Review Article

Epigenetic mechanisms in cancer

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Abstract: This review aims to give a brief summary of the most common epigenetic mechanisms, and their possible relations with cancer initiation and progression, focusing on the possible physico-chemical factors that might control these epigenetic mechanisms, and giving examples of the epigenetic therapy approaches. Original and review articles encompassing epigenetics and inflammation were screened from major databases including PubMed, Medline, Science Direct, Scopus, etc. in English and analyzed for the writing of this review paper. The importance of epigenetics in linking the effects of environmental factors to changes in gene expression is gaining acceptance more and more in recent years. It is becoming more evident that epigenetics plays an important role in health and disease, cancer being no exception. Although effects of environmental factors on cancer initiation and progression have been known for decades, the exact mechanisms that control these interactions are yet to be discovered. The breakthrough that most epigenetic alterations are reversible brings out a new exciting target for cancer therapeutics. Cancer initiation and progression are controlled by both genetic and epigenetic events. Unlike genetic changes, epigenetic modulations are potentially reversible. Epigenetic drugs that inhibit DNA methylation or histone deacetylation enable reactivation of tumor suppressor genes and suppression of cancer cell growth. Taking advantage of these situations allows the reduction of malignant cell clusters. In addition, clinical results, such as epigenetic drugs targeting specific enzymes for cancer treatment and re-sensitizing cells that do not respond to treatment are promising as cancer therapeutics. To date, numerous epigenetic agents have been developed, several DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors have been definitively approved by regulatory agencies. Combined multidrug approaches for cancer treatment have overcome the limitations of single-agent epigenetic therapies, increased antitumor effects, and reduced drug resistance. It is evident that as our knowledge on epigenetic mechanisms expand, epigenomics-targeted treatments will become more common in cancer therapy, either as primary therapy or as complementary and alternative treatment options to increase the efficacy of conventional treatments for cancer patients, and epigenetics will maintain its increasing importance for cancer diagnostic, prognostic and therapeutic studies for many years to come.

Keywords: Epigenetics; gene regulation; cancer development and progression; epigenetic drugs

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History/introduction

A decade and a half ago it would have been unthinkable to see the emergence of headings like "The International Human Epigenome Consortium", "The NIH Roadmap Epigenomics Mapping Consortium", "The ENCODE Project", or the NIH's National Human Genome Research Institute's definition of Epigenome: "The epigenome consists of chemical compounds that modify, or mark the genome in a way that tells it what to do, where to do it, and when to do it" (1). After all, it was only 2003 when glorious assessments of the Human Genome Project were flooding scientific and popular publications alike. At the same time, however, the mechanisms for gene regulations were identified as "epigenetic" (2).

The observation that the environment influenced, or sculpted the phenotype of individuals, and these effects were represented in their descendants, goes all the way back, at least to 4th century BC, to Aristoteles (3). In more recent times it was Lamarck (beginning of 19th century), who, in his comprehensive framework for evolution, proposed the idea of inheritance of acquired characteristics, which nowadays is also termed as "soft inheritance" (4). A few years later the genius of Darwin came forward with his proposal on evolution by natural selection. Since those times Lamarckian and Darwinian formulations related to evolution and inheritance, with certain similarities, but also differences, occupied the mainstream debates in biological circles, with the Lamarckian line of thought steadily getting less and less attention (4,5).

The related debates were not only scientific in nature, but were colored with philosophical, religious and political overtones, especially in mid-twentieth century. It was 1942, when C. H. Waddington, a member of the theoretical biology club in Cambridge, UK (6) published what is considered by many the first modern description of epigenetics (7). Ten years later, around 1953, the polemics between the modern synthesis followers, who excluded/opposed the soft inheritance idea, and those who supported it (5) reached a point where ideological allegiances obscured the scientific differences; after all it was the height of the Cold War.

Whereas during the last half of the 20th century the celebrated discovery of the DNA's double helix structure catalyzed more attention to be paid to the genes and genomics (in 1990 the effort for the Human Genome Project started), in the beginning of this century more attention was given to a multitude of non-genetic influences in biology and society in general. As, unfortunately, it is usual practice in science sometimes to forget, or keep in oblivion important scientific discoveries that set the stage for specific ones to be the celebrated ones (8), in other cases there is a slow but persistent comeback, even from the grave (9).

The vast literature on epigenetics (there were more than 17,000 papers with the root "epigene" between 2010 and 2013) (10) is ever expanding, not only in basic biological systems (11) but in societal aspects, including psychology as well (12). Even dedicated conferences to the subject seem to deal with multiple aspects, from clinical epigenetics (epidemiology, autism) to mechanisms (RNAs as vectors of information transmission) (13).

