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Epigenetics and lifestyle

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Abstract

The concept of “lifestyle” includes different factors such as nutrition, behavior, stress, physical activity, working habits, smoking and alcohol consumption. Increasing evidence shows that environmental and lifestyle factors may influence epigenetic mechanisms, such as DNA methylation, histone acetylation and microRNA expression.

Several lifestyle factors have been identified that might modify epigenetic patterns, such as diet, obesity, physical activity, tobacco smoking, alcohol consumption, environmental pollutants, psychological stress, and working on night shifts.

Most studies conducted so far have been centered on DNA methylation, whereas only a few investigations have studied lifestyle factors in relation to histone modifications and miRNAs.

Here, we review current evidence indicating that lifestyle factors might affect human health via epigenetic mechanisms.

Keywords

Epigenetics; DNA methylation; Histone modifications; Environmental exposures; Lifestyle

Introduction

The term lifestyle is broadly used to describe the “typical way of life or manner of living characteristic of an individual or group” [1]. This concept includes different factors such as diet, behavior, stress, physical activity, working habits, smoking and alcohol consumption.

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Individual genetic background and environmental factors are intertwined to lifestyle in determining the health status of individuals (Figure 1). Increasing evidence shows that environmental and lifestyle factors may influence epigenetic mechanisms, such as DNA methylation, histone modifications and microRNA expression. Epigenetic mechanisms are flexible genomic parameters that can change genome function under exogenous influence but also provide a mechanism that allows for the stable propagation of gene activity states from one generation of cells to the next [2]. Alterations in epigenetic marks have also been associated with a variety of human diseases, including cancer, cardiovascular, respiratory and neurodegenerative diseases [3]. In this review we will discuss examples of lifestyle factors that have been investigated in relation to possible epigenetic effects, and the implication of lifestyle-related epigenetic changes in disease etiology (Table 1).

Foods

A possible role for nutrition in modifying epigenetic mechanisms has been examined in multiple investigations. For example, a diet rich in polyunsaturated fatty acids could generate mutagenic free radicals and oxidative stress [4], which has been directly linked to epigenetic alterations [5, 6]. Modulation of gene methylation has been observed in human endothelial cells incubated with arachidonic acid promoting up-regulation of a pro-angiogenic mechanisms [7]. Conversely, polyunsaturated fatty acids may have a suppressive function in tumorigenic processes through dampening of inflammation and NF-kappaB pathway [8]. Moreover, diets rich in fruits and vegetables, which contain many natural anti-oxidants, can yield anticancer protection [9]. Chen and Xu [10] have extensively reviewed the potential epigenetic effects of several nutritional components, mostly derived from vegetables. For instance, a study in healthy human subjects fed with a single serving of broccoli sprouts showed inhibition of histone deacetylase activity in circulating peripheral blood mononuclear cells 3–6 hours after consumption, with concurrent induction of histone H3 and H4 acetylation [11]. An in-vitro study on human tumor colon cell lines revealed that high doses of diallyl-disulfide from garlic increased histone H3 and H4 acetylation [12].

Folate and Vitamin B12 Intake

Folic acid and Vitamin B12 play an important role in DNA metabolism and are required for the synthesis of methionine and S-adenosylmethionine (SAM), the common methyl donor required for the maintenance of methylation patterns in DNA [13]. Methylation reactions could be influenced through the modification of the ratio between S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) ratio [14]. The SAM:SAH ratio is a primary determinant of the methylation capacity because SAM is converted to SAH by methionine adenosyltransferase. Taking into consideration that methionine is regenerated by methylation of homocysteine via the folate and B12 dependent reactions, a folate-deficient diet could interfere with this system [15]. The SAM/SAH ratio has been related with DNA methylation patterns. For example, a study conducted in rats examined the maternal folate status and DNA methylation in placenta. A significant positive correlation was found between placental DNA methylation, hepatic and plasma folate levels, and hepatic SAM/SAH ratio [16].

