

Review Article

Nutritional Influence on Epigenetics and Disease

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Abstract

Nutrition plays an important role in disease prevention and even in therapeutic interventions. Nutrigenomics has provided invaluable information of the relationship between food intake and gene expression. Nutrition has also been linked to epigenetic mechanisms, which can substantially affect disease development. In this context, aberrant DNA methylation, histone modifications and RNA interference have been associated with increased risk and progress of a wide variety of diseases such as cancer, metabolic, and cardiovascular diseases and neurological disorders. In this review, examples will be presented on how nutritional interventions affect epigenetic mechanisms influencing disease development. Furthermore, design of personalized nutrition and its relationship to epigenetics is discussed.

Keywords: Nutrigenomics; Epigenetics; Personalized medicine; Nutrition and disease; DNA methylation; Histone modifications; RNA interference; Micro-RNA

Introduction

During the past decade the importance of nutrition for human health has received more and more attention at both population and individual levels. In this context, numerous studies suggest a significant contribution of diet to global occurrence of cancer [1] and other diseases. Moreover, the rapid development in bioinformatics and DNA sequencing has allowed closer analysis of the effect of dietary intake on individual gene expression, leading to the establishment of nutrigenomics [2,3]. Similarly, the term foodomics has been introduced for the comprehensive high-throughput approach to exploit the relation between food science and improved nutrition [4]. Most importantly, modified epigenetic mechanisms in disease development have also been strongly linked to nutritional factors and life-style changes [5].

In this review, an overview of the effect on food intake on disease risk, prevention and therapy will be presented. The current status of nutrigenomics research will also be summarized. Attention will be paid to the influence of nutrition on epigenetic mechanisms. Finally, personalized nutritional and epigenetic solutions will be highlighted.

Nutrition and disease

There are numerous examples of direct and indirect effects of dietary intake on health and disease prevention. For instance, it has been suggested that over two-thirds of cancer-related deaths could most likely be prevented by nutritional interventions and life-style changes [6]. In this context, nutrition plays a substantial role in risk reduction and treatment of diseases such as metabolic and cardiovascular diseases, neurological disorders and cancer (Table 1).

Metabolic disease

Studies on food intake have revealed that children with the genetic variant rs9939609 SNP in the first intron of the fat mass- and obesity associated (FTO) gene is associated with increased risk of obesity and type 2 diabetes [7]. Furthermore, children with the FTO variant showed increased calorie intake compared to a control group when

subjected to unlimited food intake suggesting that the enhanced energy consumption was rather related to the energy density of the nutrition than the weight of the consumed food [8]. Additional studies have revealed a relationship between the FTO variant and physical activity [9,10], which suggested an increased susceptibility to obesity for the FTO variant when physical activity was not encouraged. Obesity has been linked to insulin resistance with over-nutrition a potential cause, although other factors might be involved [11]. For instance, the relationship between insulin-resistance and the intake of saturated fat is associated with polymorphism at the perilipin (PLIN) (storage of lipids in adipose tissue) locus and not related to obesity [12]. Another study showed that high saturated fatty acid intake induced insulin secretion in healthy volunteers via increased gastric inhibitory polypeptide levels [13].

Cardiovascular disease

The influence of diet on cardiovascular diseases has received much attention particularly through studies such as the Seven Countries' Study linking coronary heart disease (CHD) mortality to lifestyle factors [14]. Application of the Mediterranean diet rich in vegetables and fruits and low intake of meat and dairy products resulted in significant differences in CHD deaths compared to a control group. Similarly, 605 patients who had experienced a first myocardial infarction were assigned to a Mediterranean diet and compared to individuals receiving a diet recommended by the American Heart Association (AHA) in the Lyon Diet Heart Study [15]. A remarkable 72% reduction in cardiac deaths and non-fatal acute myocardial infarction was observed after 46 months in individuals subjected to the Mediterranean diet in comparison to the control group. Furthermore, a 65% and a 55% reduction in CHD mortality and in all-cause mortality, respectively, were observed. Similarly, in patients with a recent history of acute myocardial infarction (AMI) moderate wine drinking was associated with a reduced risk of CHD complications [16]. In another study, a rigorous lifestyle regimen including low-fat vegetarian food, smoking cessation and regular exercise reduced the progression of coronary arterial disease and even

Table 1: Examples of Nutrition and Disease.

