Nutrition and epigenetic mechanisms

Nutrição e mecanismos epigenéticos

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Tipo de documento: Monografia

Porto, 2012
Agradecimentos

Muito especialmente, agradeço à minha orientadora Mestre Renata Barros pela disponibilidade, atenção dispensada, paciência e simpatia.

Aos meus pais e irmã por todo o amor, apoio e compreensão, coragem e positivismo que sempre me transmitiram. Muito Obrigada!

Aos amigos, pela amizade, conforto, sorrisos e alegria que me deram ao longo de todo este percurso.
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Abbreviations

AA - Arachidonic acid
AM - Allyl mercaptan
APE - Annurca polyphenol extract
C - Control
CCND2 - Retinoic cyclin D2 gene
cpt-1a - Carnitine palmitoyltransferase-1a
C/EBPb - CCAAT/Enhancer binding protein
DADS - Diallyl disulfide
DHA - Docosahexaenoic acid
DNA - Deoxyribonucleic acid
DNMT – DNA methyl transferase
EPA - Eicosapentaenoic acid
EZH2 - Enhancer of zeste homologue
HAT – Histone acetylase
HDAC – Histone deacetylase RNA - Ribonucleic acid
HDACi - Histone deacetylase inhibitors
HCD – High cholesterol diet
HF – High fat
IGF2 - Insulin growth factor 2
mRNA – messenger ribonucleic acid
miRNA- micro ribonucleic acid
MOR - µ-Opioid receptor
OSC - Organosulfur compounds
ppar-α - Peroxisome proliferator-activated receptor alpha
PR - Protein restricted

*RAR*β<sub>2</sub> - Retinoic acid receptor β2 gene

RASSF-1α - *Ras association domain-containing protein 1*

RNA – Ribonucleic acid

SAM - S-Adenosyl-methionine

SAM - S-allyl mercaptocysteine

SCFA - Short-chain fatty acids
Abstract

Diet is one of the major -environmental exposure that influences all aspects of health through the life course. Adequate nutrition is essential during the life cycle and particularly during early life (both pre- and postnatal). Food patterns have a great impact on health, particularly the dietary fat excess, that had become a dietary pattern in developed countries have revealed, potential on modulation of epigenetic mechanisms. Several bioactive components, present in foods like genistein, reverastrol, polyphenols from apples, allium compounds and fatty acids all have been associated with benefits to health and are of particular interest in the field of epigenetics. These compounds might protect from cancer, obesity and cardiovascular disease. This review focus on how dietary factors modulate epigenetic mechanisms, thereby influencing gene expression and health and disease.

Key-words: Epigenetic, epigenetic modulators, nutrition, diet and health
Resumo

A Nutrição é um dos maiores fatores de exposição do ambiente com efeitos na saúde, sendo uma nutrição adequada fundamental ao longo de toda a vida, e particularmente importante nos inícios de vida (pré- e pós-natal). Padrões alimentares tem um impacto profundo na saúde, particularmente o excesso de ingestão de gordura, que se tem revelado nos hábitos alimentares das pessoas dos países desenvolvidos, e que manifestou potencial para afetar mecanismos epigenéticos. Vários componentes bioativos presentes nos alimentos como a genisteina, reverastrol, polifenóis das maçãs e compostos *allium* têm sido associados a benefícios para a saúde e estudados no campo da epigenética. Muitos destes compostos revelam propriedades protetoras na obesidade, doenças cardiovasculares, cancro, entre outras, podendo desempenhar uma função preventiva das mesmas.

Este trabalho revê a atividade de fatores nutricionais na modulação de mecanismos epigenéticos, influenciando a expressão genética e efeitos na saúde.