Low folate intakes have been associated with risk of colorectal cancer [17]. Moreover, folate depletion has been shown to cause lymphocyte DNA hypomethylation in healthy postmenopausal women, an alteration reverted by folate repletion [18, 19]. A recent study carried out among individuals susceptible to folate deficiency showed that methylation status can be corrected with choline supply at higher-than-recommended doses (500 mg/day) for 12-weeks [20]. In the context of the SAM cycle, choline can donate methyl groups to SAM since it is a trimethylated molecule. Folate has also been shown to reverse the dysregulation of miRNA expression associated with hepatocellular carcinogenesis,

potentially by restoring dietary methyl donors [21]. The growing body of evidence showing that folate intake modulate epigenetic mechanisms has been actively investigated in relation to potential anticarcinogenic properties suggested by epidemiological studies [22–25]. Also, investigating epigenetic effects from folate might help understand paradoxical observations, such as those linking very high folate intakes with the development of colorectal carcinoma from adenomatous polyps [26].

Polyphenols

Polyphenols are a large family of natural compounds widely distributed in plant foods, that have been shown to modify the activity of DNA methyltransferases, histone acetylases (HATs) and histone deacetylases (HDACs) [27, 28]. In particular, studies on cancer cells have shown that polyphenols can reverse in in-vitro models some of the epigenetic aberrations associated with malignant transformation [29]. Inhibitory effects on DNA methyltransferases have been observed both in-vitro and in-vivo using different dietary sources of polyphenols [28]. A retrospective analysis associated *CDX2* and *BMP-2* gene hypermethylation with past low intake of polyphenol sources such as cruciferous vegetables and green tea in patients with primary gastrocarcinoma [30, 31]. Green tea contains (−)-epigallocatechin-3-gallate (EGCG), which is an inhibitor of DNA methyltransferases activity. EGCG has been shown to reactivate methylation-silenced genes in cancer cell lines [32, 33]. In in-vitro experiments on esophageal, prostate, colon and breast cancer cells lines, several CpG islands in various loci were efficiently demethylated by EGCG, thus leading to the expression of previously silenced genes [32–35].

Soy beans are also extremely rich in polyphenols [28]. Soy polyphenols include phytoestrogens such as genistein, biochanin A, and daidzein [36]. These compounds have also been shown to inhibit DNA methyltransferases and histone deacetylases in cancer cell lines and to revert aberrant CpG island methylation [37]. Li et al. showed in benign (MCF-10AT) and cancer (MCF7) breast cells that all the three main DNA methyltransferases (*DNMT1*, *DNMT3a*, and *DNMT3b*) were down regulated by genistein [38]. These results might help explain epidemiology data indicating that soy consumption is associated with reduced risk of hormone-related cancers [39].

Selenium

Selenium can epigenetically modulate DNA and histones to activate methylation-silenced genes [40]. Increasing data suggest that selenium may have anticarcinogenic properties through modifications of epigenetic processes in the cell [41–43]. Selenium has been shown to directly inhibit DNMT expression and activity [44, 45]. Selenium can also restore the expression of hypermethylated genes, such as *GSTP1*, *APC* and *CSR1,* in human prostate cancer cells by downregulating *DNMTs* and inhibiting HDAC activity [40]. These genes are known to have anticancer activity by protection against oxidative damage, detoxification of carcinogenetic chemicals or tumor suppression [40]. Moreover, in animal models, a selenium-deficient diet has been shown to induce DNA hypomethylation [46, 47].

Obesity and Physical Activity

Overweight, obesity, and sedentary lifestyle are established and prevalent risk factors for several diseases, including cancer and cardiovascular disease [48–50]. Because body weight is regulated by genes controlling energy homeostasis, it has been hypothesized that dietary macronutrients that affect DNA methylation could contribute to develop obesity through epigenetic mechanisms [51]. Epigenetic biomarkers of obesity, including genes involved in adipogenesis, (SOCS1/SOCS3), methylation pattern of obesity-related genes (FGF2, PTEN,

CDKN1A and ESR1), inflammation genes as well as intermediary metabolism and insulin signaling pathway genes, could help to predict susceptibility and prevent obesity [52].

