

Epigenetics and Nutrition

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Abstract

Epigenetic mechanisms based on DNA methylation, histone modifications and RNA interference have recently showed important association to the development of a wide variety of diseases such as cancer, cardiovascular, metabolic, skin, autoimmune diseases and neurologic disorders. In the context of preventive aspects, the importance of nutrition on epigenetic function has been revealed. Therefore, drastic changes in dietary modifications may contribute to reduced disease risk. For instance, dietary intervention has been showed to affect DNA methylation in Alzheimer's disease patients. Moreover, maternal high-fat diet can regulate gene expression through promoter histone modifications. Most importantly, RNA interference and particularly micro-RNA mediated regulation of gene expression has been linked to disease development. Remarkably, dietary intake has been demonstrated to significantly affect various miRNAs and their regulation on gene function. In this review, the relationship between epigenetics and disease and development of drugs based on epigenetic targets is presented as well as the influence of dietary intake on epigenetic mechanisms and its effect on disease prevention and therapy will be discussed.

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Academic Editor: Marco Innamorati, Milan State University

Citation: Kenneth Lundstrom (2015) Epigenetics and Nutrition. International Journal of Nutrition - 1(1):46-63. <https://doi.org/10.14302/issn.2379-7835.ijn-14-603>

Key words: epigenetics, nutrition, DNA methylation, histone modifications, RNA interference, micro-RNA, disease prevention

Received August 29, 2014; **Accepted** November 26, 2014; **Published** May 13, 2015;

Introduction

The importance of nutrition in relation to disease prevention and therapeutic interventions has become evident during the past few years. In fact, the daily food intake presents the most important “drugs” used by every one of us [1]. Furthermore, the recent progress in genome sequencing and the establishment of nutrigenomics has further revealed the close connection between nutrition and disease [2]. In addition, recently nutritional scientists have introduced the term foodomics to describe as the comprehensive high-throughput approach for the exploitation of food science in relation to the improvement of human nutrition [3]. In parallel, new findings have closely linked epigenetic mechanisms to disease development, which can be substantially affected by dietary interventions and life-style modifications [4]. Therefore, epigenetics has become an important factor also in modern drug discovery and development.

Epigenetic functions can be defined as mechanisms outside the scope of conventional genetic activities and therefore do not generate any modifications of the primary DNA sequence [5]. The three main mechanisms of epigenetics are DNA methylation, histone modifications and RNA interference.

Concerning DNA methylations, generally a methyl group (CH₃) is covalently added to the 5'-position of cytosine upstream of guanosine affecting gene expression in relation to differentiation, genomic imprinting and DNA repair [6]. Typically, the methylated CpG dinucleotides are located in promoter regions and therefore can result in down- or up-regulation of gene expression [7]. Aberrant DNA methylation patterns have been linked to disease, particularly cancer [8]. Furthermore, inactivation of tumor suppressor genes has been associated with hypermethylation [9]. In the context of DNA packaging histones play an important role, which

has confirmed their epigenetic association [5]. Typically, histones H3 and H4 are modified by a number of mechanisms such as acetylation, methylation, ubiquitination and phosphorylation [10]. For example, histone methylation due to increased acetylation is associated with repression or activation of transcription [11]. Furthermore, deregulation of histone modifications has been associated with mutations in oncogenes, tumor suppressor genes and DNA repair genes. The third epigenetic mechanism relates to RNA interference and particularly micro RNAs (miRNAs) and their role in the regulation of gene expression [12]. The 21-23 nucleotide single-stranded miRNAs interfere with mRNA resulting in the modification of gene expression including both down- and up-regulation [13, 14]. As at least one-third of human mRNAs are estimated to be regulated by miRNAs they have been frequently linked to cancer and other diseases [15].

In this review, the relationship between epigenetics and disease are described through examples from different disease indications. Furthermore, emphasis is put on recent development of drugs based on epigenetic targets. Attention is also paid to the association of nutrition and epigenetics and how dietary interventions and life-style changes can significantly contribute to reduced health risk and disease prevention.

