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MINI REVIEW

Epigenetics and diet: how does food regulate our genes?

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Abstract

In recent decades, research into how our cells function using cellular and molecular approaches has further opened our understanding of how homeostasis is disrupted by environmental insults. Unhealthy diet over time generates a wide range of problems that lead to morbidity and mortality. Previously, the causes of diseases were attributed solely to the genetic makeup of individuals, however, epigenetics emerged to help understand how lifestyles can influence the expression of an individual's genes. Therefore, in this review article, we discuss recent evidence indicating that dietary components can modulate gene function through epigenetic control (e.g., DNA methylation, histone modifications, and microRNAs) to maintain homeostasis. In addition, it is discussed what happens when harmful nutritional habits predominant (e.g., high fat and sugar diet and low consumption of vitamins-rich foods); a situation that deteriorates and interrupts the way our genes work. The importance of this field lies in the fact that nutritionists, in the future, could direct personalized nutritional therapies and, above all, they could practice health promotion with an integrated knowledge on how diet regulates our genes.

1. Introduction

In 2022, the release of the complete sequence of the human genome opens the way to understand how faults in specific areas of DNA lead to diseases. There are ~20 thousand protein-coding genes that make up ~2% of all human genomic information (Nurk *et al*., 2022). The non -coding regions of the genome are diverse and play a pivotal role in the regulation of coding genes involved in a multitude of biological processes (Gloss and Dinger, 2018).

Human coding and non-coding genomic regions are sensitive to regulation by the environment, and this way of regulation involves the field of epigenetics. Epigenetics, which means “above DNA”, includes adjustments in gene expression profiles without the need of replacing any nucleotides. For instance, these epigenetic changes involve the aggregation of chemical groups on DNA and on histones; the dynamics of histone and nucleosome assembly; and non-coding RNAs. These epigenetic changes can be passed on to daughter cells during mitosis and depending on the cell type, they are found in different patterns and inappropriate regulation leads to chronic diseases (Al Aboud *et al*., 2021).

The connection between diet and disease is observed mainly in epidemiological and animal studies. For example, studies support the hypothesis that a Western dietary pattern plays a role in cancer development (Flores-García *et al*., 2022). On the other hand, nutritional regimens such as Mediterranean diet that are rich in vegetables are associated with a decreased risk of disease (Aune *et al*., 2017; Schwingshackl *et al*., 2020; Flores-García *et al*., 2022).

Experimental studies corroborate the notion that the diet contains compounds, that at the molecular level, alter the gene expression of hundreds of genes (Herrera-Marcos *et al*., 2017). This suggests that genetics is not the only contributor to disease risk. We pose this scenario: certain individuals may have been born with "good genes," but if they are exposed to harmful environmental factors, they may develop some disease; and depending on the gene involved, it could cause diseases such as cancer.

In this minireview, we briefly discuss recent findings on how diet and the food components, through epigenetic mechanisms, play a role in homeostasis and disease development. In addition, our goal is to provide insights to health science professionals of the possible

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effects of nutritional habits during health and disease.

2. Epigenetic regulation by nutrients

Central dogma of molecular biology posits that the expression of protein-coding genes involves a) formation of messenger ARN by transcription and b) protein synthesis by translation. This simplistic view of gene expression is regulated by environmental signals that do not change the nucleotide sequence of DNA; this way of regulation is called epigenetics. There are three mechanisms of epigenetic control: a) DNA methylation, b) histone modification and c) non-coding RNA. In all of them, diet and food constituents play a role.

2.1 DNA methylation

It consists of the placement of “chemical labels", such as methyl groups, on top of the DNA sequence and specifically on the cytosine’s nucleotide to form 5-methylcytosine (5mC) in a promoter region of hundreds of genes. When the promoter region of a gene is methylated, the gene is turned off or silenced at the transcriptional level. This process is carried out by DNMTs or DNA methyltransferases that use S-adenosylmethionine (SAM) as the methyl group donor (Figure 1-A). However, the hypermethylation of promoters, sometimes and in a context-dependent manner, turns out in transcriptional activation (Smith *et al*., 2020). Demethylation is also a dynamic event that is carried out in the human genome by ten-eleven translocation (TET) dioxygenases (Figure 1-B) (Shi *et al*., 2021).

