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Review Article

Nutrition and Epigenetics

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Abstract

Nutrition plays an important role in epigenetic modifications related to DNA methylation, histone modifications and RNA interference contributing to the development of cancer, cardiovascular, metabolic, skin, autoimmune diseases and neurologic disorders. Life style and nutritional changes have been demonstrated to decrease epigenetic modifications with significant reduction in disease risk. Poor perinatal nutrition has been linked to neurologic and psychiatric disorders and memory impairments. Moreover, dietary intake has been associated with epigenetic modifications in children with asthma. A link has also been established between nutrition, epigenetics and pancreatic cancer. RNA interference, particularly microRNA mediated regulation of gene expression is strongly affected by dietary intake and plays an important role in both prevention and development of disease. In this review, the relationship between nutrition and epigenetic mechanisms, nutrition and disease, and clinical trials based on nutritional input are presented through various examples.

Keywords: *Epigenetics; DNA Methylation; Histone Modifications; RNA Interference; Nutrigenomics*

Abbreviations

BDNF: Brain-Derived Neurotrophic Factor; CMD: Choline-Methionine Deficient; COL18A1: Collagen Type XVIII Alpha 1; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; DRD2: Dopamine D2 Receptor; EEF2: Eukaryotic Translation Elongation Factor 2; H19: Gene For Long Non-Coding RNA; IFNγ: Interferon γ; IFRD1: Interferon Related Developmental Regulator 1; IGF-2: Insulin Growth Factor 2; IL4I1: Interleukin 4 Induced 1 Isoform; LEPR: Leptin Receptor; LDLRAP1: Low-Density Lipoprotein Receptor Adapter Protein 1; MAPKAPK2: Mitogen-Activated Protein Kinase-Activated Protein Kinase 2; MeCP2: Methyl CpG Binding Protein 2; miRNA : MicroRNA ; NPAS2 : Neuronal PAS Domain Protein 2; OXPHOS : Oxidative Phosporylation; PKCε: Protein Kinase Cε; PLAGL1 : Zinc Finger Protein PLAGL1 ; PPARGC1A: Peroxisome Proliferator-Activated Receptor Gamma-1 Alpha; PPARGC18: Peroxisome Proliferator-Activated Receptor Associated with the GC18; RNAi: RNA Interference; TNF-α: Tumor Necrosis Factor-α

Introduction

The remarkable progress in bioinformatics, genomics and proteomics research has substantially improved our understanding of disease development, treatment and prevention [1]. This has included the revelation of the impact of epigenetic mechanisms as a major factor in parallel to genetic composition in development and progress of disease. Epigenetics has been defined as the study on heritable but reversible changes in gene expression without modifications of the primary DNA sequence [2]. The three main epigenetic modifications comprise of DNA methylations [3], histone modifications [4] and RNA interference (RNAi) [5]. Both DNA methylation and histone modifications can result in up- or down-regulation of transcription [6,7], while RNAi down-regulates gene expression by the interaction of 21 - 23 nucleotide long single-stranded micro-RNAs (miRNAs) with mRNA [8]. Today, more than 1800 miRNAs have been identified [9], many of which have been demonstrated to be associated with disease [8,10].

The link between nutrition and epigenetic modifications was established already some time ago, illustrated by methylation of the Agouti gene resulting in fur color change [11]. More recently, numerous examples related to the effect of dietary intake on DNA methyla-

tion, histone modifications and miRNA expression have been described [12]. In this review, the relationship between nutrition and epigenetics is described. Moreover, examples of the effect on dietary intake on disease development and prevention are presented. Finally, examples of clinical studies targeting epigenetic mechanisms affected by nutritional input are discussed.