Epigenetics and Disease

Due to the close association of epigenetics and disease much attention has been given to evaluate epigenetics in the light of drug targets and the development of novel medicines. In addition to the potential discovery of novel drug mechanisms the reversible nature of epigenetic mechanisms makes them attractive targets for therapy. Epigenetic mechanisms have been linked to a variety of medical indications including cancer, cardiovascular, liver and skin diseases and neurologic disorders (Table 1).

Table 1. Epigenetics and Disease.

Disease	Epigenetic function	Effect	Reference
Autoimmune			
Inflammation	miR-124 dysregulation	pathogenesis	[55]
RA	miRNA dysregulation	RA pathogenesis	[56]
MS	miRNA dysregulation	disease indicator for MS	[57]
Cancer			
AML	DNA MT inhibition	AML treatment	[59]
Bone	miRNA down-regulation	bone metastasis	[26]
Brain	DNA, H3K27 methylation	ependymoma therapy	[100]
Breast	DNA methylation	cancer association	[18]
Colon	histone modifications	up-regulated acetylation	[22]
CTCL	histone deacetylase	CTCL treatment	[60, 61]
Endometrial	hypermethylation	disease association	[17]
Gastric	DNA methylation	biomarker	[101]
Glioma	DNA methylation	reduced survival	[102]
Kidney	hypermethylation	biomarkers	[103]
Liver	miRNA up-regulation	reduced cell death	[104]
Ovarian	histone modifications	anti-cancer activity	[105]
Prostate	miRNA, tumor suppressor	tumor regression	[27, 106]
Cardiovascular			
Stroke	DNA methylation, miRNAs	association with stroke	[53, 107]
PH	miR-21 based regulation	control of PH	[108]
CH	HDACs	suppression of CH	[109]
Heart failure	differential expression	heart disease association	[110]
Liver			
ACHBLF	DNA methylation	disease associated	[41]
NAFLD	differential methylation	inhibition of HSC	[111]
Liver fibrosis	miRNA	HSC phenotype	[45]
NASH	DNA methylation	correlation to NASH	[112]
	miR-122	circadian rhythm linkage	[113]
Metabolic			
Diabetes	DNA methylation	diabetes association	[114]
	histone modification	diabetes protection	[115]
Neurological			
Alzheimer	HDAC inhibitors	reinstated learning	[48]
	DNA methylation	reduced pathology	[75]
	miR-29	pathology promotion	[35]
	miR-107, miR-298, miR-328	link to Alzheimer	[38, 37]
Huntington	histone modifications	neurodegeneration	[33]
Epilepsy	hypermethylation	epilepsy therapy	[29]
Parkinson	DNA methylation	Parkinson association	[31]
Skin			
Psoriasis	DNA methylation	psoriasis pathogenesis	[48]
	histone modifications	PASI correlation	[48]
	miR.143, miR-223 dysregulation	biomarkers for psoriasis	[49]

ACHBFL, acute-on-chronic hepatitis B liver failure; AML, acute myeloid leukemia; CH, cardiac hypertrophy; CTCL, cutaneous T-cell lymphoma; DNA MT, DNA methyltransferase;; HDACs, histone deacetylases; HSCs, hepatic stellate cells; MS, multiple sclerosis; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PASI, psoriasis area severity index; PH, pulmonary hypertension; RA, rheumatoid arthritis;

Cancer

Altered DNA methylation has been suggested as the epigenetic mechanism associated with cancer [16]. For example, hypermethylation of the *SPRY2*, *RASSF1A*, *RSK4*, *CHFR* and *CDH1* genes has been associated with endometrial cancer [17]. A genome-wide analysis of DNA methylation in breast cancer and normal tissue suggested that the function and pathways of several genes showed altered methylation status in cancer tissue indicating a role for DNA methylation in breast cancer [18]. Similarly, altered DNA methylation patterns have been observed in prostate [19] and rectal [20] cancer patients. Analysis of the DNA methylome of primary breast cancers revealed heterogeneity in transcription activity and differences in metastatic behavior [21]. Profiling of the DNA methylome and transcriptome of 44 matched primary breast tumors and regional metastasis revealed divergent changes primarily in CpG island-poor areas.