Disease	Nutrition	Effect	Reference	
Autoimmune				
MS	Vitamins, fish oil	slow-down of disease	[42]	
ALS	Balanced diet	prevention of malnutrition	[43]	
Cancer				
Breast	Adolescent red meat	increased risk on pre-menopausal breast cancer	[57]	
	Dietary fiber	meta-analysis on reduced cancer risk	[142]	
	Dairy products (not milk)	meta-analysis on reduced cancer risk	[143]	
Colon	Soy isoflavones	reduced cancer risk in Asian women	[144]	
	Vegetables, fruits	reduced risk of cancer	[145]	
	Green tea	anticancer activity	[51]	
Colorectal	Myrosinase hydrolysate	reduced risk of colon cancer	[99]	
	Vitamin D	lower cancer risk, improved survival	[56]	
Esophageal	Vegetables, fruits	decreased risk of esophageal carcinoma	[146]	
	Vegetables, fruits	prevention of cancer	[145]	
Gastric	Vegetables, fruits	prevention of cancer	[145]	
Head & neck	Zinc	beneficial effects in cancer patients	[93]	
Liver	Coffee, tea	inverse correlation with risk of HCC	[58]	
Lung	Tea	reduced risk of lung cancer	[59]	
Ovarian	Green tea	Anticancer activity	[51]	
Prostate	fruits, vegetables	change in cancer-related gene expression	[54]	
	Urolithin A & B	reduced proliferation and growth of cancer cells	[55]	
	Polyphenols, green tea	inhibition of tumor xenograft growth in mice	[147]	
Skin	Nigerian diet	chemoprevention of prostate cancer	[148]	
	Sulforaphane, tea	prevention of prostate cancer	[90]	
	Folate	protection of sun-exposed skin to cancer	[149]	
Stomach	Epicatechins, green tea	chemoprevention of carcinogenesis	[47]	
	Proanthocyanid, grape	chemoprevention of carcinogenesis	[47]	
	Vitamin D	reduced mortality	[150]	
Cardiovascular	Green tea	anticancer activity	[51]	
	CHD	Mediterranean diet	reduced risk of disease	[14]
	Myocardial infarction	Low CH, high prot & fat	inverse association with cardiovascular disease	[26]
		Vitamin A	deficiency and excess: increased CHD mortality	[28]
		Vitamin D	association between CHD and vitamin-deficiency	[27]
	AMI	Mediterranean diet	72% reduction in cardiac deaths	[15]
		Polysaturated fatty acid	PPARG polymorphism enhances infarction risk	[20]
		Saturated fat intake	APOE SNPs linked to myocardial infarction risk	[25]
		Alcohol consumption	ADH3 SNPs linked to myocardial infarction risk	[22]
		Coffee	CYP1A2 polymorphism linked to infarction	[24]
Stroke	Moderate wine drinking	reduced risk of CHD complications	[16]	
Arterial disease	Folate	MTHFR SNPs linked to ischemic stroke risk	[23]	
Liver diseases	Low-fat vegetarian diet	coronary arterial disease stopped	[49]	
	Fatty liver disease	Polyphenols	miR-103/107, miR-122 prevents disease	[127]

NAFLD	High-fat diet	miRNAs linked to disease	[132]
Metabolic			
Obesity	Calorie intake	FTO SNPs increase disease risk	[7, 8]
	Calorie-controlled diet	weight loss and weight management	[141]
Insulin-resistance	Saturated fat	PLIN polymorphism increases disease risk	[12]
	High saturated fatty acid	induced insulin secretion	[13]
Coeliac	Gluten-free diet	successful treatment of disease	[134]
Neurological disorders			
Alzheimer's disease	Phytonutrient suppl.	potential disease protection	[33]
	Antioxidants	protection against oxidative stress, disease	[35]
	Fruits, nuts, vegetables	reduces disease risk in the elderly	[36]
Parkinson's disease	Phytonutrient suppl.	potential disease protection	[34]
	Low vitamin B6	increased disease risk	[37]
Cognition	Clorogenic acid	improved cognition	[39]
Traumatic brain injury	Omega-3 fatty acids	protection at neuronal level	[40]
Neurodegeneration	PC (spices, herbs)	prevention against neurodegeneration	[41]
	PC, Curcumin (in curry)	neuronal protection	[41]
	PC, tea catechin	neuronal protection	[41]
ALS	Balanced diet	improved quality of life	[43]
ASD	Gluten-, casein-free diet	therapeutic effect	[45]

ADH3: Alcohol Dehydrogenase type 2; ALS: Amyotrophic Lateral Sclerosis; AMI: Acute Myocardial Infarction; ASD: Autism Spectrum Disorder; CH: carbohydrate; CHD: Coronary Heart Disease; CYP1A2: Cytochrome P450 1A2; FTO: Fat Mass and Obesity Associated; HCC: Hepatocellular Carcinoma; MS: Multiple Sclerosis; MTHFR: Methylene tetrahydrofolate; NAFLD: Non-Alcoholic Fatty Liver Disease; PC: Phenolic Compounds; PLIN: Storage of Lipids in Adipose Tissue; PPAR: Peroxisome Proliferator—Activated Receptor Gamma

showed disease reversion by effective reduction of sclerotic plaques [17].