**Palavras-chave:** Epigenética, moduladores epigenéticos, nutrição, alimentação e asma
1. INTRODUCTION

Nutrition is one of the major environmental factors that exert a profound effect on many aspects of health and disease, being a main environmental exposure that influences all aspects of health through the life course.\(^{(1)}\)

Epigenetic is the study of stable inheritance of gene expression that occurs without modifications in the DNA sequence, being a molecular mechanism by which nutrients can alter gene expression.\(^{(2)}\) The most common epigenetic mechanisms include DNA methylation, histone modifications, and noncoding RNAs (miRNA).\(^{(3)}\)

DNA methylation, consist in a covalent addition of a methyl group to a cytosine residue in a CpG site (i.e., where a cytosine lies next to guanine in the DNA sequence).\(^{(4)}\) CpG sites generally are clustered in high frequency near gene promoters and these regions are referred to as CpG islands. The methylation states of CpG islands in turn may affect gene activity and expression, being typically associated with gene repression.\(^{(4)}\)

Modifications of histone tails by methylation, acetylation, phosphorylation, biotinylation and ubiquitination modulate the compaction of the DNA around the core histones and serve as docking sites for transcriptional regulators.\(^{(5)}\)

Histone modifications can either activate or repress gene expression depending on the type of modification and the placement along the histone tail.\(^{(1)}\) miRNA (miRNA) are small RNA molecules encoded in the genome that bind to their target mRNA and down-regulate their stabilities and/or translation, inducing degradation of target mRNA.\(^{(6)}\)

Extensive synergy exists between epigenetic mechanisms to determine accessibility of genes to transcriptional regulators.\(^{(5)}\) Nutrition affects epigenetic
phenomena at multiple levels. Nutrients act as a source of methyl groups or as co-enzymes for one-carbon metabolism that regulates methyl transferring.\(^{(7)}\) B-vitamins including folic acid, are involved as coenzymes with methionine, choline, betaine and serine as methyl donors for DNA methylation and histone methylation.\(^{(7)}\) Also, nutritional status (especially during pregnancy) and bioactive food components can affect enzymes that catalyse DNA methylation, histone modifications and miRNA function.\(^{(1)}\) This review will focus on the influences of nutrition on epigenetics and how these influences may affect the human health.

2. NUTRITIONAL FACTORS ON MODULATION OF DNA METHYLATION

S-Adenosyl-methionine (SAM) is the universal methyl-donor for methyltransferases, including both DNA methyltransferases and protein methyltransferases.\(^{(1)}\) SAM is synthesized in the methionine cycle from several precursors present in the diet, including methionine, folate, choline and betaine.\(^{(7)}\) All of them enter at different sites in the methionine pathway and contribute to its synthesis.\(^{(7)}\) Therefore, it has been proposed that reduced availability of methyl donors will result in low SAM synthesis and global DNA hypomethylation.\(^{(3)}\) Conversely, increased availability of methyl donors will result in the opposite effect.\(^{(3)}\)

2.1 Folic acid.

During pregnancy folate deficiency is associated with an increased risk of neural tube defects.\(^{(8)}\) Aberrant reprogramming of DNA methylation by low dietary folate has been suggested as a candidate mechanism.\(^{(9)}\) In a cross sectional study, using a self-administered questionnaire, Hoyo and colleagues, assessed folic acid
intake before and during pregnancy in 438 pregnant women. After born, umbilical cord blood leukocytes were collected and measured methylation at Insulin Grow Factor-2 gene (IGF2), (a key factor in human growth and development especially during fetal life but also during lifetime). Relationship between maternal folic acid supplementation before or during pregnancy and DNA methylation levels at birth was investigated. They found methylation levels at the decreased with increasing folic acid intake (2.8%, p = 0.03 and 4.9%, p = 0.04, for intake before and during pregnancy, respectively).\(^{(10)}\)

A low dietary folate intake can cause genomic DNA hypomethylation and may increase the risk of colorectal neoplasia.\(^{(11)}\) In a cross-sectional study, Pufulete and colleagues assessed the folate status (serum and erythrocyte folate and plasma homocysteine concentrations) and compared with the DNA methylation pattern. Sixty-eight subjects (33 men and 35 women, 36–78 years) free from colorectal polyps or cancer were recruited. Tissue biopsies were obtained for determination of DNA methylation. After adjusting for gender, age, body mass index, smoking and genotype, there were weak negative associations between serum and erythrocyte folate and colonic DNA hypomethylation (P=0.07 and P=0.08, respectively).\(^{(11)}\) The same author, in a double blind, randomized, placebo controlled, parallel design, assessed thirty-one patients with histologically confirmed colorectal adenoma. They were randomised to receive either 400 µg/day folic acid supplement (n = 15) or placebo (n = 16) for 10 weeks. Folic acid supplementation resulted in increased DNA methylation of 25% (95% CI 11–39%; p = 0.09 v placebo) in colonic mucosa.\(^{(12)}\)
2.2 Maternal nutritional restriction