In the context of histone modifications, it was demonstrated that histone H3 lysine 27 acetylation was up-regulated in colon cancer [22]. Moreover, epigenomic-based therapies targeting histone modifications have been developed for the treatment of ovarian cancer [23]. In another study, a novel class I histone deacetylase (HDAC) inhibitor MPT0G030 has showed induced cell apoptosis and differentiation in human colorectal cancer cells [24]. This in vivo anti-cancer activity suggests a great potential for cancer therapy.

Several studies have revealed the association between miRNAs and cancer. As an example, expression of the p53-specific miR-34a is capable of inhibition of clonogenic expansion and tumor regression [25]. However, when the expression was down-regulated by miR-34a antagonists, tumor development and metastasis

was promoted and prolonged survival in tumor-bearing mice. Down-regulation of miR-143 and miR-145 has been linked to metastasis of the bone [26], whereas miR-200 decrease has been observed in clinical prostate tumors and prostate cancer cell lines [27].

Neurological disorders

DNA methylation plays an important role in normal brain function and aberrant methylation has recently been linked to neurological disorders and mental illnesses [28]. Recently, it was demonstrated that hypermethylation of a 5' end regulatory region of the *gria2* gene correlated with epilepsy seizures in a rat model suggesting that inhibitors of DNA methylation could potentially provide therapy for epilepsy [29]. Furthermore, it has been revealed that significant differences in DNA methylation exist between control and Alzheimer patients as well as in animal models for Alzheimer's disease [30]. Similarly, distinctive DNA methylation patterns have been associated with Parkinson's disease [31]. Genome-wide analysis of methylation in brain and blood samples showed substantial differences between patients with Parkinson's disease and healthy individuals.

Histone modifications have also been linked to Parkinson's disease. In this context, pathological imbalance between deacetylation and acetylation of histone proteins has been observed in Parkinson patients, which has drawn the attention to HDAC inhibitors for therapeutic applications [32]. Likewise, histone modifications have been associated with neurodegeneration in Huntington's disease [33]. Similarly to treatment of Parkinson's patients, HDAC inhibitors have demonstrated therapeutic efficacy in individuals with Huntington's disease. Moreover, histone modifications have been suggested to regulate hyperactivity in rats induced by lead exposure [34].

Increased histone acetylation was observed after chronic exposure to lead, which provides a better understanding of the etiology of attention-deficit/hyperactivity disorder (ADHD) and potential therapeutic interventions.

Moreover, miRNAs have been linked to Alzheimer's disease development, where for instance the miR29 cluster targeting beta-secretase BACE1 is down-regulated in Alzheimer brains leading to elevated BACE1 promoting amyloid pathology [35]. Likewise, SNPs within miR29 binding sites of the bace1 gene have been associated to sporadic Alzheimer's disease [36]. Furthermore, miR-107, miR-298 and miR-328 target BACE1 and have also been suggested to being linked to Alzheimer's disease [37, 38].

Liver diseases

In a recent study, DNA methylation profiles of 59 hepatocellular carcinoma (HCC) patients identified three tumor subgroups, which could be correlated with clinic-pathological parameters [39]. Studies on disease progression from chronic hepatitis C to cirrhosis and hepatocellular carcinoma indicated an association with increased DNA promoter methylation [40]. The DNA methylation frequency could therefore be used to monitor disease progress and methylation accumulates with progression into cancer. Moreover, aberrant DNA methylation of the G protein-coupled bile acid receptor 1 (Gpbar1) promoter has been linked to acute-on-chronic hepatitis B liver failure (ACHBLF) [41]. In this context, the frequency of the Gpbar1 promoter methylation was significantly higher in ACHBLF patients compared to individuals with chronic hepatitis B.

Related to histone modifications there are a number of suggestions linking them to liver disease [42]. For example, histone modifications have been associated with alcoholic liver disease [43]. Additionally, inactivation

of the tumor suppressor gene RIZ1 in hepatocellular carcinoma involved histone H3 lysine 9 (H3K9) modifications in combination with DNA methylation [44]. A number of miRNAs have been identified in regulating proliferation, apoptosis, TGF β 1 signaling, and collagen expression of the hepatitis stellate cell (HSC) phenotype and progression of fibrosis [45]. Moreover, differential expression of 100 miRNAs has been demonstrated in non-alcoholic steatohepatitis (NASH) [46]. Several miRNAs control lipid and glucose metabolism and such as miR-122 has showed close linkage to the circadian rhythm [47]. Also, miR-122 expression is down-regulated in NASH patients and functionally implicated in mice with non-alcoholic fatty liver disease (NAFLD).