Genetic factors also play an important role in the relationship between nutrition and cardiovascular disease [18]. For instance, the complex interaction of genetic and environmental factors in cardiovascular disease is illustrated by polymorphism at the peroxisome proliferator-activated receptor alpha (PPARA) and PLIN loci [19]. Likewise, polyunsaturated fatty acid intake by individuals with polymorphism of the Pro12Ala peroxisome proliferator-activated receptor gamma (PPARG) gene showed enhanced risk of myocardial infarction [20]. Moreover, individuals with the CETP-TaqIB SNP showed sensitivity to alcohol consumption triggering myocardial infarction [21]. Similarly, alcohol consumption showed correlation with the alcohol dehydrogenase type 3 (ADH3) SNP in relation to myocardial infarction [22]. In this context, moderate drinkers homozygous for the ADH3 gamma-2 allele accumulate higher HDL levels and therefore present a substantially lower risk of myocardial infarction. Also, serum folate intake plays a role in determining the risk of ischemic stroke in individuals with the C677T SNP in the methylenetetrahydrofolate reductase (MTHFR) gene [23]. Moreover, polymorphism at the cytochrome P450 1A2 (CYP1A2) influenced the metabolism after coffee drinking, where homozygotes for the CYP1A2*1A showed a “rapid” caffeine metabolism while carriers of the CYP1A2*1F allele provided “slow” caffeine metabolism [24]. For this reason, individuals with the CYP1A2*1F allele have been associated with an increased risk of non-fatal myocardial infarction. Likewise, increased risk of myocardial infarction has been associated with intake of saturated fat in carriers of the APOE SNP E2 and E4

gene variants [25].

In a recent 29-year follow-up study in Japan it was observed that moderate diets lower in carbohydrates and higher in protein and fat were inversely associated with cardiovascular disease and total mortality in women [26]. In association with the Heart and Soul Study, the effect of vitamin D deficiency on cardiovascular events in CHD patients was evaluated [27]. Adjustment for socio-demographic factors showed an association between vitamin deficiency (<20 ng/L) and cardiovascular events. However, there was no longer association after further adjustment for potential biological mediators, which highlighted the needs for controlled trials to establish the role of vitamin D supplementation in prevention of cardiovascular disease. As vitamin A has also been associated with cardiovascular events, a study on serum levels of vitamin A and the harmful effects on the cardiovascular system were investigated in older adults in the US [28]. The results indicated that both vitamin A deficiency and excessive vitamin A serum levels presented increased death from all-cause and cause-specific mortality and coronary artery disease-related mortality.

Neurologic disorders

The increase in neurological disorders has often been linked to the ageing population, but also genetics and nutrition has been demonstrated to play an important role. For instance, gene variants involved in lipid metabolism have been linked to the development of Alzheimer's disease and Parkinson's disease [29]. In this context, the APOE ε4 allele presents a significant risk factor for Alzheimer's disease [30]. Similarly, the cytochrome P450 mono-oxygenase

CYP2D6 polymorphism has been linked to Alzheimer's disease and Parkinson's disease [31]. Moreover, the leucine-rich repeat kinase 2 (LRRK2, PARK8) gene has been indicated as the most common cause of Parkinson's disease [32]. Meta-analysis revealed that G2019S, G2385R, R1628P and A419V gene variations present risk factors associated with increased susceptibility to Parkinson's disease. Furthermore, dietary phytonutrient supplements have provided potential protection against Alzheimer's disease [33] and Parkinson's disease [34]. Related to Alzheimer's disease, antioxidants have demonstrated protection against amyloid β -peptide induced oxidative stress thereby slowing down disease development [35]. Various polyphenols like quercetin and resveratrol have been suggested to promote treatment of Alzheimer's disease. Moreover, a higher intake of fruits, vegetables, fish, nuts and legumes combined with reduced consumption of meats, high fat dairy and sweets was associated with reduced risk of Alzheimer's disease in the elderly [36]. Another study in Parkinson's patients in Japan indicated that low intake of vitamin B6, but not folate, vitamin B12 or riboflavin showed an increase in disease risk [37]. Furthermore, higher intake of vitamin E and β -carotene might be associated with a decreased risk of Parkinson's disease [38]. A number of studies have linked Chlorogenic Acid (CGA) consumption to a wide range of benefits on cognition and neurological health [39]. Mounting evidence suggests that intake of polyphenols including CGAs can reduce the risk of developing neurodegenerative conditions.

Related to traumatic brain injury, omega-3 fatty acids (ω -3 FAs) provide protective mechanisms at the cellular and neuronal levels including the modulation of inflammatory cascades [40]. Moreover, beneficial effects of ω -3 FAs such as eicosapentaenoic acid and docosahexaenoic acid should be considered for preventive general health, particularly for athletes and soldiers exposed to risk of high exposure to brain impacts. Also some phenolic compounds present in spices and herbs have been demonstrated to provide prevention against various age-related pathologic conditions in neurodegenerative disease [41]. For instance, heme-oxygenase-1 (HO-1) expression provides strong protection against oxidative damage and cell death in astrocytes, plays a crucial role in the pathogenesis of neurodegenerative disorders and is induced by curcumin present in curry. Furthermore, HO-1 induction by epigallocatechin-3-gallate, the major green tea catechin, can enable protection of neurons. Other phenolics such as caffeic acid phenethyl ester and ethyl ferulate show neuron protection by HO-1 induction.

In the context of Multiple Sclerosis (MS), nutrition has been shown to play an important role [42]. Dietary interventions can provide a pleiotropic role by changing cell metabolism from anabolism to catabolism and down-regulation of inflammation through interaction with nuclear receptors and transcriptional factors. Therefore, low fat diets including specific vitamins, oligo-elements and dietary integrators such as fish oil and polyphenols might slow down disease progression and improve the quality of life of MS patients. Similarly, changes in nutritional state, energy intake and energy expenditure are important factors to prevent malnutrition in patients with Amyotrophic Lateral Sclerosis (ALS) [43].