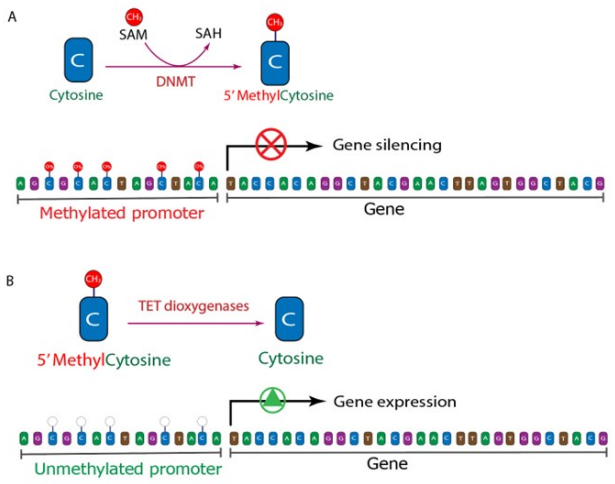

Figure 1. DNA methylation: A) methylation of the promoter regions (cytosine residues) results in gene silencing, and B) Demethylation of the promoter region leads to gene expression.

Dietary folate, betaine, choline, and other B vitamins are sources of methyl groups (Ducker and Rabinowitz, 2017). Hundreds of genes are regulated by methylation and therefore inappropriate methylation can cause genome instability, which in turn could increase the incidence of disease (Jones and Gonzalgo, 1997). For example, aberrant methylation in many different types of cancer is present (Mahmoud and Ali, 2019).

In the line of cancer, tumor suppressor genes are methylated in certain promoter regions and, for instance, bioactive substances such as curcumin have shown to restore the function *in vitro* of the gene BRCA1 involved in breast cancer, also this compound induces methylation of the proto-oncogene SNCG involved in this type of cancer (Al-Yousef *et al*., 2020).

In the case of vitamin D, Zhang *et al.* (2014) found that vitamin D-deficient rats during pregnancy had an offspring with insulin resistance during adulthood. Aberrant immune parameters (persistent inflammation) were also present; this effect may be related to the methylation of the Iκbα gene; a gene related to immune function (Zhang *et al*., 2014). In humans, a randomized controlled pilot study indicates that supplementation with vitamin D during pregnancy impacts the methylation marks of the DNA’s child (Anderson *et al*., 2018). In addition, vitamin D, as expected, has antitumorigenic properties and the potential molecular mechanisms are based on suitable methylation patterns in genes regulated by Vitamin D (Li *et al*., 2021). These genes are involved in immune function, metabolism, cell proliferation and cell death (Fetahu *et al*., 2014; O'Brien *et al*., 2018).

Vitamin C, another micronutrient found mainly in plant sources, also has a pivotal role in the epigenetic marks such as methylation in humans. In a study conducted by Shorey-Kendrick *et al*. (2021) indicates that vitamin C supplementation rescued the negative methylation changes in the placenta caused by smoking during pregnancy. The authors indicated a potential positive role of vitamin C in the infant’s epigenome and the impact in appropriate methylation in genes involved in respiratory function.

2.2 Histone modifications

Histones are proteins that wrap around the DNA sequence and are responsible for DNA condensation. Histones contain residues susceptible to the binding of chemical tags such as acetyl groups. When this happens, histones no longer wrap around DNA and now the gene is accessible to transcription. The addition of acetyl group (acetylation) and removal of acetyl group (deacetylation) of histones at the lysine residue allow regulation of gene expression (Acevedo *et al*., 2019; Al Aboud *et al*., 2021). Figure 2 represents the acetylated histones that generate chromatin unpacking and, therefore, facilitate gene expression. Other chemical tags such as methyl groups also bind to histone residues, but

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the outcome (silencing or activation) will depend on the amount of methyl groups and the residues that are methylated; and diet contributes to this heterogeneous landscape (Molina-Serrano *et al*., 2019).

Diet and its compounds regulate histone acetylation and deacetylation (Vahid *et al*., 2015). Phytochemicals such as polyphenols are widely known for their beneficial effects on gene expression and now, they are more relevant because they modulate the acetylation of histones, and in this way could prevent the development of chronic diseases (Russo *et al*., 2017).