Other diseases

Epigenetic mechanisms have also been linked to a number of other diseases. For instance, the DNA methylation pattern for multiple genes involved in psoriasis pathogenesis is abnormal and hypoacetylation of histone H4 was observed in peripheral blood mononuclear cells from psoriasis patients [48]. Furthermore, miRNAs have been linked to psoriasis, particularly miR-223 and miR-143 showing differential expression in psoriasis patients [49]. Epigenetic differences have also been observed in obese and diabetic individuals [50]. In this case, epigenetic mechanisms have been associated with maternal diabetes mellitus [51]. Related to type 1 diabetes histamine deacetylase 3 (HDAC3) inhibitors protect β -cells from cytokine-induced apoptosis [52]. In the case of type 2 diabetes, HDAC3 regulates genes involved in insulin resistance and pancreatic β -cell failure and HDAC3 inhibitors could therefore provide an attractive therapeutic strategy. Furthermore, in stroke patients the total DNA methylation of the tumor necrosis factor- α (TNF- α) promoter was lower [53]. Epigenetic function by miRNAs has also been associated with autoimmune

disease and rheumatoid arthritis [54]. In this context, miR-124 was demonstrated to regulate the proliferation and secretion of monocyte chemoattractant protein-1 (MCP-1) and dysregulation might cause inflammatory pathogenesis [55]. Additionally, Let-7a and miR-132 have been linked to rheumatoid arthritis pathogenesis [56] and miR-21 an indicator of progress of multiple sclerosis [57].

Epigenetic Drugs

Progress in understanding epigenetic mechanisms and their link to disease has accelerated the development of novel epigenetic drugs. Several epigenome-targeted drugs have already been approved by the US Food and Drug Administration [58]. In this context, the DNA methyltransferase inhibitors azacitidine and decitabine have been approved for the treatment of acute myeloid leukemia (AML) [59]. Moreover, two HDAC inhibitors, vorinostat [60] and romidepsin [61], are used for cutaneous T-cell lymphoma (CTCL) treatment. Additionally, several epigenetic drugs have been demonstrated to enhance memory function in rodents. Therapeutic efficacy has been observed for Alzheimer's disease, Schizophrenia and depression in animal models [62]. Evaluation of HDAC inhibitors in a murine model of the cyclin-dependent kinase 5 activator p25 protein reinstated learning behavior and synaptic plasticity even after severe neuronal loss [63].

Related to liver diseases epigenetics has provided some considerable impact on drug development [64]. For instance, the DNMT1 inhibitor 5-azadeoxycytidine (5-Azac) and the EZH2 inhibitor 3-deazaneplanocin A (dZNep) are potent inhibitors of HSC activation [65]. Furthermore, in 76% of NAFLD patients differentially methylated CpG sites became hypomethylated in advanced disease whereas 24% underwent hypermethylation [64].

Personalized Epigenetics & Biomarkers

In the context of drug development, genetic and epigenetic variations between individuals have triggered the need of designing personalized medicines. Diagnostic biomarkers play an important role in this context, particularly in the prediction of clinical drug responses before treatment [66]. This type of pre-screening will allow for disease-specific therapy without the need of subjecting patients to drugs unlikely to provide any clinical benefit. In the case of oncology, isolation and analysis of genetic, biochemical and immunohistochemical markers from tumors and biofluids aid in defining selective treatment [67]. Investigation of 19 candidate genes demonstrated that hypermethylation of the AKR1B1 and TM6SF1 promoters can serve as biomarkers for the early detection of breast cancer [68]. Likewise, methylation profile studies of 59 patients with hepatocellular carcinoma identified three tumor subgroups, which correlated with clinic-pathological parameters [69].