Nutrition and Epigenetics

The dietary intake has proven important in health and therefore in both risk of disease development and prophylactic interventions [13]. For instance, heightened perinatal plasticity plays a crucial role in the establishment of neuronal connections and when perinatal nutrition either lacks specific micro- and macronutrients or is overloaded with excess calories, the effects can be significant [14]. In this context, a poor *in utero* environment has been associated with neurologic and psychiatric disorders. Many diseases characterized by learning and memory impairment such as autism, schizophrenia and Alzheimer's disease have been indicated to originate in environmental instability very early in life. Furthermore, over the past decade a number of studies have demonstrated that ancestral nutrition plays an important role in altering the metabolic phenotype of off-spring indicating a close link between metabolism and epigenetic modifications [15]. Maternal malnutrition has also been linked to miRNA biogenesis in mouse brain [16]. For instance, exposition to a protein-deficient diet during gestation and lactation reduced the weight of the hippocampus, delayed the development of offspring and deregulated the expression of the Xpo3 and Ago2 genes in the hippocampus and hypothalamus of weaning mice. Similarly, it has been demonstrated that primates fed on a high-fat diet significantly modified *in utero* expression of the fetal hepatic circadian gene NPAS2 resulting a 7.1-fold increase in primates [17]. Exposure to a maternal high-fat diet also affected differential NPAS2 promoter occupancy of fetal histone H3K14ac. Genetic imprinting may also cause gene silencing after fertilization as demonstrated by active demethylation of the paternal genome while the female genome is passively demethylated [18]. The outcome is parent-of-origin-dependent mono-allelic expression of critical autosomal genes [19].

Environmental factors including nutrition play an important role prior to birth resulting in neurological developmental deficits in offspring [20]. For example, alcohol-induced fetal alcohol syndrome is caused by DNA methylation in sperm, embryos and the developing brain after alcohol exposure [21-23]. Smoking during pregnancy has also been demonstrated to affect fetal growth, preterm birth and long term health issues in offspring [24]. In this context, epigenetic changes in DNA methylation and miR-16, miR-21 and miR-146a expression were observed in human placenta in maternal smokers [25]. Also, children exposed prenatally to tobacco smoke showed lower DNA methylation levels in the transposable element AluYb8 in buccal cells indicating a link to disease pathogenesis [26]. Moreover, related to drug abuse during pregnancy, exposure to cocaine has resulted in premature birth, cardiac defects and attention deficit disorders based on differential DNA methylation and altered gene expression [27,28]. Moreover, rats treated with cocaine increase H3 acetylation and decreased methyl CpG binding protein 2 (MeCP2)-association with the BNDF promoter IV was observed [29]. Paternal cocaine intake showed impaired memory in female offspring and led to hyperactivity in male offspring [30]. Furthermore, studies have been conducted on the impact of fetal cardiac development when pregnant rats were exposed to cocaine leading to myocardiate apoptosis due to DNA methylation-induced protein kinase Cε (PKCε) expression [31]. Cannabis has also been associated with restricted fetal growth and altered behavior after *in utero* exposure [32,33]. Furthermore, reduced dopamine D2 receptor (DRD2) expression was detected in the ventral striatum of human fetuses, which had been maternally exposed to cannabis [34].

In the context of livestock production, the influence of nutritional epigenetics has been demonstrated by altered carbohydrate metabolism and rates of fat and protein deposition based on diet-induced hypo- or hyper-methylation [35]. The link of nutrition to epigenetic mechanisms was also demonstrated by feeding mice with a choline-methionine deficient (CMD) diet, which enhanced the expression levels of IGF-2 and H19 in prostate tissue of mice [36]. The reversible nature of epigenetic regulation was observed at shorter exposure to the CMD diet. Furthermore, the lack of change in DNA methylation in the promoter regions and IGF-2 and H19 imprinting strongly suggested epigenetic plasticity and indicated that the impact of the CMD diet was more prominent on chromatin modifications than DNA methylation. In another study, men with a low birth weight overfed on a high-fat diet induced DNA methylation, which resulted in peripheral insulin resistance and decrease in peroxisome proliferation-activated receptor gamma-1 alpha (PPARGC1A) and oxidative phosphorylation (OXPHOS)-related gene expression after five days [37].