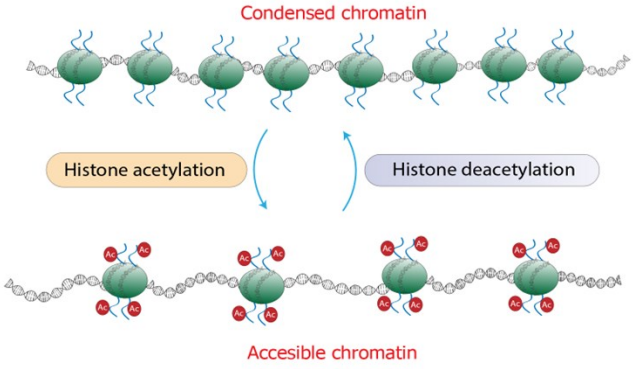

Figure 2. Histone acetylation and deacetylation.

Nutrients modulates the histone marks throughout the life of an individual, even before birth the mother's diet is critical. For example, a study on 173 human placentas showed that olive oil consumption during pregnancy plays a role in the modulation of histone acetylation; impacting genes associated with immune function in this critical tissue. Polyphenols and polyunsaturated fatty acids (PUFAs) may be the drivers (Acevedo *et al*., 2019). This example poses a scenario about how maternal diet impacts a tissue that is crucial in the dialogue between mother and the child, probably impacting the gene expression of the future newborn. In fact, researchers of the same group previously found that prenatal fish oil supplementation is associated with appropriate cord blood T cell maturation, through acetylation mechanisms involving the expression of the PKCζ gene (Harb *et al*., 2017).

2.3 Non-coding RNA

Within this group, we have microRNAs that consist of ~21 nucleotides and are complementary to a 6-8 nucleotide "seed region" in messenger RNA (mRNA). By binding to mRNA, specifically at the 3'untranslated region (3-UTR), microRNA prevents the mRNA from being translated into protein. This mechanism is critical in the regulation of signaling pathways involved in cellular homeostasis (Otsuka and Ochiya, 2011).

In animal models, choline and folic acid deficiencies increase the expression of microRNAs that promote non-alcoholic fatty liver disease (NAFLD), for example, microRNA-134, microRNA-409-3p, microRNA-410, microRNA-495, microRNA-34-a, microRNA-122, etc. (Tryndyak *et al*., 2012; Tryndyak *et al*., 2016). In vitro experiments carried out by Ma *et al.* (2016), indicate that microRNA-409-3p participates in some malignant features of breast cancer.

The administration of fish oil, as well as its component docosahexaenoic acid (DHA), positively regulates the expression of microRNA-19b, microRNA-26b, microRNA-203, microRNA-192 and microRNA-30 in order to dampen down the activity of the oncogenic and lipogenic genes (Shah *et al*., 2011; Acevedo *et al*., 2019*et al*., 2014). Moreover, the polyphenols in extra virgin olive oil, resveratrol, epigallocatechin-3-gallate, sulforaphane and genistein –in addition to regulation mediated by methylation– have been related to the expression of microRNAs that reduce oncogenic activity and other metabolic alterations (De Santis *et al*., 2019; Del Saz-Lara *et al*., 2022). Figure 3 shows a representation about the possible role of food components in the regulation of host's genes, particularly in the context of cancer.

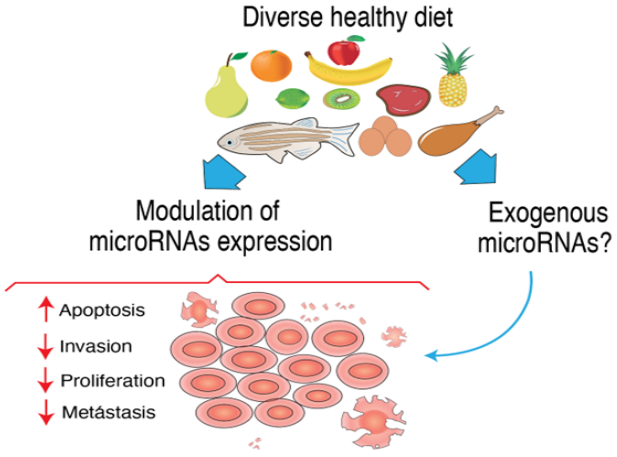

Figure 3. The possible role of diet in the modulation of microRNAs involved in cancer development and progression. The question is about how exogenous microRNAs could be involved in cancer events.