Maternal nutrition during gestation has important effects on offspring gene expression mediated by DNA methylation. Dutch famine survivors have an excess risk of several common chronic diseases, as cancer, cardiovascular and obesity.\(^{(13)}\) Aberrant DNA methylation at the *IGF2* gene has been associated with increased risk of obesity, and many types of cancers.\(^{(14,15)}\) Heijmans et al.\(^{(16)}\) have reported, in a cross-sectional study, that methylation of *IGF2*, was lower, in blood cells, in individuals who were prenatally exposed to famine during the “Dutch Hunger Winter” in 1944–1945 than in their unexposed, same-sex siblings when investigated at 60 years old. Periconceptional exposure was associated with lower 5.6% *IGF2* methylation (\(p=0.002\)).\(^{(16)}\)

These studies suggest that DNA methylation induced by folic acid intake could play a critical role in development regulation not only during the fetal period but also throughout the life-course.

2.3 Maternal high fat diet

In animal models was showed that maternal high fat diet can modulate DNA methylation and gene expression in the offspring. Vuceti et al.\(^{(17)}\), showed, in a mice model that maternal high fat feeding during gestation altered methylation and gene expression of dopamine and opioid related genes in the brain from the offspring.\(^{(17)}\) Dams were presented with both control diet (18.5% protein, 12% fat, and 69.5% carbohydrate) and high fat diet (18.5% protein, 60% fat, and 20.5% carbohydrate) 3 months before breeding and through lactation at weaning. Was observed in Receptor µ-Opioid (MOR) gene a decreased methylation pattern (in the hypothalamus) in the offspring from dams fed the high fat diet, comparing to control (\(p<0.05\)).\(^{(17)}\) This change may influence behavioral preference for palatable
foods, thereby increasing obesity and obesity-associated risk for metabolic syndrome.\(^{(17, 18)}\) Zhang et al, in a mice model, showed that maternal high fat (22.6% fat, 23% protein and 48.6% carbohydrate), fed offspring, comparing with control fed dams (10% fat, 18% protein and 68.8% carbohydrate) have increased expression, (reduction in the methylation pattern) of \(IGF2\) \((p<0.001)\) and of two key genes regulating hepatic fatty acid oxidation [which produce peroxisome proliferator-activated receptor alpha \((ppar-\alpha)\) \((p<0.05)\) and carnitine palmitoyltransferase-1a \((cpt-1a)\) \((p<0.01)\)]\(^{(12)}\).

3. NUTRITIONAL FACTORS INVOLVED ON HISTONE MODULATION

3.1 Cruciferous vegetable

Increased fruit and vegetable consumption is associated with reduction in the development of major chronic diseases.\(^{(19)}\) In a interventional study, healthy volunteers in the age range 18-55 years, with no history of non-nutritional supplement use, refrained from cruciferous vegetable intake for 48 h. Each subject consumed 68 g (one cup) of broccoli sprouts, and blood was drawn at 0, 3, 6, 24 and 48 h following sprout consumption. In peripheral blood mononuclear cells (PBMCs) of all subjects, HDAC activity was inhibited as early as 3 h after broccoli sprout intake, and returned to normal by 24 h. There was strong induction of histone acetylation coincident with HDAC inhibition at 3 and 6 h \((p<0.001)\), and whereas HDAC activities returned to normal by 24 h, histone hyperacetylation was evident for at least 48 h. These findings provided the first evidence that dietary intake of broccoli sprouts influences HDAC activity in normal circulating blood cells of humans.\(^{(20)}\)
3.2 Protein restriction and high fat diet