The epigenetic activity of plant miRNAs and their effect after oral intake of plant-based food has caught much attention recently. An initial report indicated that these miRNAs might accumulate in the serum in animals and thereby could affect the regulation of gene expression [38]. Interestingly, miR-168a abundantly found in rice has been demonstrated to bind to human and mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA, which potentially may regulate gene expression in mammals [39]. However, another study suggested that substantial amounts of miR-156a, miR-159a and miR169a present in the diet could not be detected in the plasma [40]. Likewise, only negligible amounts of miR-21 were detected in mice fed on a fat-rich diet containing endogenous miR-21 and miRNA delivery through food seems to be rare. In contrast, uptake of seven human miRNAs in plasma and stool samples in individuals with different dietary habits revealed differential expression of miR-92, where higher expression levels were observed in vegetarians compared to omnivores, but lower than in vegans [41]. When herb-based diets containing miR2911 were fed to mice, it was found that miR2911 levels in sera and urine correlated with dietary intake levels [42]. However, abundance was not the sole determinate of RNA availability as gavage-feeding of large doses of synthetic miR2911 generated only minor transient increase in serum levels. Furthermore, the RNA did not co-immunoprecipitate with AGO2 suggesting that dietary miR2911 was not modified by association with RNA-induced silencing complexes in the host. However, in another study applying an Aradopsis mutant deficient in miRNA processing confirmed that the genesis and increase in post-harvest levels of miR2911 is atypical in comparison to traditional plant bioactives, which normally are subjected to degradation as vegetables lose freshness [43].

Nutrition and Disease

Nutrition has been shown to directly or indirectly affect disease development. Already in the 1980s it was suggested that diet was responsible for approximately a third of the risk of developing cancer in the US [44]. Moreover, based on thousands of publications The World Cancer Research Fund and American Institute of Cancer Research concluded that nutrition provides a significant contribution globally to cancer [45]. Also, a review on cancer prevention indicated that two-thirds of cancer-related deaths could be prevented by nutritional interventions and lifestyle changes [46]. Mainly proanthocyanidins, found in plants, act as anti-carcinogenic agents through their anti-oxidant, apoptosis-inducing, immunomodulating and enzyme modulating properties effecting epigenetics. For this reason, nutrition rich in vegetables and fruits has been considered favorable. Cancer prevention and therapy have therefore recently started to focus on the input of nutrition and epigenetic mechanisms [47]. Particularly long non-coding RNAs and miRNAs have been proven to be dysregulated in various cancers. Another example relates to mounting evidence of nutrition being a key factor in development and progress of pancreatic cancer [48]. For instance, consummation of diets high in fruit and vegetable contents results in lower risk of pancreatic cancer whereas excessive intake of red meat and saturated fat has been associated with increased risk. An emerging role for the effect of dietary intake on epigenetics has also been observed in inflammation and modulation of cancer risk [49]. It was postulated that the association between nutrition and DNA methylation, histone modifications and chromatin remodeling affected the inflammation phenotype and the development of cancer. Moreover, both genetic and epigenetic components have been indicated to influence DNA methylation and may increase the risk of cardiovascular disease (CVD) development [50]. Much effort is now dedicated to integration of epigenetics in nutrition research for determination of the CVD risk.