Emerging evidence indicates that epigenetic mechanisms may be involved in mediating effects of physical activity. In a recent work, physical activity was associated with higher methylation in peripheral blood lymphocytes of LINE-1 elements, a class of repeated sequences highly repeated in the human genome [53]. Low methylation in LINE-1 repetitive elements has been associated with inflammatory responses, as well as with chromosomal instability [54]. Interestingly, elderly individuals with high LINE-1 methylation in peripheral blood lymphocytes have been recently shown to have lower incidence and mortality from ischemic heart disease and stroke [55]. Whether the decreased cardiovascular risks associated with LINE-1 methylation reflect beneficial effects from physical activity remains to be determined. In human muscle biopsies following exercise, a global increase in H3K36 acetylation has also been observed [56]. Moreover, a brief exercise has been shown to alter miRNA profiles in circulating neutrophils in humans, including 38 miRNAs involved in inflammatory pathways [57].

Tobacco smoke

Tabacco smoke contains a complex mixture of organic and inorganic chemicals, many of which have carcinogenic, pro-inflammatory and proaterogenic properties. Individual effects of these components have been examined through different epigenetic studies, but the results are still inconclusive. For example, an *in-vitro* chronic toxicity study of normal human fibroblast on Benzo[a]pyrene - a prominent carcinogenic polycyclic aromatic hydrocarbon (PAH) found in cigarette smoke - found no aberrant patterns of DNA methylation in genomic regions of relevance for lung cancer [58].

Conversely, cigarette smoke condensate has been shown in respiratory epithelial cells to decrease the nuclear levels of certain histone modifications such as H4K16 acetylation and H4K20 trimethylation [59]. These alterations were similar to changes in histone modifications that can be found in lung cancer tissues which commonly precede aberrant DNA methylation [60, 61]. For instance, demethylation in H19 and IGF2 occurred primarily to the DNA hypermethylation-mediated silencing of p16, MGMT, DAPK, E-cadherin, and cdh13 tumor suppressor genes as an early event in lung carcinonegesis induced by tobacco smoke [62].

P53 hypomethylation has been reported in peripheral blood lymphocytes of smoking lung cancer patients [63]. Despite the lack of consistent evidence for p53 gene aberrantly methylated in human cancer, p53 hypomethylation has been associated with early events in carcinogenesis such as DNA double-strand breaks and chromosomal instability [64, 65].

A study that evaluated global DNA methylation from buccal cells of children exposed to prenatal maternal smoking demonstrated hypomethylation of LINE-1 repetitive elements. In the same study, a microarray analysis of 1536 CpG sites identified differential methylation of CpG loci in eight genes. Two of them, AXL and PTPRO, were validated by pyrosequencing and showed significant increases in methylation [66]. Following findings indicating that miRNAs in human placentas are differentially expressed in association with adverse pregnancy outcomes [67], a recent study found that candidate miRNAs implicated in growth and developmental processes (i.e., miR-16, miR-21, and miR-146a) were significantly downregulated in cigarette smoke-exposed placentas compared to controls [68]. Moreover, downregulation of microRNA expression was also observed in animal experiments when lung of mice and rats were exposed to cigarette smoke. In this study, mir-34b, mir-345, mir-421, mir-450b, mir-466, and mir-469 were downregulated at high-dose of exposure; however, expression was restored one week after smoking cessation [69].