Nutrition has also been linked to learning, behavioral and mood disorders [44]. As is well recognized, modern lifestyle and social factors has strongly contributed to the limited consummation of

fruits and vegetables, whole grains and oily fish while intake of refined carbohydrates, altered fats, meat and dairy products has increased. Nutritional factors can therefore generate physiological responses, which influence mood and promote anti-social behavior. Dietary interventions and identification of potential food intolerance, hormone imbalances, blood sugar levels, enzyme deficiencies and other factors therefore play important roles in mood and behavioral disorders. Interestingly, the majority of children with Autism Spectrum Disorder (ASD) display gastrointestinal symptoms and increased intestinal permeability [45]. Furthermore, the micro biotic composition in ASD patients and control individuals show large differences. Abnormalities in carbohydrate digestion and absorption could explain some of the gastrointestinal problems in ASD patients. When ASD patients were subjected to gluten-free diets, casein-free diets, and pre- and probiotic, and multivitamin supplements contradictory but promising results were obtained. Nutrition and other environmental factors might therefore lead to the development of autism at least in a subset of ASD patients.

Although nutritional interventions have provided some encouraging results in both disease prevention and treatment, failures have also been encountered. For instance, the combination of vitamin E, vitamin C and alpha-lipoic acid (ALA) supplements did not show a significant effect on Cerebrospinal Fluid (CSF) biomarkers for Alzheimer's disease in relation to amyloid or tau pathology in a randomized controlled trial [46]. Despite the reduction of oxidative stress in the brain due to lower CSF F2-isoprostane levels, the treatment raised the concern of an accelerated decline in cognitive performance.

Cancer

The impact of dietary intake on cancer has received significant attention as it was suggested already in 1981 that nutrition accounted for approximately a third of the risk of developing cancer in the US [47]. However, the many parameters such as individual variation in the amount of food consumed, digestion, metabolism and other factors has complicated the identification of those specific food components most important for human health [48,49]. In this context, a diet rich in vegetables and fruits could significantly inverse the association with the risk for development of gastric and esophageal cancer [50]. Furthermore, tea and particularly green tea has demonstrated benefits in relation to anticancer properties as it prevented stomach, ovarian and colon cancers [51].

Bioactive food compounds such as folate, polyphenols, selenium and retinoids have been demonstrated to influence epigenetic function through DNA methylation and histone modifications affecting early carcinogenesis [52]. Furthermore, nutritional modifications can result in aberrant epigenetic mechanisms through gene silencing by micro-RNA (miRNA), which may contribute to enhanced risk of cancer development [53]. It was also recently discovered that bioactive food compounds are capable of modifying miRNA expression resulting in protection against cancer.

Remarkably, drastic nutritional changes and lifestyle modifications showed a strong impact in low-risk prostate cancer patients [54]. These patients demonstrated substantial improvement in treatment of obesity, blood pressure and lipid profiles. Monitoring of gene expression profiles from RNA samples before and three

months after the intervention revealed up- or down-regulation of 501 genes. Interestingly, significant changes were observed in pathways for protein metabolism, intracellular protein traffic and phosphorylation related to cancer development. Moreover, walnut polyphenol metabolites such as urolithins A and B were demonstrated to slow the proliferation and growth of different types of cancer cells [55]. Urolithins showed down-regulation of mRNA and protein levels of prostate specific antigen (PSA) and androgen receptor in human LNCaP prostate cancer cells. Therefore, a diet rich in polyphenols such as walnuts may contribute to prostate cancer prevention. In another aspect of nutrition, vitamin D deficiency has been associated with health issues. In this context, higher vitamin D levels have been linked to lower risk of colorectal cancer and improved survival in colorectal cancer patients [56].

In the recent Nurses' Health Study II cohort adolescent consumption of red meat was evaluated for breast cancer risk [57]. Greater intake of adolescent total red meat showed a significant correlation with higher pre-menopausal breast cancer risk, but not post-menopausal breast cancer risk. Moreover, the risk was lower in case of poultry consumption. When one serving/day of red meat was replaced with a combination of poultry, fish, legumes and nuts, the overall breast cancer risk decreased by 16% and the pre-menopausal risk was 24% lower. In another multicenter, prospective cohort study, the inverse association of coffee and tea in relation to Hepatocellular Carcinoma (HCC) risk was confirmed [58]. Increased coffee and tea consumption was consistently associated with a lower risk of HCC. Tea consumption has also been associated with a reduced risk of lung cancer [59]. In a meta-analysis of 26 case-control and 12 cohort studies overall tea consumption was significantly associated with decreased risk of lung cancer. Both green tea and black tea intake reduced the risk of lung cancer [59].

Nutritional interventions have also demonstrated an impact on quality of life in cancer patients. When patients with malnutrition disorders received ice cream as an adapted nutrition supplement significant differences in anxiety and depression was observed in comparison to the control group [60]. In conclusion, administration of ice cream presented in part the social aspect of food provision and could improve the quality of life in malnourished cancer patients.