Perturbations in the gestational life influence the development of diseases later in life.\(^{(7)}\) This supposition has been gaining support mainly from animal models. Zheng and colleagues, in a mouse model, assessed low protein availability during gestation, (90 g casein/kg) compared with normal protein diet control (180 g casein/kg). Altered amino acid and energy homeostasis, in the offspring were observed with increased acetylation histone patterns in C/EBP\(\beta\) (CCAAT/Enhancer binding protein – thought it is a potent transcription factor involved in muscle amino acid and carbohydrate metabolism) (p<0.05), in skeletal muscle. These findings might suggest a difference in energy metabolism during early life, regarding different nutritional status during pregnancy.\(^{(22)}\)

Lillycrop and colleagues\(^{(21)}\), investigated the effect of altered maternal protein intake during pregnancy on the epigenetic regulation of the hepatic Glucocorticoid Receptor promoter in the adult offspring.\(^{(21)}\)

Protein restriction during gestation may also result in locus-specific changes in DNA methylation. Rats were fed a control (180 g casein/kg) or a protein restricted (PR) (90 g casein/kg) isocaloric diet throughout pregnancy, and chow during lactation. Offspring were killed at postnatal day 34. They found an increased hepatic glucocorticoid receptor expression, in the PR offspring, associated significantly with increased covalent modifications, which facilitate transcription, to histones at the glucocorticoid receptor promoter (p<0.001).\(^{(21)}\)

Maternal high-fat diet also alters the epigenomic profile of the developing offspring, resulting in alterations in fetal gene expression.\(^{(23)}\) Female macaques were placed on control (13% fat) or high-fat (35% fat) diets during gestation and fetal histones from the offspring were analyzed. They found the consumption of a maternal high-
fat diet resulted in increased fetal liver triglycerides and histologic correlated with non-alcoholic fatty liver disease. These gross changes in the fetal liver were accompanied by a statistically significant hyperacetylation in histone H3 of fetal hepatic tissue ($P=0.038$). \(^{(23)}\)

4. NUTRITIONAL FACTORS INVOLVED ON miRNA MODULATION

4.1 Methyl deficient diet

Aberrations in methylation profile of the genome occur in human hepatic cancers, induced by folate deficiency. To elucidate the underlying, Lynn and colleagues\(^{(24)}\) in an animal study, tested mice fed with a methyl-deficient diet. Compared to control, they contracted nonalcoholic steatohepatitis, which was accompanied by changes in the expression of specific microRNA. Mice from the experimental group were maintained on a low-methionine (0.18%) diet, lacking in choline and folic acid for 12 weeks. The mice from the control group received diet supplemented with 0.4% methionine, 0.3% choline bitartrate, and 2 mg/kg folic acid. show a profound downregulation of miRNA-122, a liver-specific miRNA, which is important for normal lipid metabolism\(^{(25)}\) and dramatic upregulation of mice fed a methyl-deficient diet ($p<0.05$).\(^{(24)}\) This experimental study suggest that alterations in the expression of microRNA are a prominent event during the development of liver cancer and nonalcoholic steatohepatitis caused by dietary methyl deficiency.

4.2 High fat diet

Nonalcoholic fatty liver disease, a hepatic manifestation of the metabolic syndrome, related with high-fat food patterns in humans\(^{(26)}\), have been shown to progress to cirrhosis and hepatocellular carcinoma.\(^{(26)}\) Cirera and colleagues\(^{(27)}\),
assessed alterations in expression of specific miRNA-122 (related with control of lipidic metabolism) were also observed in minipigs fed a high-cholesterol diet compared with those fed a standard diet, during 11 weeks (the high-cholesterol diet was a modified minipig standard diet, with more 2% cholesterol and 22.77% crude fat). The metabolizable energy of the standard chow was 10.5 MJ/Kg and that of the high-cholesterol diet was 19.3 MJ/Kg). They found that miRNA-122 was 1.4 times less abundant in the HCD pigs compared with the standard diet pigs ($p=0.0015$). These alterations were accompanied by higher body weight ($p=0.049$), total cholesterol ($p=0.042$), and high-density lipoproteins ($p=0.019$) in pigs fed the high cholesterol compared with the standard diet. These findings indicate the potential implications of miRNA also in obesity.\textsuperscript{(27)}