Alcohol consumption

In contrast to polycyclic aromatic hydrocarbons (PAHs) and other carcinogenic molecules found in tobacco smoke and tar, ethyl alcohol is not per se mutagenic, but rather acts mainly as a cocarcinogen [70]. A Netherlands cohort study on diet and cancer correlated the intake of folate and alcohol with changes in methylation of tumor suppressor and DNA repair genes (APC-1A, p14ARF, p16INK4A, hMLH1, O6-MGMT, and RASSF1A) in paraffin-embedded colorectal cancer tissues [71]. Also, this work suggested the association between the intake of other methyl donors such as methionine, vitamins B6, and B12 with an increased frequency of promoter hypermethylation of genes involved in colorectal carcinogenesis [71]. However, a second cohort study did not find any association of folate intake, methionine or alcohol with MLH1 hypermethylation, a frequent and well-characterized early event in the development of colorectal cancer [72]. A positive association between vitamin B6 intake and tumors showing MLH1 hypermethylation was found, suggesting B6 vitamin may enhance colorectal cancer risk [72]. Alcohol consumption has also been suggested to modify the association between blood markers of DNA methylation and disease. In a population-based case-control study on a Polish population, Hou et al. showed that repetitive elements hypomethylation in blood leukocyte DNA was associated with gastric cancer and that the association between LINE-1 hypomethylation and gastric cancer was stronger among individuals who were current alcohol drinkers [73].

Currently, there are demonstrations of alcohol effects on growth and neuronal development through epigenetic marks. Mouse fetal cortical neurons chronically exposed to ethanol *in vitro,* had NR2B gene demethylation which encodes an ionotropic glutamate receptor possibly involved in certain memory and learning processes [74, 75]. Instead, acute exposure to ethanol induced hypermethylation of specific cell cycle genes inhibiting the growth factor-regulated cell cycle progression in monolayer cultures of neural stem cells. Lengthening the time between G1 and S phase was observed when cells were exposed for 48 h [76]. In the mouse strain C57BL/6, alcohol exposure at early embryonic altered the DNA methylation in embryos with a neural tube defect phenotype changing the expression for genes involved in metabolism and development such as Nlgn3, Elavl2, Sox21, Sim1, Nlgn3, Elavl2, Sox21 and Sim1. These disturbances may contribute to malformations and abnormal fetal development [77]. Subsequently, Zhou et al. found a reduction in expression of neurogenin, Sox5, Bhlhe22, Igf1, Efemp1, Tieg and Edil3 in mice embryo cultures. In this case, the gene expression responsible for the neural tube development is modulated by changes in DNA methylation patterns [78].

Environmental pollutants

In environmental studies, the flexibility of epigenetic states has generated growing interest in evaluating whether environmental exposures can modify epigenetic states, including DNA methylation and histone modifications [79]. Studies of DNA methylation and histone modification in relation to environmental exposures to potentially toxic chemicals have been examined in detail in a recent review article [80]. Here, we briefly review the main classes of environmental exposures that are most frequently considered epigenetic toxicants.

Arsenic

In a human study from India, significant DNA hypermethylation of p53 and p16 promoter regions was observed in blood DNA of subjects exposed to toxic arsenic levels compared to controls [81]. In this study, p53 and p16 hypermethylation showed a dose-response relationship with arsenic measured in drinking water. A large body of in vitro and animal studies have shown that arsenic subtracts methyl donors from DNA methylation reactions and induces global DNA hypomethylation [82]. An unexpected finding was recently

reported in vivo, as a global dose-dependent hypermethylation of blood DNA was observed in Bangladeshi adults with chronic arsenic exposure. This effect was modified by folate, suggesting that arsenic-induced increases in DNA methylation were dependent from methyl availability [82]. The same group, however, subsequently reported that lower blood DNA methylation was a strongly associated with arsenic-induced skin lesions in a related Bangladeshi population [83].