Nutrigenomics

The impact of nutrigenomics in disease prevention and treatment by targeting food intake can be compared to how genomics information has influenced drug development. Obviously, the emerging area of personalized medicine and individually designed diets will play an important part in future disease prevention and improved health. Moreover, to establish a more complete picture of nutrigenomics, a metagenomic approach covering the interaction of the genomes of food, gut microbes and the human host needs to be addressed [61]. In this context, food proteomes of both animal and plant origin have been characterized [62,63]. Plants provide a variety of bioactive food compounds, which function as growth factors, anti-hypertensive agents, anti-microbials and immune regulators. Bioactive food compounds containing soy, rice, cereals and sunflower can provide protection against oxidative stress and different types of cancer and are released through proteolysis by host or microbial gut enzymes during food processing and ripening [64].

Milk is an important food source, which has been demonstrated to present significant differences dependent on whether of human or bovine origin [65]. For instance, the protein/peptide, lipid and carbohydrate contents are different with human milk containing caseins and whey proteins at a 50:50 weight/weight ratio in comparison to 80% caseins and 20% whey proteins in bovine milk [66]. Human milk also presents a strong impact on the host defense system as it contains various immunoglobulins and the iron-binding protein lactoferrin [67]. Milk provides protection against bacterial pathogens supports the growth of protective colonic microbes, reduces gastro-intestinal infections, inflammation, and allergic disorders [68]. Furthermore, food-derived peptides have demonstrated reduced cardiovascular disease risk by affecting blood pressure, oxidative stress, appetite, and lipid metabolism [69]. In this context, lactotriptides were shown to inhibit angiotensin-converting enzyme (ACE) resulting in reduced blood pressure in rats [70]. Soybean can also provide significant health benefits as they contain high amounts of all essential amino acids, isoflavones and saponins [71]. Moreover, phytochemicals, lunasin Bowman-Birk inhibitor, lectin and beta-conglycinin have been associated with prevention of cancer cell division and histone acetylation [72,73].

A bioinformatics-based strategy called "reverse-genome engineering" was applied for in silico discovery and evaluation of bioactive food compounds [74]. In this approach, public domains are searched for known bioactive peptides and mapped onto suitable animal or plant food genomes for identification of their location in parent protein sequences. Moreover, human digestive or food processing-related conditions can be mimicked to reveal the proteolytic release of bioactive peptides by in silico analysis. Currently, bioactivity prediction based on only amino acid sequences is not possible, but in the future the technology might be expanded to peptide sequences in general.

Obviously, human health is strongly affected by the complex composition of the gut microbiota, which consists of a huge biomass of more than 100,000 billion bacteria representing more than 400 species [75]. The gut microflora is involved in an intense metabolic activity, degradation of otherwise non-digestible substances and providing resistance to colonization by external bacterial strains. When germ free (GF) mice were colonized by a human baby flora (HBF) resistance to obesity was observed in animals fed on a high-fat and high carbohydrate diet, which indicated that GF mice consumed fewer calories, excreted more fecal lipids and weight significantly less than control mice [76]. In addition, GF mice showed higher sensitivity to insulin and glucose tolerance. Human obesity has also been linked to the microbiota. For instance, the beneficial gut bacteria group *Bacteroidetes* was found in obese individuals compared to lean people in reduced proportion and it increased with weight loss [77]. When GF mice were colonized with *Bacteroides thetaiotaomicron* the outcome was intestinal cellular differentiation and gene expression, which resulted in benefits to both the host and the microbe [78]. Further studies of the gut microbial system has also revealed how age-related changes affect the gastro-intestinal tract, the lifestyle, nutritional behavior and the host immune system [79]. In ageing individuals the changes in gut microbiota balance has resulted in "inflamm-aging" and "immunosenescence" [61]. Also, studies on the relationship between the gut microbiota and

human intestinal dendritic cells revealed enhanced IL-6 production in patients with Crohn's disease, which correlated with disease progression [80]. Related to inflammatory bowel disease, bacterial-driven metalloproteases caused degradation of extracellular matrix components [81].

The gut microbiota has recently been shown to contribute to the etiology of colorectal cancer (CRC) [82]. For instance, the short-chain fatty acid acetate, propionate and butyrate are linked to the suppression of inflammation and cancer. Moreover, other microbial metabolites like secondary bile acids promote carcinogenesis. Furthermore stool profiling identified intestinal bacteria and metabolites, which are differentially expressed in patients with CRC compared to healthy controls [83]. Particularly, butyrate-producing species were under-represented in CRC patients, while the mucin-degrading *Akkermansia muciniphila* showed 4-fold higher levels. When the combined datasets were subjected to correlative analysis some potential relationships between stool metabolites and certain bacterial species was discovered.