Zhang and colleagues\textsuperscript{(28)}, performed an experimental trial were seven mouses were randomly assigned to either a high fat (22.6% fat, 23% protein and 48.6% carbohydrate) or standard chow diet (10% fat, 18% protein and 68.8% carbohydrate) diet. Dams were fed either the high fat or chow diet 4 weeks prior to conception and during pregnancy (day 1 of pregnancy indicated by presence of copulation plug) and lactation. They found that maternal high fat diet during pregnancy and lactation induced expression of IGF2 ($p < 0.01$) and of miRNA-122 in the offspring.\textsuperscript{(28)} HF vs C offspring have increased IGF2 expression and a trend toward increased liver weight [~16% increase, compared with the control mice ($p = 0.44$)]. The body weight of maternal HF fed offspring at weaning is ~19.6% ($p < 0.05$) greater than control mice, consistent with increased hepatic $IGF2$ expression.\textsuperscript{(28)}
5. BIOACTIVE COMPONENTS FROM FOODS AND MODULATION OF EPIGENETIC MECHANISMS

5.1 Genistein

Is the major isoflavone present in soybeans, is perhaps one of the most studied bioactive compound. Investigations have demonstrated that genistein-mediated hypomethylation and hyperacetylation reactivate the expression of tumor suppressor genes in prostate cancer cells.

Importantly, the effects of genistein have recently been tested in humans. For instance, in studies conducted by Qin et al., thirty-four healthy premenopausal women received either 40 mg or 140 mg of isoflavones, including genistein, daily through one menstrual cycle. Methylation assessment genes known to be methylated in breast cancer (retinoic acid receptor β2 gene - RARβ2 and retinoic cyclin D2 gene - CCND2) was conducted on intraductal samples. The findings revealed hypermethylation (which typically leads to gene silencing) of cancer-related genes RARβ2 and CCND2. Increased methylation in these genes after genistein treatment are correlated with serum genistein levels (p=0.0017 and p=0.011, respectively).

5.2. Resveratrol

Resveratrol is a dietary polyphenol, naturally found in several plants including peanuts, mulberries, and blueberries, but is most abundant in the skin of grapes. Resveratrol is also consumed in the form of red wine. Its benefits have been associated to antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic effects.
Thirty-nine adult women at increased breast cancer risk were randomized in double-blind trial to placebo, 5 or 50 mg transresveratrol twice daily for 12 weeks. Methylation assessment of cancer-related gene (Ras association domain-containing protein 1 - RASSF-1α, a tumor suppressor gene) was performed on mammary ductoscopy specimens. The predominant resveratrol species in serum was the glucuronide metabolite. Total trans-resveratrol and glucuronide metabolite serum levels increased after consuming both trans-resveratrol doses (p<0.001 for both). RASSF-1α methylation decreased with increasing levels of serum trans-resveratrol (P =0.047). (32) This work provides insights into the effects of trans-resveratrol on the breast of women at increased breast cancer risk, as CpG islands of many genes that are mostly unmethylated in normal tissue, are hypermethylated to varying degrees in breast cancer. (33)

5.3 Allium compounds

Garlic has long been used medicinally, most recently for its cardiovascular, antineoplastic, and antimicrobial properties. (34) Also benefits have been associated to a number of conditions, including hypertension, hypercholesterolemia, diabetes. (34) Present mainly in garlic (but also onions, shallots and other members of the allium family) contain an interesting and complex range of water-soluble and fat-soluble organosulfur compounds (OSC), some of which have been implicated as protective agents. (35) Allyl derivatives from garlic were described to impact histone acetylation status as allyl mercaptan (AM), diallyl disulfide (DADS) and S-allyl mercaptocysteine (SAM) in human cancer cells. (35)