Air pollution

Exposure to air pollution, particularly to particulate matter (PM), has been associated with increased morbidity and mortality from cardiorespiratory disease, as well as with increased lung cancer risk [84–88]. In a human study, Tarantini et al recently demonstrated that *iNOS* (*inducible Nitric Oxide Synthase*) promoter methylation decreased in blood samples of foundry workers with well-characterized exposure to PM_{10} in samples taken at the end of a four-day work week compared to baseline samples [89]. *iNOS* demethylation is expected to increase expression and activity of the iNOS protein, an established key player in inflammation and oxidative stress generation, two primary mechanisms that have been suggested to link inhalation of air pollutants to their acute health effects [90–92]. In the same study, long-term exposure to PM_{10} was negatively associated with methylation in both Alu and LINE-1 [89]. Decreased LINE-1 methylation was also observed in association to exposure to black carbon (BC), a marker of traffic particles, on 1,097 blood DNA samples from the Normative Aging Study (NAS), a repeated measure investigation of elderly men in the Boston area. As blood LINE-1 hypomethylation has been found in patients with cancer [93] and cardiovascular disease [94], such changes may reproduce epigenetic processes related to disease development and represent mechanisms by which particulate air pollution affects human health [94]. A recent occupational study has recently examined the effects of exposure to PM and metal components on miRNAs expression in 63 workers at an electric-furnace steel plant. miR-222 and miR-21 – two candidate miRNAs related to oxidative stress and inflammation – were overexpressed and positively correlated with the levels of lead exposure and oxidative DNA damage, respectively [95].

Aromatic hydrocarbons and other organic pollutants

High-level exposure to benzene has been associated with increased risk of acute myelogenous leukemia (AML) [96], which is characterized by aberrant global hypomethylation and gene-specific hypermethylation/hypomethylation. In a study of gasoline station attendants and traffic police officers, airborne benzene exposure was shown to be associated with a significant reduction in LINE-1 and Alu methylation in peripheral blood DNA [97]. Airborne benzene was also associated with hypermethylation in p15 and hypomethylation of the MAGE-1 cancer-antigen gene [97]. These findings show that benzene exposure at relatively low levels may induce altered DNA methylation reproducing the aberrant epigenetic patterns found in malignant cells. Also, benzene-associated demethylation of repetitive elements may help explain the epidemiological data linking benzene exposure with increases risk of multiple myeloma [98, 99], which also exhibits reduced methylation in Alu e LINE-1 repetitive elements [97]. These human data were recently confirmed by the finding of global hypomethylation in human TK6 lymphoblastoid cells treated for 48 hours with hydroquinone, one of the active benzene metabolites [100]. In a study of Polish male nonsmoking coke-oven workers, chronic exposure to PAHs has been shown to modify the methylation status of specific gene promoters (p53, p16, HIC1 and IL-6), as well as of Alu and LINE-1 repetitive elements [101]. Perera et al. published an exploratory study that used methylation sensitive restriction fingerprinting to analyze umbilical cord white blood cell DNA of 20 children exposed to PAHs. Over 30 DNA sequences were identified whose methylation status was dependent on the level of maternal PAH exposure [102]. Rusiecki et al. evaluated the relationship between plasma

concentrations of persistent organic pollutants and blood global DNA methylation, estimated in Alu repeated elements, in 70 Greenlandic Inuit, a population presenting some of the highest reported levels of POPs worldwide. In this work, a significant inverse linear relationship was found for DDT, DDE, β-BHC, oxychlordane, α-chlordane, mirex, several PCBs, and sum of all POPs [103].

Psychological stress

Earlier studies have indicated that DNA methylation is sensitive to environmental stressful exposures in early development and later in life [104–109]. The glucocorticoid receptor gene promoter was studied in the hippocampus of human suicide victims and controls [109]. Hypermethylation of the glucocorticoid receptor gene was found among suicide victims with a history of abuse in childhood, but not among controls or suicide victims with a negative history of childhood abuse [109]. On the contrary, positive early social experience might have a mitigating effect on stress responses later in life via epigenetic mechanisms, suggesting a protective role for positive early parental care [110, 111]. This is shown in animal studies that have demonstrated that higher maternal care, as reflected in higher licking and grooming of the pups, induces hypomethylation of the glucocorticoid receptor gene in the hippocampus and reduces responses to stress [110].