Food intake in humans is also strongly influenced by a number of factors such as age, physical activity and special conditions like pregnancy. Additionally cultural and ethnic aspects as well as lifestyle have a great impact. Obviously genetic factors should not be neglected. In this context, the most prominent genetic individual differences are SNPs, but also deletions, insertions and copy number variations play important roles. G proteins, which act as central signal translation mediators for G protein-coupled receptors (GPCRs) have shown relevant responses on the gene level to nutritional interventions [84]. For instance, the C825T polymorphism in the G β 3 subunit and the G659C in the G α 11 subunit have been associated with weight loss after sibutramine treatment [85]. Likewise, carriers of the 825T allele in the GNB3 subunit indicated an enhanced hypertension risk [86]. The first signs of metabolic syndrome with increased total cholesterol and uric acid were observed in lean mice carrying the C825T mutation [87]. In older hypertensive subjects insulin resistance was more prominent for the 825TT and 825TC genotypes than the 825CC genotype. In another study, the C to T substitution in the methylene-tetrahydrofolate-reductase (MTHFR) gene resulted in elevated plasma homocysteine and a different response to folic acid supplements [88], which affected the risk for such chronic diseases as vascular disease, cancer and neural tube defects.

Epigenetics

Epigenetics has received plenty of attention recently because of mechanisms leading to modifications outside the scope of conventional genetics and does not involve any modifications of the primary DNA sequence [89]. The reversibility of epigenetic functions has also made their application as targets for therapeutic interventions attractive. The three main mechanisms for epigenetic functions are DNA methylations, histone modifications and RNA interference. DNA methylation involves covalent addition of methyl groups to the 5'-position of cytosines upstream of guanines, which affects regulation of gene expression, genomic imprinting and DNA repair mechanisms [90]. Methylated CpG dinucleotides affect mRNA transcription resulting in reduced or terminated transcription but also in its up-regulation, which has been linked to cancer [91, 92]. In this context, hypermethylation in promoter regions has been linked

to the inactivation of HIC1, INK4b and TIMP3 tumor suppressor genes [93]. Histone modifications such as acetylation, methylation, ubiquitination and phosphorylation can modify histones H3 and H4 and thereby provide essential epigenetic mechanisms resulting in either repression or activation of transcription [94,95]. Similarly, RNA interference (RNAi) strongly contributes to the regulation of gene expression [96]. In this context, 21-23 nucleotide single-stranded microRNAs (miRNAs) interfere with mRNA leading to down-regulation of gene expression [97]. Alternatively, miRNAs can increase transcription and gene expression [98]. Currently, more than 1000 human miRNAs have been isolated and it is believed that up to a third of all human mRNAs are regulated by miRNAs [99].

Nutrition and epigenetics

There are numerous indications of how nutrition affects epigenetic functions (Table 2). The classic example of how nutrition causes epigenetic modification is from the Agouti mouse model where the fur color is linked to the methylation of the Agouti gene [100]. When pregnant black mice carrying the eumelanin (a) gene are fed on a methyl-supplemented diet a shift in offspring color occurred. However, when the food intake of pregnant yellow mice contained methyl donors (folic acid, vitamin B12, choline and betaine) the color of the offspring changed [101]. In the presence of a complete unmethylated *Agouti* gene, the coat color is yellow and the mice become obese and show a high risk for diabetes and cancer. Another approach relates to feeding mice with a choline-methionine deficient (CMD) diet, which resulted in elevated expression of Igf2 and H19 in prostate tissue compared to control mice [102]. Shorter exposure to the CMD diet demonstrated the reversibility of the epigenetic regulation of gene expression. The lack of change in DNA methylation in the promoter regions and H19 and Igf2 imprinting was a strong indication of epigenetic plasticity and suggested that methyl deficient diets have a stronger effect on chromatin modifications than DNA methylation. In humans, overfeeding with a high-fat diet induced DNA methylation in men with low birth weight leading to peripheral insulin resistance and decrease in peroxisome proliferator-activated receptor gamma-1 alpha (PPARGC1A) and oxidative phosphorylation (OXPHOS)-related gene expression in five days [103].

In primates a maternal high-fat diet significantly modified in utero the expression of the fetal hepatic circadian gene *Npas2* [104]. Analysis of the mRNA copy number suggested that components of the peripheral circadian machinery were transcribed in the fetal liver in an intact phase anti-phase fashion and the *Npas2* paralog of the Clock transcription factor served as a rate-limiting transcript. When fetuses were exposed to a high-fat diet in utero the hepatic *Npas2* expression increased by 7.1-fold. Interestingly, in obese mothers subjected to a control diet the effect was reversible in fetal offspring. Moreover, exposure to the maternal high-fat diet seemed to affect differential *Npas2* promoter occupancy of fetal histone H3 at lysine 14 (H3K14ac). Another interesting phenomenon is the silencing of genes based on paternal or maternal origin by genetic imprinting. In this context, after fertilization the paternal genome is actively demethylated whereas the maternal genome is passively demethylated [105], which results in parent-of-origin-dependent mono-allelic expression of critical autosomal genes [106]. Loss of methylation therefore results in either decrease or increase in gene expression.

Table 2: Examples of Association of Nutrition with Epigenetics.