In addition to nutrient-altered intrinsic microRNAs, the regulation by exogenous microRNAs is opening our understanding of how our diet might regulate our gene expression in this way. For example, microRNA-168a, which is commonly found in rice, can be acquired through food intake. This finding is supported by analysis of the sera and tissues of various organisms, including humans. The physiological importance is based on the regulation of the low-density lipoprotein receptor adapter protein 1 (LDLRAP1) messenger RNA of mice and humans. Experiments in mice showed that microRNA-168a interferes with LDL clearance by elevating its concentration in the liver after only six

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hours of rice feeding (Zhang *et al*., 2012; Lang *et al*., 2018).

Some findings show that mice that ingested "rapeseed bee pollen" had microRNA-166a and microRNA-159 in their blood (Chen *et al*., 2016). Both are widely studied in plant physiology, and it remains a question whether they regulate the expression of human genes. These last two studies are examples that show that diet contains epigenetics regulators, and this is a case of cross-kingdom regulation. Figure 3 highlights a question mark about the possible role of exogenous microRNAs in the context of neoplastic events.

3. Clinical relevance

There are experimental and epidemiological studies that support the idea that a diet rich in minerals, vitamins, fiber, phenolic compounds, and essential fatty acids improves chronic diseases such as cancer (Nasir *et al*., 2020), diabetes (Basile *et al*., 2022) and Alzheimer (Romanenko *et al*., 2021). In addition, it has been suggested that a correct balance of the microbiota contributes with epigenetic modifiers (metabolites) with great potential to prevent or treat these diseases in humans (Zhao *et al*., 2021; Romanenko *et al*., 2021). This idea justifies the reason why microbiota is strongly linked to the regulation of the immune system, and at the same time, the immune system keeps host homeostasis; in other words, they work synergistically.

Zimmet *et al*. (2018), based on the example of the Chinese famine (1959-1961) that increased the intergenerational risk of type 2 diabetes mellitus, it is suggested that public health interventions should be integrated with pregnancy planning, care of children and mothers during and after the months of pregnancy. This is supported by the notion that there are critical periods during development that the mother and fetus need certain amounts of good nutrients, and in this way avoid epigenetic dysregulation, that even could impact in a transgenerational way (Danielewicz *et al*., 2017).

In 2011, Hardy and Tollefsbol, introduced the term "epigenetic diet", a name strongly based on evidence indicating that chemical compounds from the human diet could modulate the state of the epigenome, and this could prevent or treat cell abnormalities such as cancer (Hardy and Tollefsbol, 2011). Chemical marks could be considered a biomarker for aging (Duan *et al*., 2022), for example, in a randomized controlled investigation in men adults (50 to 72 years old), Fitzgerald *et al*. (2021) showed that eight weeks of healthy lifestyles (including diet) improved the methylation marks of the tested group. This study suggests that deleterious chemical marks accumulated during lifespan could be "erased" or "prevented" by healthy lifestyles.

In a pharmacological scenario, vitamins, minerals, and bioactive substances may have the desired effect in a dose-dependent manner and this could be limited when it is impossible to acquire higher amounts in a daily realistic nutritional regimen (Lewis and Tollefsbol, 2017). Lewis and Tollefsbol (2017), suggest that combinatorial studies are needed to understand whether nutrients (epigenetic regulators) act in synergistic, additive, or antagonistic ways, particularly in the context of cancer (Otsuka and Ochiya, 2021). Therefore, we suggest further pharmacological studies to test the activity of epigenetic modifiers from the human diet in realistic settings, considering cultural, socioeconomic, and geographical factors. Finally, more emphasis must be given to communicate efficiently (to patients, governments, schools, hospitals, and food services) about the role of diet in the epigenome.

4. Conclusion

The close relationship between epigenetics and nutrients has implications in the understanding of the development and progression of many diseases. Although the composition of the metabolites of various foods is still unclear, more emphasis is being placed on the nutrients consumed and their benefits in homeostasis and disease. To date, preclinical research paves the path for the personalized use of nutrition as a therapeutic intervention. This would open greater public health interest in nutritionists for epigenetic and nutritional scientific research leading to future clinical applications.