Generally speaking, epigenetics comprises the studies of variance of gene expression during development and somatic cell proliferation. Or, in other terms, epigenetic mechanisms allow an organism to respond to the environment through changes in gene expression (2). The three most published molecular mechanisms that mediate epigenetic phenomena are DNA methylation, post translational histone modifications, and regulation of non-coding RNAs such as microRNA (miRNA) (14). With respect to cancer, epigenetic approaches to both understand its development, and treatment (14,15).

The increase of knowledge on epigenetics resulted in its reflection on the clinic with new diagnostic and therapeutic strategies. Epigenetics not only offers new insights into the changes in gene regulation that occur during the disease process, but also provides the basis for epigenomics-based targeted therapies. There are many agents currently being tested in clinical trials and some of them are already in clinical use. In addition, drug research and development studies carried out to correct epigenetic errors have gained great speed in recent years. Targeting histone deacetylases (HDACs) and DNA methyltransferase (DNMT)/histone methyltransferase (HMT) are used as possible targets in the treatment of various types of cancer. There are FDA-approved HDAC inhibitors and DNA methylation inhibitors (DNMTIs). Their clinical use gives successful results. Apart from these, histone methylation and miRNAs have also attracted attention as potential therapeutic targets. Combined treatment options of standard chemotherapeutic drugs with epigenetic targeting drugs make it possible to reactivate genes sensitive to chemotherapeutic drugs. It is thought that epigenetic studies will continue for many years and will provide indispensable advantages in many diseases.

This review aims to give a brief summary of the most common epigenetic mechanisms, their possible relations

with cancer initiation and progression, focusing on the possible physico-chemical factors that might control these epigenetic mechanisms, and giving examples of the epigenetic therapy approaches. Research articles, books, and other published texts were examined using integrative methodology.

Epigenetic mechanisms of gene regulation

In cancer development, epigenetic mechanisms may directly alter the expression of oncogenes, tumor suppressor genes and other tumor-related genes. Hypermethylation or hypomethylation, especially in the gene promoter regions, global genomic hypomethylation, improper expression of DNMT, histone modification disorders and abnormal expression of non-coding RNAs are the most common epigenetic changes observed in cancer.

DNA and RNA methylation

Among all epigenetic mechanisms, DNA methylation is the most studied. DNMT enzyme catalyze DNA methylation reaction using S-adenosyl methionine as the methyl donor, resulting in 5-methylcytosine (16-18). The most important DNMT enzyme in cancer development is DNMT1 (19). Methylation usually occurs in CpG (cytosine nucleotide followed by a guanine nucleotide) islets clustered in concentrated DNA. While the promoter region that is located at the 5'-end of the human gene is in unmethylated state, the gene is active and allows expression (20). Methylation of this promoter region is usually results in "gene silencing". Inactivation continues in the daughter cells (21,22). This epigenetic change appears as an alternative pathway to mutation or deletion, which are other causes of gene suppression. Aberrant promoter methylation has been reported to affect several genes regulating cell cycle, adhesion, apoptosis, signal transduction, DNA repair, adhesion and cell differentiation (23,24).

A proportion of 60–80% of the ~29 million CpGs in the human genome are methylated. At least 98% of DNA methylation observed in somatic cells is at a CpG dinucleotide site, while in embryonic stem cells (ESCs) up to a quarter of methylations occur at a non-CpG site. Defects in DNA methylation have been shown to be related with cancer, but no DNMT mutation or deficiency has been identified as a cause of tumor development. Distinctive features of epigenetic changes seen in cancer include global DNA hypomethylation and locus-specific hypermethylation of CpG islands (CGIs) (25). To date, all tumor samples examined show reductions in global DNA methylation (26).

In summary, DNA hypomethylation is mainly observed in heavily methylated repeating body elements and intergenic regions, which causes instability in the genome and activation of oncogenes. Locus-specific hypermethylation, on the other hand, is usually observed in the promoter CGI islets of tumor suppressor genes and results in inherited transcriptional silencing (27).