Furthermore, histone-modifying genes have also been evaluated as diagnostic markers. For instance, studies on HCC and adjacent non-cancerous patient tissue revealed by RT-qPCR and tissue microarray-based immunohistochemistry (TMA-based IHC) analysis showed up-regulation of the histone phosphorylation gene ARK2 and methylation genes G9a, SUV39H2 and EZH2 [70]. Clearly, overexpression of EZH2 and SUV39H2 was associated with HCC prognosis and could serve as novel prognostic biomarkers. Another approach has been to apply imaging mass spectrometry to identify modified forms of histone H4 as new biomarkers of microvascular invasion in HCC [71]. The analysis showed that 28 of 30 differential protein peaks were overexpressed in HCC patients, of which two peaks were identified as N-terminal acetylated histone H4

dimethylated at lysine 20 and acetylated at lysine 16, respectively.

Epigenetics and Nutrition

There are plenty of indications that dietary intake has a strong influence on epigenetics [72] (Table 2). When rodents are subjected to a diet depleted of methyl donors it promotes DNA hypomethylation and the development of steatosis [73]. In contrast, a high-calorie diet supplemented with methyl donors prevented NAFLD suggesting that epigenetic modifications which affected hepatic fat metabolism were related to DNA methylation changes.

Another example is the potential link of nutrition to histone modifications and alcohol-induced liver disease (ALD) [74]. Particularly, critical metabolites such as acetate, S-adenosylmethionine (SAM), nicotinamide adenine dinucleotide, and zinc are relevant to alcohol metabolism and ALD. Furthermore, high SAM levels are boosted by a folic acid rich diet, which has been showed to reduce pathology in a mouse model for amyloid pathology [75]. Similarly, vitamin deficiency was observed in mice suffering from memory impairment [76]. For instance, vitamins and minerals play an important role in miRNA modulation and the potential of viable exogenous miRNAs entering human blood circulation from food sources has added a new dimension to the impact of nutrition on miRNAs and its effect on health [77]. Related to breast cancer, selenium has proven promising as an anti-breast cancer trace element affecting DNA methylation and histone modifications [78]. Treatment of MCF-7 human breast carcinoma cells with methylselenic acid or selenite resulted in a dose-dependent inhibition of cell proliferation.

Recently, the understanding of the relationship between epigenetics, ageing and nutrition has been enlightened

by a number of new findings. Emerging evidence suggests that long term changes in DNA methylation during early life, especially related to nutrition, can cause altered susceptibility to a variety of diseases associated with ageing [79]. One aspect of early life nutrition is breast feeding, which is well-known for its favorable effects in preventing acute and chronic diseases [80] and association with better neuronal-behavioral development [81]. Epigenetic effects of human breast milk might occur and several components of breast milk have been linked to epigenetic changes. In this case, lactoferrin has been associated with reduced NF- κ B expression contributing to the prevention of disorders of the immune system [82]. Likewise, prostaglandin J enhances peroxisome proliferator-activated receptor gamma (PPAR γ) expression and has been associated with obesity prevention [83]. However, additional studies have to be conducted to further determine the link between human breast milk and epigenetic functions. Furthermore, intra-uterine development has been showed to influence health outcome in adult life and epigenetic regulation has been implied [84]. In this context, the impact of prenatal drug and substance exposure on childhood development has received plenty of attention, but even life-long health outcome due to epigenetic memory has generated interest.

In the context of epigenetics and breast milk, miRNAs packaged in exosomes in porcine milk have been suggested to influence development in piglets [85]. Isolation of exosomes from porcine milk identified 176 known miRNAs and 315 novel mature miRNAs. Genome pathway analysis indicated that some miRNAs targeted genes enriched in transcription, immunity and metabolism and may be involved in the regulation of the IgA immune network. Moreover, a number of miRNAs encapsulated in exosomes have been isolated from

Table 2. Epigenetics and Nutrition.