The following points needs to be taken into consideration in the understanding on how diet exerts its effects in the epigenetics of individuals:

a. Basic research to elucidate other epigenetic mechanisms controlled/regulated by nutrients.
b. Clinical evidence, particularly in randomized controlled clinical trials.
c. Synergistic and antagonistic activity of bioactive substances.
d. Epigenomic studies on populations.
e. Food and cultural biodiversity in countries.
f. Transgenerational inheritance in a context-dependent manner.
g. Technologies and powerful bioinformatics tools to understand complex epigenetic mechanisms.

Conflict of interest

The authors declare no conflict of interest.

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References

Acevedo, N., Frumento, P., Harb, H., Alashkar Alhamwe, B., Johansson, C., Eick, L., Alm, J., Renz, H., Scheynius, A. and Potaczek, D.P. (2019). Histone Acetylation of Immune Regulatory Genes in Human Placenta in Association with Maternal Intake of Olive Oil and Fish Consumption. *International Journal of Molecular Sciences*, 20(5), 1060. https://doi.org/10.3390/ijms20051060

Al Aboud, N.M., Tupper, C. and Jialal, I. (2021). Genetics, Epigenetic Mechanism. In StatPearls [Internet]. Treasure Island, Florida, USA: StatPearls Publishing.

Al-Yousef, N., Shinwari, Z., Al-Shahrani, B., Al-Showimi, M. and Al-Moghrabi, N. (2020). Curcumin induces re-expression of BRCA1 and suppression of γ synuclein by modulating DNA promoter methylation in breast cancer cell lines. *Oncology Reports*, 43(3), 827-838. https://doi.org/10.3892/or.2020.7473

Anderson, C.M., Gillespie, S.L., Thiele, D.K., Ralph, J.L. and Ohm, J.E. (2018). Effects of Maternal Vitamin D Supplementation on the Maternal and Infant Epigenome. *Breastfeeding Medicine*, 13(5), 371-380. https://doi.org/10.1089/bfm.2017.0231

Aune, D., Giovannucci, E., Boffetta, P., Fadnes, L.T., Keum, N., Norat, T., Greenwood, D.C., Riboli, E., Vatten, L.J. and Tonstad, S. (2017). Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *International Journal of Epidemiology*, 46(3), 1029-1056. https://doi.org/10.1093/ije/dyw319

Basile, G., De Maio, A.C., Catalano, A., Ceramella, J., Iacopetta, D., Bonofiglio, D., Saturnino, C. and Sinicropi, M.S. (2022). Ancient Wheats as Promising Nutraceuticals for the Prevention of Chronic and Degenerative Diseases. *Current Medicinal Chemistry*, 30(30), 3384-3403. https://doi.org/10.2174/0929867329666220915122216

Chen, X., Dai, G.H., Ren, Z.M., Tong, Y.L., Yang, F. and Zhu, Y.Q. (2016). Identification of Dietetically Absorbed Rapeseed (*Brassica campestris* L.) Bee Pollen MicroRNAs in Serum of Mice. *BioMed Research International*, 2016, 5413849. https://doi.org/10.1155/2016/5413849

Danielewicz, H., Myszczyszyn, G., Dębińska, A., Myszkal, A., Boznański, A. and Hirnle, L. (2017). Diet in pregnancy-more than food. *European Journal of Pediatrics*, 176(12), 1573-1579. https://doi.org/10.1007/s00431-017-3026-5

De Santis, S., Cariello, M., Piccinin, E., Sabbà, C. and Moschetta, A. (2019). Extra Virgin Olive Oil: Lesson from Nutrigenomics. *Nutrients*, 11(9), 2085. https://doi.org/10.3390/nu11092085

Del Saz-Lara, A., López de Las Hazas, M.C., Visioli, F. and Dávalos, A. (2022). Nutri-Epigenetic Effects of Phenolic Compounds from Extra Virgin Olive Oil: A Systematic Review. *Advances in Nutrition*, 13(5), 2039-2060. https://doi.org/10.1093/advances/nmac067

Duan, R., Fu, Q., Sun, Y. and Li, Q. (2022). Epigenetic clock: A promising biomarker and practical tool in aging. *Ageing Research Reviews*, 81, 101743. https://doi.org/10.1016/j.arr.2022.101743

Ducker, G.S. and Rabinowitz, J.D. (2017). One-Carbon Metabolism in Health and Disease. *Cell Metabolism*, 25(1), 27-42. https://doi.org/10.1016/j.cmet.2016.08.009

Fetahu, I.S., Höbaus, J. and Kállay, E. (2014). Vitamin D and the epigenome. *Frontiers in Physiology*, 5, 164. https://doi.org/10.3389/fphys.2014.00164