Lea et al. (36) reported increased acetylation of H3 and H4 histones (p<0.05), in human leukemic cells after treatment with SAM, compared to control. It was also
associated with growth inhibitory effect \( p<0.05 \).\(^{36}\) Druesne et al.\(^{37}\) have shown that DADS-induced acetylation of histones is connected with the inhibition of histone deacetylase activity and with hyperacetylation of histones H3 and H4. In this study results suggest that DADS could inhibit cell proliferation through the inhibition of HDAC activity, histone hyperacetylation.\(^{37}\) Thereafter, allyl compounds from garlic such DADS and SAM have been demonstrated to have HDAC inhibitory effects.\(^{38}\) Today a family of chemotherapeutic drugs are known as HDAC inhibitors. These previous studies suggest a potential functional significance of this family of bioactive food components as chemopreventive agents to regulate histone acetylation status.\(^{39}\)

### 5.4 Apple polyphenols

Exposure to apples and apple products has been associated with beneficial effects on risk, markers, and etiology of cancer, cardiovascular disease, asthma, and Alzheimer's disease.\(^{40}\)

A pilot experimental study, assessed the anticancer properties of Annurca apple polyphenol extract (APE) (variety of southern Italy) were tested in vitro models in human colon rectal cancer cell lines, containing: chlorogenic acid, 0.43 mmol/L; caffeic acid, 0.1 mmol/L; catechin, 0.70 mmol/L; epicatechin, 0.63 mmol/L; rutin, 0.01 mmol/L; and phlorizin 0.07 mmol/L).\(^{41}\) DNA methylation of selected tumor suppressor genes was evaluated after treatment with APE and was compared with a synthetic demethylating agent. APE lead to the reactivation of silenced tumor suppression genes by inhibiting specific DNMT expression \( p<0.05 \). The effects of APE were similar to the clinically used synthetic compound, a potent but toxic DNMTinhibitor. Results were obtained with doses of APE reflecting the dietary
consumption. The concentration of APE we used in this study (i.e. 2 µmol/L) is comparable to that obtained in the lower gut following the consumption of 1 apple, which contains ~1mmol/L polyphenols.\(^{(41)}\)

### 5.5 Butyrate

The intestinal microbiota plays a critical role in the establishment and maintenance of body health. Short-chain fatty acids (SCFA), such butyrate, a main end product of microbial fermentation of dietary fibres in the human intestine, plays an important role in the maintenance of intestinal homeostasis and overall health status.\(^{(42)}\) Butyrate is also an important class of therapeutic compounds, epigenetic drugs known as histone deacetylase inhibitors (HDACi) that have a central role as anti-cancer agents with strong anti-proliferative effects on tumour cells. Is hypothesized that biological function, of intestinal microflora, may be a result of epigenetic modifications, through SCFA, that may explain the wide range of effects observed.\(^{(43)}\)

To test butyrate effects in human colon tumor cells, Waldecker and colleagues\(^{(44)}\), investigated fermentation supernatants from incubations (during 24 hours) of human fecal slurry with apple pectin (resistant to digestion in the small intestine, shown to serve as substrates for butyrate formation by the microflora of the colon\(^{(45)}\) comparing with basal control (without any addiction to the fezes). They found the supernatants, with pectin, richer in butyrate and after testing its ability to modulate HDAC activity in the cells, they found that it exhibited strong HDAC inhibitory activity in comparison with supernatants without the apple pectin (p<0,05).\(^{(44)}\)

In an animal model, Gao et al.\(^{(46)}\), through an experimental trial in mouses, showed that dietary supplementation of butyrate can prevent and treat diet-induced obesity
and insulin resistance in mouse models. During 16 weeks, the mice were fed with a diet, free access, which 58% calories derived from fat. The test group had 5% of butyrate and the control didn’t. In the obese mice, supplementation of butyrate led to an increase in insulin sensitivity and a reduction in adiposity. Adaptive thermogenesis and fatty acid oxidation were enhanced by an increase in mitochondrial function and biogenesis in skeletal muscle and brown fat. The histone deacetylase was also tested, in skeletal muscle, and it’s activity was reduced by 50% in the butyrate group comparing with control (p<0.05). These results suggest that the metabolic activities of butyrate may be dependent on the inhibition of histone deacetylase. 