Unlike DNA methylation, which is a transcriptional modification, RNA methylation is a post-transcriptional modulation. Although it was discovered about 50 years ago, RNA methylation has only recently attracted attention, due to lack of analytical techniques for determining, characterization and sequencing it. There are more than 170 kinds of RNA modifications identified, yet more is expected to follow (28,29). The demethylases, or "erasers" (like ALKBH5, FTO), and methyltransferases, or "writers" (like METTL3/14, KIAA1429 WTAP), and decoder proteins, or "readers" (like YTH, HNRNP) have been discovered more recently, and have led to important discoveries in "epitranscriptomics". Among other RNA methylations like m^1A, m^5C or m^6Am, the most commonly observed and studied RNA methylation is the N^6-methyladenosine (m^6A). This notation describes methylation of the adenosine residue at the N-6 position (28-30). These reversible and very dynamic modifications affect all types of coding and non-coding RNAs, therefore are effective in all fundamental cellular processes (30). So, it is no surprise that they have also been found to be associated to several types of cancers, including leukemia, breast, bladder, colorectal, endometrial, hepatocellular, gastrointestinal, lung, liver and pancreas cancers, and epithelial mesenchymal transition (EMT) of metastatic cancer cells (30-32). METTL3, in particular, is now accepted as a biomarker for cancer (30). RNA methylation is shown to also interact with other types of epigenetic modulations, pointing out its strong regulatory role (28). With its broad range of biological effects, RNA methylation modifications have a great potential for unraveling complex cellular mechanisms in health and disease, and are powerful epigenetic therapy targets.

Histone modifications

Histones, the proteins by which the DNA is packaged in chromatin, undergo various post-translational modifications like acetylation, phosphorylation, ubiquitination and ADP ribosylation, usually at their N-terminal tails (33,34).

Histone modifications can interact with each other, as well as with DNA methylation, and these interactions can modify the higher order chromatin structure.

Lysine residue acetylation forms chromatin, while their deacetylation correlates to transcriptional repression (35). On the other hand, lysine and arginine residue methylation takes place at histones H3 and H4 by HMTs (36). Different transcriptional events take place based on the location and type of methylated histone. Trithorax group (TrxG) and polycomb group (PcG) of proteins are the two main types of complexes found in histone modifications. Some of these protein groups exhibit HMT activity (37). It has been shown that covalent modifications of histones constitute the link between DNA methylation and gene chromatin silencing (38,39).

miRNAs

MiRNAs are small molecules consisting of approximately 25 nucleotides, synthesized in the nucleus and released into the cytoplasm, binding to mRNAs and causing their expression to change (40). As each miRNA can affect many mRNAs, each mRNA is also under the influence of many miRNAs (41). MiRNAs are encoded within the intergenic regions, introns or exons of protein-coding genes, and they are believed to be co-regulated by host genes (42-44). First a few kb-long primary miRNAs (pri-miRNAs) are synthesized by RNA polymerase II (45,46). Pri-miRNAs are then processed in the nucleus into a precursor miRNA (pre-miRNA) of approximately 70 kb in length (47). The pre-miRNA binds with exportin 5, and is transported from the nucleus to the cytosol. This reaction is catalyzed by a Ran-GTP. Mature miRNA duplex of 22–25 nucleotides in length is synthesized by RNase III enzymes in the cytosol (48,49). After the double-stranded miRNA complex binds to the RNA-induced silencing complex (RISC), the passenger strand is removed while the guide strand remains in the complex and acts as a template to form a new RISC (50). MiRNA molecules can bind to their target genes through the 3' untranslated region (3'UTR), 5'UTR or other gene regions to induce translational repression (51). The “seed” of the miRNA molecule, which is 2–8 nucleotides, binds to the target site, and is essential for functionality and target specificity. The degree of complementarity between the seed and the target is essential for the regulatory mechanism (52,53).

MiRNAs are highly conserved across different species and they regulate several cellular processes, including development, proliferation, differentiation and apoptosis (54-56).

MiRNAs are shown to be linked to cancer, and they can function as oncogenes, as well as tumor suppressor genes (52,57-60). MiRNA expression is epigenetically altered in a tissue-specific manner in both physiological and pathological conditions. They affect the protein levels of target mRNAs without altering their gene sequences. They function at different levels of the genome, can regulate and/or be regulated by other epigenetic actors, such as DNA methylation and histone modifications (61-63), or key enzymes responsible for epigenetic reactions, such as DNMTs, HDACs, and HMTs (64,65). Aberrant methylation patterns of CGIs near or within miRNA genes have been reported to cause a failure in the expression of key miRNAs and resulting pathogenic changes, including tumorigenesis (66). Moreover, some miRNAs can directly affect gene expression at the transcriptional level in the nucleus by complementing the promoter regions of specific genes. In contrast, other miRNAs can affect other chromatin modifiers that cause transcriptional silencing. The interaction between miRNAs and other epigenetic is orchestrated to maintain normal physiological functions. The disruption of this interaction has been associated with many diseases, including cancer (61). CGI hypermethylation that is shown to downregulate tumor suppressor miRNAs is emerging as a common feature of cancer (67,68). On the other hand, hypomethylation of CGIs activates gene expression and has been reported to promote cancer formation (4).