Fitzgerald, K.N., Hodges, R., Hanes, D., Stack, E., Cheishvili, D., Szyf, M., Henkel, J., Twedt, M.W., Giannopoulou, D., Herdell, J., Logan, S. and Bradley, R. (2021). Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial. *Aging*, 13(7), 9419-9432. https://doi.org/10.18632/aging.202913

Flores-García, M.K., Mérida-Ortega, Á., Denova-Gutiérrez, E., Rothenberg, S.J. and López-Carrillo, L. (2022). "Western" and "prudent" dietary patterns are associated with breast cancer among Mexican pre - and postmenopausal women. *Nutrition Research*, 105, 138-146. https://doi.org/10.1016/j.nutres.2022.06.007

Gil-Zamorano, J., Martin, R., Daimiel, L., Richardson, K., Giordano, E., Nicod, N., García-Carrasco, B., Soares, S.M., Iglesias-Gutiérrez, E., Lasunción, M.A., Sala-Vila, A., Ros, E., Ordovás, J.M., Visioli, F. and Dávalos, A. (2014). Docosahexaenoic acid modulates the enterocyte Caco-2 cell expression of microRNAs involved in lipid metabolism. *The Journal of Nutrition*, 144(5), 575-585. https://doi.org/10.3945/jn.113.189050

Gloss, B.S. and Dinger, M.E. (2018). Realizing the significance of noncoding functionality in clinical genomics. *Experimental and Molecular Medicine*, 50, 1-8. https://doi.org/10.1038/s12276-018-0087-0

Harb, H., Irvine, J., Amarasekera, M., Hii, C.S., Kesper, D.A., Ma, Y., D'Vaz, N., Renz, H., Potaczek, D.P., Prescott, S.L. and Ferrante, A. (2017). The role of PKCζ in cord blood T-cell maturation towards Th1

cytokine profile and its epigenetic regulation by fish oil. *Bioscience Reports*, 37(2), BSR20160485. https://doi.org/10.1042/BSR20160485

Hardy, T.M. and Tollefsbol, T.O. (2011). Epigenetic diet: impact on the epigenome and cancer. *Epigenomics*, 3(4), 503-518. https://doi.org/10.2217/epi.11.71

Herrera-Marcos, L.V., Lou-Bonafonte, J.M., Arnal, C., Navarro, M.A. and Osada, J. (2017). Transcriptomics and the Mediterranean Diet: A Systematic Review. *Nutrients*, 9(5), 472. https://doi.org/10.3390/nu9050472

Jones, P.A. and Gonzalgo, M.L. (1997). Altered DNA methylation and genome instability: a new pathway to cancer?. *Proceedings of the National Academy of Sciences of the United States of America*, 94(6), 2103-2105. https://doi.org/10.1073/pnas.94.6.2103

Lang, C., Karunairetnam, S., Lo, K.R., Kralicek, A.V., Crowhurst, R.N., Gleave, A.P., MacDiarmid, R.M. and Ingram, J.R. (2019). Common Variants of the Plant microRNA-168a Exhibit Differing Silencing Efficacy for Human Low-Density Lipoprotein Receptor Adaptor Protein 1 (LDLRAP1). *MicroRNA*, 8(2), 166-170. https://doi.org/10.2174/2211536608666181203103233

Lewis, K.A. and Tollefsbol, T.O. (2017). The influence of an epigenetics diet on the cancer epigenome. *Epigenomics*, 9(9), 1153-1155. https://doi.org/10.2217/epi-2017-0077

Li, Q., Li, Y., Jiang, H., Xiao, Z., Wu, X., Zhang, H., Zhao, Y., Du, F., Chen, Y., Wu, Z., Li, J., Hu, W., Cho, C.H., Shen, J. and Li, M. (2021). Vitamin D suppressed gastric cancer cell growth through downregulating CD44 expression in vitro and in vivo. *Nutrition*, 91-92, 111413. https://doi.org/10.1016/j.nut.2021.111413

Ma, Z., Li, Y., Xu, J., Ren, Q., Yao, J. and Tian, X. (2016). MicroRNA-409-3p regulates cell invasion and metastasis by targeting ZEB1 in breast cancer. *IUBMB Life*, 68(5), 394-402. https://doi.org/10.1002/iub.1494