Nutrition	Epigenetic effect	Reference
Polyphenols		
Fatty liver disease	miR-103/107, 122 dysregulation	[127]
ApoE mutant mice	miR-30c, 291, 296, 374, 476b dysregulation	[128]
Proanthocyanidines in HepG2 cells	miR-30b, 197, 532-3p, 1224-3p dysregulation	[129]
High-fat diet		
Obesity	up-regulation of miR-21, 142, 146	[130]
C57BLJ6 mice	down-regulation of miR-1, 30, 122	[130]
Diabetes	up-regulation of 8 miRNAs	[131]
Skeletal muscle	down-regulation of 22 miRNAs	[131]
NAFLD	miR-467b dysregulation	[132]
Insulin resistance	DNA methylation decreased PPARGC1A, OXPHOS levels	[103]
Circadian Npas2 gene in primates	histone modification affected Npas2 promoter activity	[104]
Alcohol		
Alcohol-induced fetal alcohol-syndrome	induced methylation in sperm embryo, developing brain	[107]
Maternal smoking		
Fetal growth, long-term health	aberrant DNA methylation, reduced miR16, 21, 146a levels	[112]
Link to disease pathogenesis	lower DNA methylation in transposable element AluYb8	[113]
Maternal drug use		
Premature birth, cardiac defects	aberrant DNA methylation after maternal cocaine use	[114]
Impaired memory, hyperactivity	histone modifications after parental cocaine use	[117]
Impaired fetal cardiac development	aberrant DNA methylation after maternal cocaine use	[118]
Impaired fetal growth	epigenetic modifications after cannabis use	[121]
Special diet		
Agouti mouse fur color	aberrant DNA methylation after methyl-supplemented diet	[100]
Choline-methionine deficient diet	DNA methylation led to increased Igf2 and H19 expression	[102]
Plant intake		
Gene expression regulation in mammals	decrease of LDLRAP1 by miR-168a after rice consumption	[124]
Differential gene expression	miR-92 differences in vegans, vegetarians, omnivores	[126]
Carcinogens		
2-acetylaminofluorene	miR-34, 200b, 200c dysregulation	[151]
Diethylhexylphthlate	miR-429 dysregulation	[151]
Metapyrilene	miR-429 dysregulation	[151]

LDLRAP1: Low-Density Lipoprotein Receptor Adapter Protein 1; NAFLD: Non-Alcoholic Fatty Liver Disease; OXPHOS: Oxidative Phosphorylation; PPARGC1A: Peroxisome Proliferator-Activated Receptor Gamma-1 alpha

Environmental factors and not the least nutrition have been shown to play an important role in epigenetics prior to birth leading to increased vulnerability to neurodevelopmental deficit in offspring [107]. For instance, alcohol exposure induces DNA methylation in sperm, embryos and developing brain resulting in alcohol-induced fetal alcohol syndrome [108-110]. Likewise, maternal smoking affects fetal growth, preterm delivery and long term health of offspring [111]. Examination of human placenta has revealed epigenetic changes such as alteration in DNA methylation and reduced miR-16, miR-21 and miR-146a expression related to smoking. [112]. Analysis of buccal cells from children exposed prenatally to tobacco smoke demonstrated lower DNA methylation in the transposable element AluYb8 suggesting a link to disease pathogenesis [113].

Drug abuse during pregnancy has obviously been associated with fetal deficits. For instance, cocaine promotes premature birth, cardiac defects and attention deficit disorders [114]. Differential DNA methylation has been associated with altered expression in selected genes [115]. For example, increased H3 acetylation and decreased methyl CpG binding protein 2 (MeCP2) -association with BDNF promoter IV was observed in cocaine treated rats [116]. Moreover, paternal cocaine administration showed impaired memory in female offspring and caused hyperactivity in male offspring rats [117]. The impact on fetal cardiac development indicated that pregnant rats exposed to cocaine resulted in myocardial apoptosis in fetal heart because of DNA methylation induced reduction in protein kinase C ϵ (PKC ϵ) expression [118]. Similarly to cocaine, cannabis, the major

ingredient in marijuana, when exposed in utero restricts fetal growth and alters fetal behavior [119, 120]. The epigenetic relevance was shown by reduced dopamine D2 (DRD2) receptor expression in human ventral striatum of fetuses maternally exposed to cannabis [121]. In a rat model, it was further demonstrated that decreased DRD2 expression resulted in long term disruption of the transcription machinery for DRD2, which suggests the link between prenatal drug exposure and adulthood addiction [122].

The direct effect of regulatory components present in food has received much attention lately. It was recently discovered that oral intake of plant miRNAs in the food might accumulate in the serum of humans or animals and to provide regulation of gene expression in a sequence-specific manner [123]. It was suggested that micro-vesicles and specific RNA-transporter-like proteins are involved in the miRNA transport between species. Moreover, miR-168a abundant in rice has been shown to bind to the human and mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA [124]. Exogenous miR-168a can therefore potentially regulate gene expression in mammals as decreased LDL removal from the plasma corresponds to reduced LDLRAP1 expression. In contrast, another study indicated that substantial miRNA amounts present in the diet did not show detectable levels of miR-156a, miR-159a and miR-169a in the plasma [125]. Similarly, mice subjected to a fat-rich diet with endogenous miR-21 showed only negligible miRNA levels in the plasma. Furthermore, plant miRNA showed hardly any presence in honeybees subjected to oral pollen uptake. Therefore, miRNA delivery through food uptake seems to be rare. However, a recent study on the uptake of seven human miRNAs in plasma and stool samples in individuals with different dietary habits showed differential expression of miR-92 with vegetarians showing higher expression than omnivores but lower than vegans [126]. This clearly suggested that nutritional intervention can modulate miRNA expression.