Clinical Trials and Epigenetics

The effect of nutrition and especially drastic changes in dietary intake in relation to risk and treatment of disease has been evaluated in a number of studies. For instance, 30 low-risk prostate cancer patients, which had not been subjected to surgery, radiation or hormonal treatment, were placed on a modified diet and change in lifestyle [51]. These changes resulted already after three months in modification of gene expression profiles related to protein metabolism, intracellular protein traffic and phosphorylation, essential for tumorigenesis. A two-year follow-up study in early-stage prostate cancer patients subjected to lifestyle and dietary changes in the Prostate Cancer Lifestyle Trial indicated that conventional prostate cancer treatment could be delayed or omitted [52]. Furthermore, a multicenter trial on high-risk CVD patients investigated the effect of Mediterranean diet supplemented with extra-virgin oil or mixed nuts [53]. The outcome was that the incidence of major cardiovascular events was reduced in individuals subjected to a Mediterranean diet with extra-virgin olive oil

or nuts, whereas people receiving a fat reducing diet (control group) showed no change. A Mediterranean diet-based study investigated the association with changes in the methylation status of peripheral blood cells [54]. The study was conducted in individuals with high cardiovascular risk. Eight genes related to inflammation and immunocompetence (EEF2, COL18A1, IL4I1, LEPR, PLAGL1, IFRD1, MAPKAPK2, PPARGC18) showed a correlation between changes and DNA methylation for persons subjected to the Mediterranean diet, but not to the control group receiving a low-fat diet. Moreover, EEF2 methylation levels correlated with concentrations of TNF-α and CRP. In another study, the relationship between diet and asthma was investigated in 32 children in Montana [55]. Intake of methyl donating nutrients such as folate demonstrated a positive association with LINE-1 methylation, but a negative link to the IFNγ promoter CpG site -186. However, the IFNγ promoter CpG site -54 showed no association to intake of selected dietary nutrients. Moreover, as the IFNγ promoter CpG sites were not associated with respiratory health measures, it remains unclear through which epigenetic mechanism these nutrients impact the quality of life. Moreover, selenium and several methyl donor dietary nutrients showed an association with significant improvement in quality of life in children with asthma.

Disease	Nutrient/Source	Effect	Ref
Cancer - prostate	Modified diet, lifestyle change	Favorable gene expression profiles Delayed or omitted treatment	[51] [52]
Cancer – pancreas	Fruits, vegetables Red meat, saturated fat	Reduced cancer risk Increased cancer risk	[48] [48]
Inflammation	Nutritional supplements	Affected DNA methylation, histone modifications, chromatin remodelling	[49]
Cardiovascular	Mediterranean diet + extra-virgin oil or nuts	Reduced incidence of major cardiovascular events	[53]
Cardiovascular	Mediterranean diet	Change in inflammation-related genes and DNA methylation	[54]
Asthma	Methyl donating nutrients (folate)	Positive association with LINE-1 methylation, negative link to IFNCpG-186	[55]
Alzheimer's	Vegetables, fruits, nuts	Lower risk of cognitive defects	[56]
Multiple sclerosis	Low-fat diet, fish oil	Slow down of disease	[57]
Brain development	Maternal malnutrition, protein-deficient diet linked to miRNA biogenesis	Deregulation of Xpo3 and Ago2 gene expression, delayed development	[16]

Table 1: *Examples of associations between nutrition and epigenetic mechanisms.*

Conclusions

In summary, numerous studies have confirmed the involvement of nutrition related to prevention of and even therapeutic interventions of various diseases including prenatal maternal exposure. Interestingly, a strong association between nutrition and epigenetic mechanisms has been established. Both preclinical and clinical studies have indicated that nutrition can affect DNA methylation, histone modifications and miRNA expression promoting disease development. Most encouragingly, changes in dietary composition have proven crucial in reversibility of epigenetic mechanisms in experimental animal models, but also in trials on human patients. Significant decrease related to expression of genes supporting tumorigenesis was observed in prostate cancer patients after a drastic change in diet. Likewise, children with asthma subjected to a diet rich in methyl donating donors provided a better quality of life. Obviously, progress in nutrigenomics and epigenetics will further improve our understanding of the complex interaction between nutrition and epigenetics, which will provide better means to prevent and treat various diseases.

Conflict of Interest

The author declares that no conflict of interest exists.

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