Mahmoud, A.M. and Ali, M.M. (2019). Methyl Donor Micronutrients that Modify DNA Methylation and Cancer Outcome. *Nutrients*, 11(3), 608. https://doi.org/10.3390/nu11030608

Molina-Serrano, D., Kyriakou, D. and Kirmizis, A. (2019). Histone Modifications as an Intersection Between Diet and Longevity. *Frontiers in Genetics*, 10, 192. https://doi.org/10.3389/fgene.2019.00192

Nasir, A., Bullo, M., Ahmed, Z., Imtiaz, A., Yaqoob, E., Jadoon, M., Ahmed, H., Afreen, A. and Yaqoob, S. (2020). Nutrigenomics: Epigenetics and cancer prevention: A comprehensive review. *Critical Reviews in Food Science and Nutrition*, 60(8), 1375-1387. https://doi.org/10.1080/10408398.2019.1571480

Nurk, S., Koren, S., Rhie, A., Rautiainen, M., Bzikadze, A. V., Mikheenko, A., Vollger, M.R., Altemose, N., Uralsky, L., Gershman, A., Aganezov, S., Hoyt, S.J., Diekhans, M., Logsdon, G.A., Alonge, M., Antonarakis, S.E., Borchers, M., Bouffard, G.G., Brooks, S.Y., Caldas, G.V., Chen, N.C., Cheng, H., Chin, C.S., Chow, W., de Lima, L.G., Dishuck, P.C., Durbin, R., Dvorkina, T., Fiddes, I.T., Formenti, G., Fulton, R.S., Fungtammasan, A., Garrison, E., Grady, P.G.S., Graves-Lindsay, T.A., Hall, I.M., Hansen, N.F., Hartley, G.A., Haukness, M., Howe, K., Hunkapiller, M.W., Jain, C., Jain, M., Jarvis, E.D., Kerpedjiev, P., Kirsche, M., Kolmogorov, M., Korlach, J., Kremitzki, M., Li, H., Maduro, V.V., Marschall, T., McCartney, A.M., McDaniel, J., Miller, D.E., Mullikin, J.C., Myers, E.W., Olson, N.D., Paten, B., Peluso, P., Pevzner, P.A., Porubsky, D., Potapova, T., Rogaev, E.I., Rosenfeld, J.A., Salzberg, S.L., Schneider, V.A., Sedlazeck, F.J., Shafin, K., Shew, C.J., Shumate, A., Sims, Y., Smit, A.F.A., Soto, D.C., Sović, I., Storer, J.M., Streets, A., Sullivan, B.A., Thibaud-Nissen, F., Torrance, J., Wagner, J., Walenz, B.P., Wenger, A., Wood, J.M.D., Xiao, C., Yan, S.M., Young, A.C., Zarate, S., Surti, U., McCoy, R.C., Dennis, M.Y., Alexandrov, I.A., Gerton, J.L., O'Neill, R.J., Timp, W., Zook, J.M., Schatz, M.C., Eichler, E.E., Miga, K.H. and Phillippy, A.M. (2022). The complete sequence of a human genome. *Science*, 376(6588), 44-53. https://doi.org/10.1126/science.abj6987

O'Brien, K.M., Sandler, D.P., Xu, Z., Kinyamu, H.K., Taylor, J.A. and Weinberg, C.R. (2018). Vitamin D, DNA methylation, and breast cancer. *Breast Cancer Research*, 20(1), 70. https://doi.org/10.1186/s13058-018-0994-y

Otsuka, K. and Ochiya, T. (2021). Possible connection between diet and microRNA in cancer scenario. *Seminars in Cancer Biology*, 73, 4-18. https://doi.org/10.1016/j.semcancer.2020.11.014

Romanenko, M., Kholin, V., Koliada, A. and Vaiserman, A. (2021). Nutrition, Gut Microbiota, and Alzheimer's Disease. *Frontiers in Psychiatry*, 12, 712673. https://doi.org/10.3389/fpsyt.2021.712673

Russo, G.L., Vastolo, V., Ciccarelli, M., Albano, L., Macchia, P.E. and Ungaro, P. (2017). Dietary polyphenols and chromatin remodeling. *Critical Reviews in Food Science and Nutrition*, 57(12), 2589-2599. https://doi.org/10.1080/10408398.2015.1062353