The epigenetic regulation of some miRNAs in cancer types is shown in *Table 1*.

Physico-chemical factors on epigenetic mechanisms

Somatic mutations have been identified in many tumor suppressor genes, oncogenes, and cancer-related genes. However, studies have shown that mutations are not sufficient to cause such a disease. When biological processes, such as the formation, proliferation and metastasis of cancer cells are examined at the molecular level, it has been observed that both genetic and epigenetic factors play a role in these biological processes. Epigenetic modifications required for mammalian development and cell proliferation are disrupted by environmental causes. Transcriptional changes occur with disruption of epigenetic processes and malignant cellular transformation is observed. It has been reported that physical and chemical factors, such

Table 1 Some shown epigenetic regulations of miRNAs in cancer types

Cancer types	Target	miRNAs	Function	References
Lung	–	miR-1973, miR-494, miR-4286, miR-29b-3p	Reduced apoptosis, higher resistance of chemotherapy	(69)
Breast	*KDM5B*	miR-137	Migration	(70)
Colorectal	*TCF4*, *SUZ12*	miR-145, miR-132, miR-212	–	(71)
Glioma	–	miR-424	Tumor suppressor, migration, down-regulated by DNA methylation	(72)
Gastric	–	miR-196b-5p	Migration, invasion	(73)
Lung	*CCNE1*	miR-1179	Tumor cell growth suppressor	(74)
Bladder	*DNMT3A*, *PETN*	miR-29	–	(75)

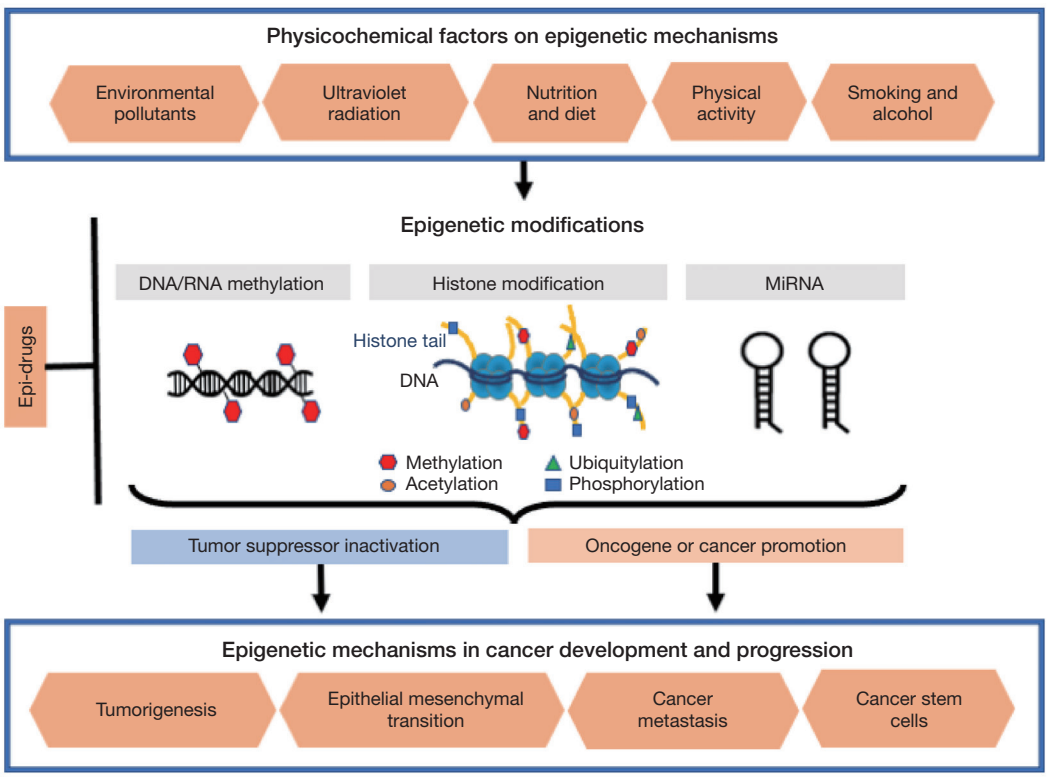

Figure 1 A summary of the physico-chemical factors that alter epigenetic modifications, and their most common routes that affect cancer development and progression.

