

## Nutriepigenomics: Mending Ideas in Nutrition, Health and Disease

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Rec Date: Jan 18, 2016; Acc date: Jan 20, 2016; Pub date: Jan 27, 2016

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### Editorial

The novel discipline of nutriepigenomics integrates knowledge on nutrigenomics and the reciprocal effects that epigenetic changes exert on gene expression under the influence of nutritional factors. Mutual interactions among genes, nutrients and nutrition-induced epigenetic modifications configure the nutriepigenomic outcome. This trinomial interaction is highly complex and this field is still in a very primitive stage; however, it is most attractive for the scientific community and probably a correct path towards a personalized nutrition in the future [1,2].

Nutriepigenomics may affect pathogenic features of cardiovascular [3,4], brain [5-7], and immune disorders [8,9], and longevity [10], cancer [11-14], neurodegeneration [15,16], and drug metabolism as well [17-19]. Similarly, nutritional strategies can be used to prevent and/or reverse the pathological consequences of these health conditions [19]. Of particular importance is the role that epigenetics may play in neonatal nutrition as a preventive strategy against diseases of adulthood and/or aging-related disorders [20].

The gene clusters involved in the nutrigenomic process are, at least, of 5 different categories (similar to those involved in pharmacogenomics): (i) pathogenic genes associated with a particular disease; (ii) food-related metabolic genes (phase I-II enzymes); (iii) detoxifying genes; (iv) transporter genes; and (v) pleiotropic genes [17]. All these genes are under the influence of the epigenetic machinery [15,18].

Epigenetics, defined as phenotypic changes transmitted from one generation to another with no apparent alterations in structural DNA, is a common phenomenon in health and disease. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA (miRNA) regulation, are among the major regulatory elements that control metabolic pathways at the molecular level. These epigenetic modifications regulate gene expression transcriptionally, and miRNAs suppress gene expression post-transcriptionally. Epigenetics has emerged as one of the most important biological mechanisms linking exposures during the course of life to long-term health. Epigenetic status is influenced by a range of constitutional conditions (structural genomics, genomic variation) and environmental exposures, including diet and nutrition, social status, chemical and emotional environment, pregnancy, pathological conditions, and pharmacological intervention. Epigenetic changes in genes associated with age affect life expectancy and longevity and altered DNA methylation patterns may account for phenotypic changes associated with human aging [15]. Epigenetic modifications are reversible and can potentially be targeted by pharmacological and dietary interventions. Epigenetic drugs and nutrients may be useful for the treatment of major problems of health. The efficacy and safety of

epigenetic nutrients depend upon the efficiency of the pharmacoeigenetic process in which different clusters of genes are involved [15-18]. Many food-derived epigenetic compounds have been characterized as: (i) DNA methyltransferase (DNMT) inhibitors (curcumin derivatives, psammaplins, tea polyphenols (epigallocatechin-3-gallate), bioflavonoids (quercetin, genistein, fisetin), catechins); (ii) histone deacetylase inhibitors (HDACs)(short-chain fatty acids, hydroxamic acids, cyclic peptides, benzamides, ketones, sirtuin inhibitors (suramin, sirtinol, splitomycin, cambiol), sirtuin activators (resveratrol, quercetin); and (iii) others (tubacin, anacardic acid, garcinol, chaetocin, parnate, vitamins) [16,21]. Although most epigenetic nutrients derive from vegetal sources, a new class of biomarine derivatives has shown a clear nutrigenomic profile and highly effective lipid-lowering, anti-atherosclerotic, immune-enhancing, and anti-tumor effects [17].

Nutritional epigenetics has emerged as a novel mechanism underlying gene-diet interactions. Nutrient-dependent epigenetic variations can significantly affect genome stability, mRNA and protein expression, and metabolic changes, which in turn influence food absorption and the activity of its constituents. Dietary bioactive compounds can affect epigenetic alterations, which are accumulated over time and have been shown to be involved in the pathogenesis of age-related diseases. Nutrients can act as a source of epigenetic modifications. Nutrients involved in one-carbon metabolism (folate, vitamin B12, vitamin B6, riboflavin, methionine, choline, and betaine) modify DNA methylation by regulating levels of the universal methyl donor S-adenosylmethionine (SAM) and methyltransferase inhibitor S-adenosylhomocysteine [22]. SAM is generated in the one-carbon metabolism cyclical cellular process by several enzymes in the presence of dietary micronutrients [23]. Other nutrients and bioactive food components such as retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols can modulate epigenetic patterns by altering the levels of SAM and S-adenosylhomocysteine or directing the enzymes that catalyze DNA methylation and histone modifications [22]. Dietary bioactive compounds such as genistein, phenylisothiocyanate, curcumin, resveratrol, indole-3-carbinol, and epigallocatechin-3-gallate can regulate HDAC and histone acetyltransferase (HAT) activities and acetylation of histones and non-histone chromatin proteins, and their health benefits are thought to be attributed to these epigenetic mechanisms [24]. Epigenetic marks are heritable but are also responsive to environmental shifts, such as changes in nutritional status, and are especially vulnerable during development. Epigenetic features can be altered by periconceptional nutritional interventions such as folate supplementation, thereby changing offspring phenotype. Variation in early environmental exposure in utero leads to differences in DNA methylation of offspring with the resulting alterations in gene expression in the offspring [25]. Dietary polyphenol-targeted epigenetics might be an attractive approach for disease prevention and

intervention [26]. Polyphenols, a class of natural compounds widely distributed in fruits, vegetables, and plants, have been reported to possess a wide range of activities in the prevention and alleviation of various diseases such as cancer, neuroinflammation, diabetes and aging [27]. Polyphenols reverse adverse epigenetic regulation by altering DNA methylation and histone modification, and modulate miRNA expression or directly interact with enzymes that result in the reactivation of silenced tumor suppressor genes or the inactivation of oncogenes [26]. Dietary supplementation with polyunsaturated fatty acid during pregnancy modulates DNA methylation at IGF2/H19 imprinted genes and growth of infants [28]. Vitamin A inhibits cytokine responses through increased expression of SUV39H2, a histone methyltransferase that induces the inhibitory mark H3K9me3. H3K9me3 at promoter sites of several cytokines is up-regulated by vitamin A, and inhibition of SUV39H2 restores cytokine production. The stimulatory histone mark H3K4me3 is down-regulated by vitamin A at several promoter locations of cytokine genes [29]. Fetal and subsequent early postnatal iron deficiency causes persistent impairments in cognitive and affective behaviors despite prompt postnatal iron repletion. The long-term cognitive impacts are accompanied by persistent downregulation of BDNF, a factor critical for hippocampal plasticity throughout the lifespan. Early-life iron deficiency epigenetically modifies the BDNF locus and dietary choline supplementation during late gestation reverses these modifications [30].

These are but a few examples illustrating the impact that nutriepigenomics may have on health and disease. The future seems to be promising; the scientific challenge is very exciting; however, the time is not yet ripe and much more work and deep commitment from the medical community is necessary before we can enter the promised land of personalized nutrition.

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