5.6 Fatty acids

Dietary consumption of polyunsaturated fatty acids (PUFAs) are known to influence the development of many diseases, having a role in cancer, cardiovascular and asthma risk. Data, in human and animal models, suggests n-3 PUFAs may function by modulating the expression of histone and chromatin modification, which collectively contribute to anti-oncogenic and chemopreventive properties of n-3 PUFA. In human cells, Enhancer of zeste Homologue 2 (EZH2), a methyltransferase that catalyzes histone H3 methylation on gene promoters, repressing genes that induce stem cell differentiation, being a direct inducer of adipogenesis. Overexpression of EZH2 is found in patients with different types of cancer. Dimri and colleagues, tested different types of fatty acids in expression of this protein in breast cancer cells. For fatty acid treatment, cells were grown to a confluence of 70–80%, starved for 24 h and then treated with n-3 (DHA and EPA) and n-6 PUFAs (LA and AA) for 3–8 h. After the treatment, the expression of EZH2 and a
control gene was determined. The results indicated that the treatment of breast cancer cells with n-3 PUFAs (DHA and EPA) led to decrease in expression of EZH2 (p<0.003). In contrast, n-6 PUFAs (LA and AA) had no effect on the expression of EZH2.\(^{50}\)

An experimental study explored the effect of n-3 polyunsaturated fatty acids on carcinogen directed non-coding microRNA signatures in rat colon.\(^{51}\) Rats were fed diets containing corn oil or fish oil, the total fat content of each diet was 15% by weight. After 2 weeks rats were injected with a colonspecific carcinogen and effects on miRNA expression in colonic mucosa were analysed. At an early stage of cancer progression, five different miRNA were significantly affected by diet-carcinogen interactions (p<0.05). Overall, fish-oil-fed animals exhibited the smallest number of differentially expressed miRNAs (p<0.05), pointing to a novel role of fish oil in protecting the colon from carcinogen-induced miRNA dysregulation.\(^{51}\)

6. CONCLUSION AND CRITICAL ANALYSIS

Different mechanisms are involved in the maintenance of epigenetic states. Studies have shown that dietary factors are likely to contribute to epigenetic alterations and in some cases may be able to reverse abnormal epigenetic states. In addition, while many of the studies were conducted using a particular dietary factor, during “people’s life” most may be consumed in combination and over a period of a lifetime. Also food may act through synergic mechanisms, for example, apples affect epigenetic mechanisms by different ways, through action of its polyphenols\(^{41}\) and through pectin (being an extract for intestinal microbiota, influencing butyrate production)\(^{52}\), protecting from proliferation of tumor colon cell lines. This may provide a rationale for studying nutrient epigenetic modifiers more
in combination studies or focused on consuming products that show the ability to stimulate beneficial epigenetic modifications, including increased consumption of fruit, vegetables and dietary components mentioned herein. Also as seen above, the same “dietary pattern” – dietary fat excess – modulates different types of epigenetic mechanisms, what may show an interaction between these mechanisms and environmental factors.

Thus specific alimentary patterns, as high adherence to Mediterranean diet (rich in vegetable, fruit, olive oil, and antioxidants)\(^{(53)}\) are associated with significant and consistent protection provided to the occurrence of many chronic degenerative diseases.\(^{(53)}\)

Asthma is a major public health problem in developed countries, epigenetic is now recognized as a key mechanism underlying the establishment of an inflammatory status in asthmatic patients.\(^{(54)}\) Dietary components as folic acid, vitamin A, C, D and n-3 PUFA have been studied on its effect on asthma risk and prevention.\(^{(48, 55-57)}\) Although there’s a lack of studies linking nutrients to epigenetic mechanisms and this type of disease.

Furthermore, would be interesting future prospective investigations in human subjects, using the latest technologies, to understand the use of nutrients or bioactive food components for maintaining human health and preventing diseases through modifiable epigenetic mechanisms. Study findings also have differences in epigenetic marks for the types (global or gene-specific), specimen sources (systemic or target tissues) and analytic methods. Therefore standardization of studies design, according to pathology, would be interesting to a better understanding of the epigenetic mechanisms related with the specific disease, in order to improve treatment and prevention.
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