as environmental pollution, ultraviolet radiation (UVR), nutrition, alcohol and smoking, and physical activity directly affect the disease mechanisms. Understanding the epigenetic mechanisms of these physicochemical factors in the development and progression of cancers will enable us to design our lifestyle and diet, thereby reduce cancer risk and monitor response to treatment. The reversibility of epigenetic modifications may enable the development of new therapeutic strategies targeting these modulations for the prevention and/or treatment of physico-chemically induced cancers. *Figure 1* summarizes the possible role of key physico-chemical factors, which along with aspects of

Table 2 Environmental pollutant effect on epigenetic modifications

Environmental pollutants	Pollutants	Functions/effect	References
Air Pollutant	Particulate matter (PM)	Global DNA hypomethylation, P16 gene promoter hypermethylation, and changes in site specific methylation, acetylation, and phosphorylation of histone H3	(83,86,87,89,94)
	Black carbon (BC)	Modulation in allergic asthma gene methylation	(89,95)
	Nitrogen dioxide (NO_2)	Global DNA methylation or gene specific CpG methylation	(96-99)
	Polyaromatic hydrocarbons (PAHs)	Global hypomethylation and hypermethylation of specific genes	(81,82,100)
Heavy metals	Arsenic (As)	Inhibition of DNA methyltransferase and induction of ROS formation	(91,101)
	Nickel	Inhibition of DNA hypermethylation (H3K9 mono- and dimethylation), DNMT, and histone H2A, H2B, H3 and H4 acetylation, DNA mutation, ROS generation	(93,102,103)
	Mercury (Hg)	Increase of DNA methylation at the promoter region of the glutathione S-transferase mu1 (GSTM1)	(90,104,105)
	Cadmium (Cd)	Inhibition of DNMTs activity, DNA hypermethylation and hypomethylation	(92,105-110)
Organic pollutants	Benzene	Decrease of DNA methylation in both Alu and LINE-1	(111-115)
	Diethylstilbestrol (DES)	Aberrant DNA methylation of the Hoxa10 gene in utero	(116)
Chemicals in drinking water	Chlorination	Increased carcinogenic risk	(117)

DNMT, DNA methyltransferase; ROS, reactive oxygen species.

everyday lifestyle, influence epigenetic mechanisms.

Environmental pollutants

Environmental pollutants, especially air pollutants, heavy metals, organic pollutants and chemicals in drinking water alter gene expression through epigenetic mechanisms (76-79). Air pollution contributes to inflammation and disease development, including cardiovascular diseases, metabolic disorders, asthma and chronic diseases, as well as cancers, due to its harmful components. For example, carbon black (usually from incomplete combustion exhaust gases), nitrogen oxides and polyaromatic hydrocarbons (PAHs) present in polluted air cause decrease in DNA methylation (76,80). PAHs, which are byproducts of the combustion of incomplete fossil fuels or organic elements, are classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) (81,82). Most studies of particulate matter and short-term exposure to carbon black have been associated with DNA methylation in steel, oil refinery or petrochemical processing industrial settings (83-86). On the other hand, there are only few studies investigating the effects of other environmental pollutants such as O_3, NO_2 or SO_4 on epigenetic modifications. NO_2 has been reported to cause high levels of DNA methylation in the *ADRB2* gene (87,88), which is associated with severe asthma patients, while SO_4 was associated with decreased LINE-1 methylation (84), and other varying methylation levels in several genes related to asthma (89).

Trace amounts of heavy elements with previously documented carcinogenicity, such as mercury (90,91), arsenic, cadmium (92), and nickel (93), which enter the body in various ways, may lead to genetic and epigenetic changes in different cancer-related genes of somatic and stem cells. For this reason, the underlying epigenetic mechanisms of these trace elements and compounds and their relationship with cancers in heavy metal-contaminated areas are investigated. Examples of studies on epigenetic changes caused by environmental factors are given in *Table 2*.