Polyphenols derived from plants have been shown to regulate miR-103/107 and miR-122 contributing to the prevention of diet-induced fatty liver disease [127]. Also miR-30c, miR-291, miR-296, miR-374 and miR-476b are modulated by polyphenols [128]. Moreover, the most abundant polyphenols in the human diet, proanthocyanidins, induced modulation of miRNA expression in human HepG2 cells [129]. Treatment with grape seed proanthocyanidin extract (GSPE), coca proanthocyanidin extract (CPE) or pure epigallocatechin gallate from green tea (EGCG) resulted in down-regulation of miR-30b*. Additionally, GSPE and CPE enhanced the expression of miR-1224-3p, miR-197 and miR-532-3p.

A high-fat diet has shown strong influence on miRNA expression in adipose tissue in a C57BL/6 mouse obesity model [130]. Several miRNAs were up- or down-regulated indicating a role for epigenetic function in adipogenesis and obesity. In relation to type 2 diabetes, high-fat diet can induce skeletal muscle insulin resistance [131]. When mice were fed on a high-fat diet 8 miRNAs were up-regulated while 22 miRNAs were down-regulated. Moreover, miRNAs have been linked to non-alcoholic fatty liver disease (NAFLD) in mice fed on a high-fat diet [132]. In this context, miR-467b expression was significantly reduced in liver tissue resulting in enhanced hepatic lipoprotein lipase (LPL) production associated with insulin resistance.

Personalized nutrition and epigenetics

The impact of nutrition in prevention and treatment of disease has been significant on a general level. Intensified bioinformatics and nutrigenomics research has generated a better understanding of individualized approaches including personalized nutrition and personalized medicines. In this context, factors such as age, sex, cultural and environmental differences has strongly influenced nutritional preferences. Taken into account these factors, a “generic” program called MyPyramid has been established for a personal eating plan through a website providing information on sex, height, weight and level of physical activity [133].

Perhaps one of the best examples of successful personalized nutrition is represented by individuals with coeliac disease, who are unable to tolerate gluten-containing food [134]. Although a hereditary component is not sufficient for disease development genetic variants in the human leucocyte antigen HLA-DQ genes provides an indication of high disease risk, the straightforward treatment strategy is to comply to a strict gluten-free diet [135]. Currently, no biomarkers for genetic screening of coeliac disease are available. Additionally, in connection to the world wide obesity epidemics much attention has been paid to nutritional interventions and the effect of lifestyle and other changes. In this context, a personalized calorie-controlled diet was designed for a weight reduction program based on 24 variants in 19 genes [136]. The personalized diet and exercise advice resulted in substantial weight loss and excellent weight loss maintenance in comparison to the control group, who received a generic diet and exercise advice. In another study, a tailor-made personalized diet was designed for 51 overweight-to-obese individuals carrying five SNP variants in four genes, which resulted in some success after six weeks [137]. However, in general the difficulties with personalized diets and exercise instructions are the slow change in implementing changes.

In a recent study, the prognostic among patients with localized cutaneous melanomas was surveyed in relation to dietary habits, which suggested that daily fruit intake was associated with improved melanoma-specific survival [138]. In contrast, red meat intake was linked to a worse outcome.

The preventive function related to disease of nutrition has played an important part in human health. For example, a meta-analysis of six randomized trials indicated that the significant weight reduction observed in obese adolescents by sibutramine can be further supported by a hypocaloric diet and modification of lifestyle [139].

The importance of epigenetic regulation has been indicated by the establishment of the new field of nutriepigenetics [140]. Epigenetic regulation has been shown to be associated with the consumption of plant-derived polyphenols, which has strengthened the link between personalized nutrition and epigenetic effects [5]. Additionally, ageing and age-related disease has demonstrated a strong link to nutritional epigenetics [127]. In this context, folate, vitamin B12, vitamin B6, riboflavin, methionine, choline and betaine have been suggested to regulate S-adenosylmethionine and methyltransferase inhibitor S-adenosylhomocysteine levels affecting DNA methylation. Furthermore, retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols have the capacity to modulate epigenetic patterns and thereby catalyze DNA methylation and histone modifications.

Conclusions and Future Prospects

In the light of the ever increasing costs related to human health rapid and cost cutting approaches are most welcome. Probably the most important approach would be to focus on preventive medicine. In this context, two factors have been indicated to play important roles. Nutrition cannot be neglected as one of the most essential components in our daily lives. A wide range of studies have demonstrated how nutritional interventions can reduce the risk of disease and can even provide therapeutic efficacy. Additionally, epigenetic mechanisms have proven to be closely associated with disease development. Interestingly, nutrition has also been shown to affect epigenetic functions. Nutrigenomics has further enlightened the understanding of individual and genetic requirements for the establishment and design of dietary interventions, which can improve human health and even prevent future disease development. In the future, additional understanding of epigenetic mechanisms and nutritional requirements will contribute immensely to the reduction of disease risk and health improvement.

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