Schwingshackl, L., Morze, J. and Hoffmann, G. (2020). Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. *British Journal of Pharmacology*, 177(6), 1241-1257. https://doi.org/10.1111/bph.14778

Shah, M.S., Schwartz, S.L., Zhao, C., Davidson, L.A., Zhou, B., Lupton, J.R., Ivanov, I. and Chapkin, R.S. (2011). Integrated microRNA and mRNA expression profiling in a rat colon carcinogenesis model: effect of a chemo-protective diet. *Physiological Genomics*, 43(10), 640-654. https://doi.org/10.1152/physiolgenomics.00213.2010

Shi, J., Xu, J., Chen, Y.E., Li, J.S., Cui, Y., Shen, L., Li, J.J. and Li, W. (2021). The concurrence of DNA methylation and demethylation is associated with transcription regulation. *Nature Communications*, 12 (1), 5285. https://doi.org/10.1038/s41467-021-25521-7

Shorey-Kendrick, L.E., McEvoy, C.T., O'Sullivan, S.M., Milner, K., Vuylsteke, B., Tepper, R.S., Haas, D.M., Park, B., Gao, L., Vu, A., Morris, C.D. and Spindel, E.R. (2021). Impact of vitamin C supplementation on placental DNA methylation changes related to maternal smoking: association with gene expression and respiratory outcomes. *Clinical Epigenetics*, 13 (1), 177. https://doi.org/10.1186/s13148-021-01161-y

Smith, J., Sen, S., Weeks, R.J., Eccles, M.R. and Chatterjee, A. (2020). Promoter DNA Hypermethylation and Paradoxical Gene Activation. *Trends in Cancer*, 6(5), 392-406. https://doi.org/10.1016/j.trecan.2020.02.007

Tryndyak, V.P., Latendresse, J.R., Montgomery, B., Ross, S.A., Beland, F.A., Rusyn, I. and Pogribny, I.P. (2012). Plasma microRNAs are sensitive indicators of inter-strain differences in the severity of liver injury induced in mice by a choline- and folate-deficient diet. *Toxicology and Applied Pharmacology*, 262(1), 52-59. https://doi.org/10.1016/j.taap.2012.04.018

Tryndyak, V.P., Marrone, A.K., Latendresse, J.R., Muskhelishvili, L., Beland, F.A. and Pogribny, I.P. (2016). MicroRNA changes, activation of progenitor cells and severity of liver injury in mice induced by choline and folate deficiency. *The Journal of Nutritional Biochemistry*, 28, 83-90. https://doi.org/10.1016/j.jnutbio.2015.10.001

Vahid, F., Zand, H., Nosrat-Mirshekarlou, E., Najafi, R. and Hekmatdoost, A. (2015). The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: a review. *Gene*, 562(1), 8-15. https://doi.org/10.1016/j.gene.2015.02.045

Zhang, H., Chu, X., Huang, Y., Li, G., Wang, Y., Li, Y. and Sun, C. (2014). Maternal vitamin D deficiency during pregnancy results in insulin resistance in rat offspring, which is associated with inflammation and Iκbα methylation. *Diabetologia*, 57(10), 2165-2172. https://doi.org/10.1007/s00125-014-3316-7

Zhang, L., Hou, D., Chen, X., Li, D., Zhu, L., Zhang, Y., Li, J., Bian, Z., Liang, X., Cai, X., Yin, Y., Wang, C., Zhang, T., Zhu, D., Zhang, D., Xu, J., Chen, Q., Ba, Y., Liu, J., Wang, Q., Chen, J., Wang, J., Wang, M., Zhang, Q., Zhang, J., Zen, K. and Zhang, C.Y. (2012). Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. *Cell Research*, 22(1), 107-126. https://doi.org/10.1038/cr.2011.158

Zhao, Y., Wang, C. and Goel, A. (2021). Role of gut microbiota in epigenetic regulation of colorectal Cancer. *Biochimica et Biophysica acta - Reviews on Cancer*, 1875(1), 188490. https://doi.org/10.1016/j.bbcan.2020.188490

Zimmet, P., Shi, Z., El-Osta, A. and Ji, L. (2018). Epidemic T2DM, early development and epigenetics: implications of the Chinese Famine. *Nature Reviews Endocrinology*, 14(12), 738-746. https://doi.org/10.1038/s41574-018-0106-1