Ultraviolet radiation

Solar UVR is expected to play a significant role in skin

tumorigenesis (118,119). Overexposure to solar UVR, especially to ultraviolet B light (UVB, 290–320 nm) component (120), can cause several harmful effects on human skin, including sunburn, photoaging and immunosuppression (121-123). UVB causes DNA damage, epigenetic lesions and irregular gene expression, leading to the main types of skin cancers, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma (124). DNA damage and epigenetic modulations may occur independently, as well as they may affect each other in response to UVR. Studies on biomarkers to distinguish skin lesions have reported hypermethylation of several known tumor suppressor genes related to skin cancers, such as *CDH1*, *CDH3*, *LAMA3*, *LAMC2*, *RASSF1A* (125), which causes gene silencing without a change in the coding region. Epigenetic inactivation of RB1/p16 and p53 pathways was also shown in cutaneous SCCs (119). Studies have also shown UVB induced hypoacetylation of histones H3 and H4 in the transcriptionally silenced regions of tumor suppressor genes (126). It is suggested that there is a C→T transition in the di-pyrimidine domains in skin lesions resulting from UVR, and resulting cyclo-butane pyrimidine dimer formation (127). C5-methylation, which occurs at position 5 of cytosine, plays an important role in epigenetic mechanisms involved in the regulation of various biological processes, from cell differentiation to gene expression (128). Recent studies show that ~40% of melanomas are associated with C5-methylation (129,130). As with other environmental factors, DNA methylation is also used as a marker for UVR exposure.

Nutrition and diet

Diet is one of the environmental factors that are more easily studied, and therefore better understood in epigenetic change. There are quite a few dietary components, such as folate, cinnamic acids, polyphenols, resveratrol, cruciferous sulforaphane and isothiocyanates, lignans, selenium and vitamin E are considered to have anti-cancer effects by affecting epigenetic modifications (131-139).

Folate regulates single carbon metabolism that is required for synthesis of DNA, proteins and phospholipids (140). Folate is acquired only through diet. In the body, it is converted to 5,10-methylenetetrahydrofolate (MTHF) which is a significant methyl donor, and is used in methylation of DNA (141-143). Folate deficiency causes a few possible cancer mechanisms, including mutations, DNMT1 inhibition and aberrant global and promoter methylation (135,144-146). Polyphenols that are abundant in plant-derived foods are powerful antioxidants (147), and they inhibit hypermethylation by interacting with the catalytic domain of DNMT1 (116,148). Certain dietary components have similar effects to HDAC inhibitory drugs, causing cell cycle arrest and/or apoptosis in cancer cells (149). A recent study in mice has shown that an omega-3 fatty acid rich maternal diet epigenetically pre-programmed particular genes in the off springs with an increase in acetylation of H3K18 histone and a decrease in H3K4me2 on nucleosomes, that caused a significant protective effect against breast cancer (150).

To investigate the effects of a food on epigenetic changes and disease risk, the intake of that food has to be evaluated in a sufficient number of human samples (78,147). There are studies that support the role of dietary components on epigenetically regulated gene expressions, but the mechanisms of action of these dietary components are still under investigation.

Smoking and alcohol

Cigarette smoke poses a risk for various diseases, such as cardiovascular diseases, chronic obstructive pulmonary disease (COPD) and cancers (151-155). Numerous chemicals in tobacco have toxic effects, including N-nitrosamines, polycyclic aromatic hydrocarbons (benzo[a] pyrene), alkaloids (nicotine and its main metabolite, cotinine), heavy metals (nickel, cadmium, chromium, and arsenic) and aromatic amines (156,157). Smoking causes DNA damage and alteration in DNA methylation and transcription regulation (151,153,157). Altered DNA methylation due to smoking has been studied a lot. Exposure to cigarette smoke raises carbon monoxide levels in the blood, which decreases oxygenation in the body and causes hypoxia, resulting in increased synthesis of S-adenosylmethionine (SAM), one of the main methyl donors, leading to DNA methylation (158).

CYP1A1 and *AHRR* are among the few genes known to be hypomethylated due to smoking. *CYP1A1* is important for the detoxification of carcinogens, while *AHRR* inhibits the aryl hydrocarbon receptor that metabolizes harmful chemicals. Therefore, inhibition of their functions by hypomethylation increase cancer risk (100,159). Although smoking, in general, leads to decreased DNA methylation, a few critical genes for cell cycle regulation, such as p16 and p53, become hypermethylated due to smoking (160). Loss of function of p16 and p53 can lead to cancer as a result of dysregulation of the cell cycle and uncontrolled cellular

divisions (160,161).

Alcohol consumption has been classified as a carcinogenic factor by the IARC and has been associated with various types of cancers (162-166). In general, studies on epigenetic effects of alcohol have focused on DNA methylation and the association of 'global' methylation levels with alcohol dependence (166,167). DNA damage induced carcinogenic effect of alcohol is usually associated with ethanol and its metabolite, acetaldehyde, and altered transmethylation reactions (164). Alcohol can also change DNMT activity. While rare alcohol consumption is associated with global hypomethylation, chronic consumption was shown to induce gene-specific DNA hypermethylation, that may lead to cancer. A global increase in histone modifications in oral carcinogenesis has been associated to exposure to ethanol and resulting increases in H3K9/14 and H3K27 acetylation and methylation (168).