Nutritional Source	Epigenetic function	Disease/Effect	Reference
Polyphenols			
Polyphenols	miR-103/107, 122	Fatty liver disease	[116]
Caffeic acid, hesperidin	miR-30c, 291, 296, 374, 476b	miRNA modulation ApoE mice	[117]
Proanthocyanidines	miR-30b, 197, 523-3p, 1224-3p	Human HepG2 cells	[118]
High-fat diet			
HFD (60% kcal fat)	miR-21, 142, 146	Obesity/miRNA modulations	[119]
HFD (58% kcal fat)	20 miRNAs	Diabetes/miRNA modulations	[120]
HFD	miR-467b	NAFLD/miR-467b down-regulation	[121]
Trace elements			
Methyl-depleted diet	DNA methylation	Hypomethylation, steatosis	[73]
Selenium	DNA methylation	Anti-breast cancer activity	[78]
Selenium	histone modifications	Anti-breast cancer activity	[78]
Vitamins			
Folic acid	histone modifications	Reduced amyloid pathology	[75]
Vitamins	DNA methylation	Memory impairment	[76]
Vitamins, minerals	miRNAs	miRNA modulation	[77]
Food intake			
Milk	miRNAs packaged in exosomes	Regulation of IgA immune network	[86]
Milk/human PNBC	miR-29b	Transcription factor expression	[86]
Milk/C57BL/6J	miR-29b	Decrease in miR-29b concentration	[86]
Tobacco			
Tobacco smoke	DNA methylation	Biomarkers	[87]
Plants			
Solanaceous plants	2239 miRNAs identified	Link to transcription, metabolism	[88]
Carcinogens			
2-AAF	miR-34, 200a/200b	DNA damage, oxidative stress	[122]
DEHP	miR-429	miRNA induction	[122]
MP	miR-429	miRNA induction	[122]
Chemoprevention			
Fish oil	miR-16, 19b, 21, 26b	miRNA modulations	[123]
Pectin	miR-27, 93, 203	miRNA modulations	[123]

2-AAF, 2-acetylaminofluorene; DEHP, diethylhexylphthalate; HFD, High-fat diet; MP, metapyrilene; NAFLD, non-alcoholic fatty liver disease; PNBC, peripheral nuclear blood cells;

bovine milk [86]. As the majority of bovine miRNA sequences are complementary to human transcript genes, there is a possibility that bovine milk miRNAs might regulate human gene expression. Analysis of peripheral blood mononuclear cells in milk drinkers demonstrated that the expression of runt-related transcription factor 2 (RUNX2), a known target for miR-29b, increased 31%. Addition of milk exosomes to mimic postprandial concentrations of miR-29b and miR-200c decreased reporter gene expression by 44% and 17%, respectively in human embryonic kidney 293 cells.

Likewise, C57BL/6J mice fed on a milk miRNA-depleted diet for four weeks showed a 61% decrease in miR-29b concentration. In contrast, broccoli sprout feeding elicited no increase in specific miRNA activity. Although additional studies are required, it can be postulated that miRNAs in milk can act as bioactive food compounds in the regulation of human genes.

Exposure to tobacco smoke was analyzed for the identification of short- and long-term DNA methylation in two cohort studies [87]. Based on genome-wide DNA

methylation profiles it was possible to establish biomarkers for short-term and lifelong tobacco smoke exposure.

Genome-wide analysis of solanaceous plants (potato, tomato, tobacco, eggplant, pepper and petunia) identified 2239 miRNAs [88]. Bioinformatics suggested that miRNAs were linked to 620 targets, which were classified as transcription factors, metabolic enzymes, and RNA and protein processing enzymes involved in plant growth and development. Furthermore, the recent discovery of oral intake of plant miRNAs through food consumption and its direct influence of gene expression in mice [89] has received much attention. The question is: do we eat gene regulators [90]? In support, exogenous plant miRNAs was detected in sera and tissues in animals fed on plants [91]. For instance, miRNAs abundant in rice such as miR-168a has been demonstrated to bind to the human and mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA. As decreased LDL removal from the plasma corresponds to inhibition of LDLRAP1 expression, exogenous food-derived plant miRNAs might potentially regulate gene expression in mammals. However, recently another study suggested that although substantial amounts of miRNAs in the diet are commonly consumed orally by humans, mice and honey bees, healthy athletes did not show detectable miR-156a, miR-159a and miR-169a levels in the plasma [92]. Likewise, when mice received a diet with animal fat rich in endogenous miR-21 only negligible miR-21 was observed in the plasma and organ tissue. Furthermore, plant miRNAs subjected to oral pollen uptake showed hardly any presence in honeybees. Horizontal delivery of miRNA through food intake therefore seems to be rather infrequent.