Shiftwork

Recent advances in the epigenetic field have revealed that chronobiological regulators may induce chromatin remodelling [see review 112]. CLOCK gene regulates circadian rhythm through a histone-acetyltransferase activity which promotes chromatin-remodelling events implicated in circadian control of gene expression [113, 114]. The circadian adjustment may be affected by different factors such as shift-work. According to several epidemiological studies shift-work that requires working at night can have a negative impact on the health and well-being of workers due to a mismatch between the endogenous circadian timing system and the environmental synchronizers (e.g. light/dark cycle) [115]. An epigenetic reprogramming of circadian genes has been proposed as a potential response altered circadian rhythms [116, 117]. A recent study on a population of night-shift workers has shown alterations in blood DNA methylation, including changes in Alu repetitive elements methylation and gene-specific methylation of inflammatory genes such as IFN-γ and TNF-α [118].

Conclusions and Future Perspectives

In the last few years, several investigations have examined the relation between epigenetic marks and lifestyle factors, including nutrition, behavior, stress, physical activity, working habits, smoking and alcohol consumption. Although epigenetic modifications are influenced by the environment, most of these changes tend to be re-established each generation; however, this does not happen at some loci in the human genome [119, 120]. The possibility that this phenomenon impacts successive generations is referred as transgenerational epigenetic inheritance [121–124]. Epigenetics is expected to help explaining how gene expression is modulated by lifestyle and environmental factors, and to bring a more complete understanding of individual responses to environmental cues and acquired risk factors (Figure 1). Because both epigenetic mechanisms and lifestyle are modifiable, epigeneticists have largely untapped opportunities to determine how tightly epigenetic markers are dependent on lifestyle factors and whether and how much epigenetic mechanisms can be modified after positive or negative lifestyle changes are acquired and sustained (Figure 2). Considering that epidemiological research are moving into new technologies such as epigenetics, many of the studies cited here should be taken as presumptive while there is no further evidence.

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Executive summary

Introduction

Lifestyle includes different factors such as nutrition, behavior, stress, physical activity, working habits, smoking and alcohol consumption.

Environmental and lifestyle factors may influence epigenetic mechanisms.

Nutrition

Folate and Vitamin B12 Intake

Epidemiological data support the anticarcinogenic property of folate.

A protective effect of low folate status against colorectal cancer was reported.

These contrasting results suggest that folic acid supplementation could exert a negative effect on already existing lesions.

Polyphenols

Polyphenols can impact DNA methyltransferases, Histone acetylases and Histone deacetylases inducing reversibility of epigenetic dysregulation.

Selenium

Selenium can impact the DNA methylation status interacting directly with DNA methyltransferases.

Obesity and Physical Activity

Macronutrient composition of the diet could help to develop obesity through epigenetic mechanisms.

Epigenetic mechanisms may be implicated in mediating the effects of physical activity.

Tobacco smoke

Tabacco smoke effects have been examined through different epigenetic studies, but the results are still under debate.

Smoking during pregnancy has been associated with increased risk for developing diseases in fetal or later life, through epigenetic mechanisms.

Alcohol consumption

Alcohol is an antagonist of folate metabolism and may have effects on DNA methylation.

Environmental pollutants

Arsenic

Hypo/hypermethylation was observed in blood DNA of subjects exposed to toxic level of arsenic.

Air pollution

Particulate air pollution may affect human health through DNA methylation alterations.

Aromatic hydrocarbons and other organic compounds

Repetitive element hypomethylation as well as either hyper- or hypomethylation of specific genes has been reported for benzene and PAH exposures.