Disruption of single carbon metabolic pathway due to alcohol induced by folate deficiency and products of ethanol metabolism has also been reported to cause epigenetic changes associated with cancer development (169,170). Long-term heavy ethanol consumption has been shown to result in elevated homocysteine and S-adenosyl-homocysteine (SAH) levels and decreased SAM and antioxidant glutathione (GSH) levels (143,144,171).

Chronic alcohol consumption has been shown to cause inhibition of the ubiquitin-proteasome pathway in the nucleus, and resulting epigenetic changes. Ethanol metabolism also produces reactive oxygen species (ROS) that can change DNA methylation patterns, increase NADH levels, lead to histone modifications, and induce cancer development (171-174). Chronic high-dose alcohol use also affects some miRNA families, which may also be associated with cancer development (175).

Physical activity

Exercise is strongly emphasized as a strategy for prevention of cancer, as well as for supporting the treatment phase. Yet, epigenetic mechanisms related to exercise are not clearly understood. Physical activity, when done regularly, leads to various epigenetic changes that will benefit cancer patients, such as hypermethylation in the promoter regions for tumor suppressor genes and hypomethylation in the promoter regions of oncogenes (176-178).

The mechanisms that physical activity affects cancer vary depending on age. A large loss of DNA methylation is seen with aging (179) due to the involvement of methyl deoxycytidine, a cytosine methylated at the 5' carbon of a cytosine (180). The intensity of physical activity is directly related to the amount of promoter demethylation and activation of the expression of many genes (178).

It has been reported that HDACs are highly expressed in muscles, and miRNAs can also be regulated by physical activity (181-183). Furthermore, histone acetylation has been reported to cause selective transcription or inhibition of specific genes related to cancer (184) posttranslational modifications in skeletal muscle (185) or behavioral diseases (180), by specifically modulating H3 and H4. A recent study has shown that sedentary and trained rats with prostate tumors have shown different levels of miR-27a-5p, and exercise increased global DNA methylation while decreasing DNMT expression in the tumor tissue (186). These results support the idea that exercise might reverse the epigenetic modifications due to cancer in tumor tissue.

Stress reduction and lifestyle

Relation between stress and cancer has been well recognized. High stress levels and unhealthy lifestyle reduces the potency of the immune system, which, in turn leaves the people prone to several diseases, including cancer. Involvement of epigenetic factors are also becoming more evident as our understanding of these mechanisms grow. A non-clinical study has shown that a group regularly exercising yoga in order to reduce stress has shown reduced DNA methylation levels in tumor necrosis factor (TNF) regions, along alterations in several other immune system markers (187).

The Lifestyle Medicine Research Summit that was assembled at the University of Pittsburgh on December 4–5, 2019 has determined six core areas of lifestyle medicine that further research needs to focus: plant-predominant nutrition, physical activity, sleep, stress, addictive behaviors, and positive psychology/social connection. All of the determined areas show evidence of epigenetic factors in health and disease and calls for the promise of epigenetic therapy options (188). A recent comprehensive review also gathers literature that correlates epigenetic alterations with lifestyle parameters, such as malnutrition, smoking, high-fat/high-sugar diets, obesity, infections, alcohol consumption, sleep deprivation, chronic stress, air pollution, and chemical exposure, particularly focusing on the effects of epigenetic mechanisms on inflammation (189).

Epigenetic mechanisms in cancer development and progression

Abnormal epigenetic alterations in tumorigenesis

Many types of cancer are associated with aberrant DNA methylation. Global hypomethylation potentially influences cancer tumorigenesis of 5mC-containing sequences, particularly through tumor suppressor genes and deamination of methylated cytosine (190). Coexisting of several epigenetic mechanisms in tumors, including promoter CGI hypermethylation or hypomethylation, and silencing of tumor suppressor genes, suggest that epigenetics might be central to cancer progression (191,192). Promoter hypermethylation has also been reported to up-regulate expression of tumor-promoting genes, such as *BCL2* (193), *MDR1* (194), *HOX11* (195), *cMYC* (196).

Some DNA methylation changes in cancer are thought to result from mutations in the citric acid cycle. Epigenetic modifications are generally considered as reversible, but some modifications are conserved throughout cancer progression. This provides the advantage that they can be used to classify the disease and predict treatment. In this respect, H3 acetylation and H3K9 di-methylation can identify prostate cancer (PCa) and non-malignant prostate tissue. Similarly, H3K4 tri-methylation is suggested as an important marker of prostate specific antigen (PSA) recurrence (197,198). EZH2 expression, is associated with the aggressiveness of prostate, breast and endometrial cancers (199).

