: hypermethylation and hypomethylation compared to normal tissue. Hypermethylation is one of the major epigenetic modifications that repress transcription via promoter region of tumour suppressor genes. Hypermethylation typically occurs at CpG islands in the promoter region and is associated with gene inactivation. Global hypomethylation has also been implicated in the development and progression of cancer through different mechanisms (Newbold *et al*., 2006).

Conclusion :

Epigenetics is an inheritable phenomenon that affects gene expression without base pair changes. Epigenetic phenomenon include DNA methylaton, histone modifications and chromatin remodeling. Modifications of chromatin structure can give rise to a variety of epigenetic effects. Due to its reversible character, epigenetics is considered an attaractive field of nutrition intervention. Our knowledge regarding nutritional epigenetics is still limited. In the future we need to investigate more nutrients or bioactive food compounds to find better ones for our health. Understanding the role of nutrients or bioactive food components in altering epigenetic patterns will aid our ability to find a better way to maintain aur health through nutritional modulation that could be more physiologic than any other pharmacothereapies.

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