Psychological stress

DNA methylation is sensitive to environmental stressful exposures early in development and later in life.

Shiftwork

An epigenetic reprogramming of circadian genes, changes in Alu repetitive elements methylation and gene-specific methylation of IFN-γ and TNF-α promoters have been observed.

Conclusion and Future Perspectives

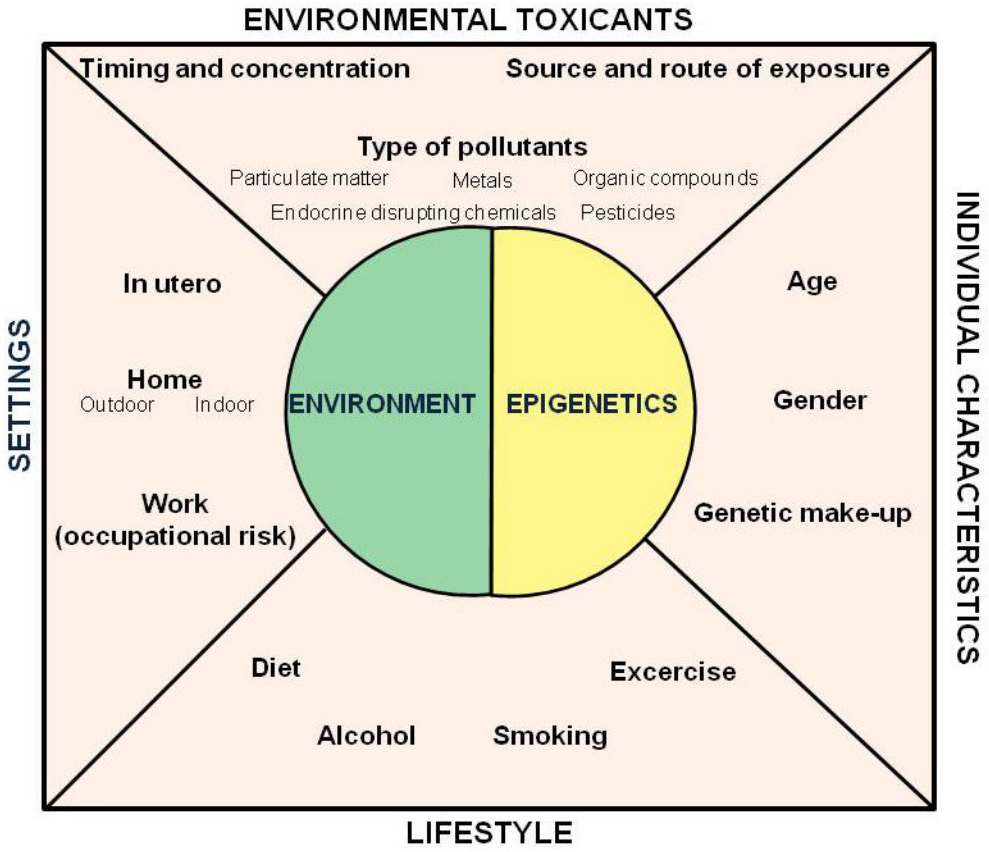

Fig. 1.
Environment-Epigenetics interactions

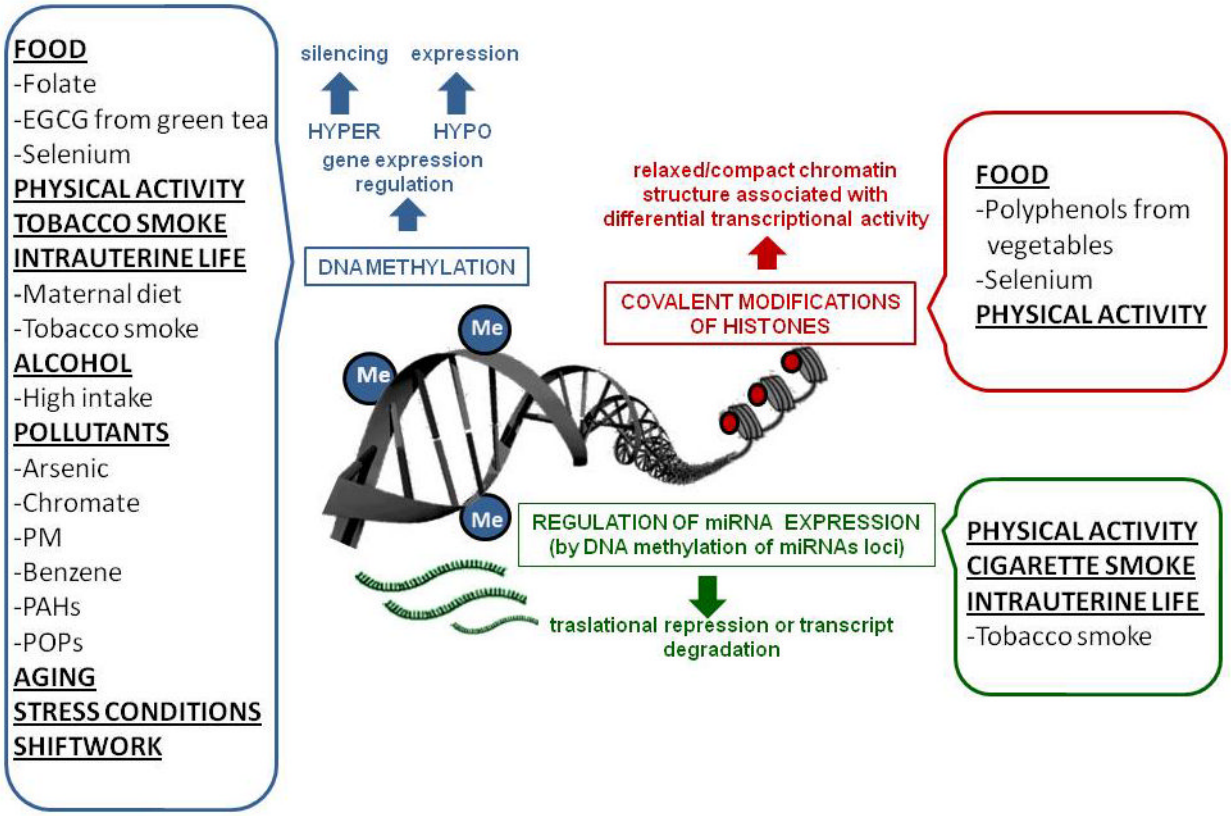

Fig. 2.
Lifestyle factors participating in environment-epigenetic interactions.

Table 1

Lifestyle factors with epigenetic effects

Factor	Example	Studies on:	Reference
Nutritional	Folate	humans	[16, 17]
	Phytoestrogen	breast benign human cells	[36]
		human cancer cells	[35]
	Polyphenols	human cancer cells	[27, 30–33]
		humans	28, 29
	Selenium	human cancer cells	[38]
Physical Activity	Exercise	human muscle biopsy tissues	[54]
		humans	[51, 55]
Tobacco Smoke	Cigarette smoke	humans	[63]
		lung cancer patients	[60]
	Cigarette smoke condensate	placentas	[65]
		respiratory epithelia	[59]
		rats and mice	[66]
Alcohol	High alcohol intake	humans	[73]
Pollutans	Arsenic	humans	[73–75]
	PM10	humans	[81, 87]
	Black carbon	humans	[86]
	Benzene	humans	[89]
	PAHs	humans	[93]
		human lymphoblastoid cells	[92]
		human umbilical cord blood	[94]
	POPs	humans	[95]
Emotional	Stressful experiences	rats	[97]
		mice	[100]
		suicide victims	[101]
Shiftwork	Working at night	humans	[107]