Interestingly, in a recent study the expression levels of a panel of seven human miRNAs were analyzed in plasma and stool samples of individuals with different dietary

habits (vegans, vegetarians and omnivores) [93]. Clearly, miR-92 was differentially expressed in both plasma and stool samples of individuals with different diet intake indicating miRNA modulation by nutrition.

Psychosocial Aspect of Nutrition and Disease Prevention

The impact of nutrition on health in general and the effect of changes in nutrition and life-style on disease development have already been described above. Furthermore, it is important to address the psychosocial factors related to nutrition and their impact on health and disease prevention. In case of weight loss success, women with morbid obesity were subjected to cognitive-behavioral methods including education of exercise and healthy eating practices [94]. The study results suggested that the treatment-induced psychosocial changes might be advantageous for more successful behavioral weight-loss management. Moreover, the global concern of the dramatic increase in childhood obesity has been demonstrated to be affected by psychosocial factors such as psychological, environmental and sociocultural factors, which might include above-average food intake of low nutritional quality [95]. In another study in adults with severe obesity the temporal aspects of psychosocial predictors were assessed on increased fruit and vegetable intake [96]. Significant improvement in self-regulation, mood, self-efficacy, fruit and vegetable intake, and physical activity were observed after 6 months in individuals receiving behavioral support in education for physical activity and nutrition intake. Furthermore, changes to increase fruit and vegetable intake in relation to psychosocial factors were investigated in a Malaysian study, which suggested that intervention strategies should emphasize on increasing perceived benefits and establishing self-efficacy [97]. This can be achieved through better knowledge and skills of consuming a diet

rich in fruits and vegetables as the mean of promoting healthy living.

The behavior to reduce the risk of obesity risk in relation to psychosocial factors was recently investigated in US- and foreign-born Chinese Americans [98]. The main reasons for the prevention of adopting obesity risk-reducing behavior related to the convenience of consuming fast food meals, cost, lack of time to prepare home-cooked meals, and the physical environment of unhealthy food. The "Western-identified" individuals showed a significant attitude to promote obesity risk-reduction behavior, whereas "Asian-identified" persons expressed a perceived behavioral control, self-efficacy and the observed benefits were important. Moreover, the effect of nutrition- and health-related psychosocial factors and the association to diet, exercise and weight status was studied in 4356 adults in the US [99]. The results indicated small ethnic differences, but the socioeconomic status differences were significant.

Conclusions

Epigenetic mechanisms have been frequently linked to a wide spectrum of disease indications and therefore provide novel and attractive means for therapeutic interventions. In this context, a number of drugs mainly based on histone deacetylase inhibitors have already been approved. The reversible nature of epigenetic functions is an additional attraction for drug development. Furthermore, epigenetics have proven fruitful for the generation of diagnostic biomarkers. In this context, DNA methylation and histone modifications have served as biomarker targets, but especially a number of miRNAs can provide valuable prognostic information.

The influence of nutrition on epigenetic mechanisms has received much attention lately. Food intake has been linked to changes in DNA methylation and histone modifications. Moreover, the presence of miRNAs in the

diet has been suggested to affect gene regulation. In this context, miRNAs are encapsulated in exosomes in milk, which have been demonstrated to increase transcription factor expression in peripheral mononuclear blood cells. Recently, some evidence suggests that food-derived plant miRNAs might regulate gene expression in mammals. However, contradictory results indicated that oral uptake of plant miRNAs was hardly detectable in the plasma of mice and men.

In conclusion, epigenetics presents a novel approach for modern drug development and even more importantly the influence by dietary interventions on epigenetic mechanisms further strengthens the importance of nutrition on health and disease risk, and particularly holds a key role in preventive medicine and improved health for the humankind at a reduced cost in comparison to long-term drug-based treatment of chronic disease.

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