Cancer development includes epigenetic changes both in DNA and chromatin (25,200-202). It is known that promoter DNA hypermethylation of DNA repair genes causes genetic changes (203,204). For example, O(6)-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme, can potentially reverse the effects of chemotherapy and radiotherapy. Silencing of MGMT by hypermethylation is suggested to support the treatment (205,206).

Role of epigenetics in EMT and cancer metastasis

The process of epithelial-mesenchymal transition (EMT) in cancer progresses through changes in the morphological features of polarized epithelium, including loss of apical-basal polarity, motility, and cell-cell adhesion (207-209), and acquisition of mesenchymal properties, such as resistance to apoptosis, increased cell motility and invasiveness (208,210,211). Therefore, it is highly associated with metastasis, poor prognosis, blood intravasation (212,213) and resistance to therapy (214). The accumulation of genetic and/or epigenetic changes in tumorigenic cancer precursor cells during cancer development, mostly during the EMT, causes the tumor cells to metastasize to other organs by acquiring a mesenchymal phenotype. EMT is modulated by a variety of stimuli, including tumor-stromal cell interactions, signal (cytokine/growth factor) transduction and hypoxia (215-218).

During EMT, epithelial cells lose E-cadherin expression, resulting in the release of β-catenin (219). Epigenetic mechanisms, such as CpG hypermethylation, acetylation of KLF5 and histone modifications were shown to initiate EMT (220-224). MiRNA-30 was shown to regulate TGF-β and TGF-α induced EMT (225). MiRNAs 143 and 145 were associated with EMT and bone metastasis of PCa (226), while miRNA-1 and miRNA-200 family were shown to inhibit EMT and metastasis by hindering ZEB1 and ZEB2 transcription factors (227-229). *p53*, a tumor suppressor gene, was shown to regulate EMT through regulating miRNA-200 family (230). Inhibition of miRNA-200 family was shown to increase EMT and metastasis in high-grade breast cancers by increasing H3K27me3-mediated chromatin remodeling and DNA methylation in immortalized human bronchial epithelial cells (227).

DNA methylation of the E-cadherin promoter induces HDACs to be recruited to the region, resulting in histone deacetylation and transcriptional silencing (231). Silencing of EZH2, which is also associated with E-cadherin repression, was also shown to inhibit migratory and invasive characteristics of different cancer cells (232,233), while treatment of some cancer cells with DNMT inhibitors increased their invasiveness, tumorigenicity, and metastatic properties through upregulation of EMT-related genes (234). It has also been reported that histone methylation of the *CDH1* promoter also increase invasiveness through suppression of E-cadherin expression (68,235,236).

Role of epigenetics on the cancer stem cell (CSC) model

CSCs, or tumor initiating cells, are a small subpopulation of cells within tumors that show stemness properties, like self-renewal and differentiation, and form the different cell types that make up the heterogeneous tumor mass. CSCs are thought to be responsible for cancer initiation and progression, and resistance to conventional treatment modalities (206,237). There is very little known about the epigenetic regulations in CSCs, but they show quite similar characteristics with ESCs. ESCs are known to maintain

their self-renewal abilities even without DNMTs (238,239). However, differentiation of ESCs was found to be almost completely inhibited in the absence of DNMTs. Global DNA hypomethylation was shown to silence pluripotency factors and induce differentiation. ESCs have been reported to preserve their epigenetic memories, and their epigenomes are considered highly stable (240,241).

DNA methylation has also been shown to regulate differentiation of somatic stem cells, like myeloid cells (242), and mesenchymal stem cells (MSCs) (240,243-245). DNA methylation patterns of human MSCs are also found to be quite stable in long-term culture. However, DNA methylation levels differ with aging in regions with H3K9me3, H3K27me3 and EZH2 targets (246,247). Thus, DNA methylation has been suggested as a good molecular marker in characterization of MSCs (247). Epigenetic characterization of CSCs is not well documented in the literature; but it is strongly possible that similar epigenetic control of CSCs with ESCs and MSCs should be observed.

Epigenetic mechanisms have been shown to transform normal stem cells into CSCs when they cause abnormal changes in the differentiation capacity of the stem cells (248,249). For example, isolated human breast CSCs appeared to express low levels of let-7 compared to differentiated breast cancer cells (249). Overexpression of let-7 decreased EZH2 levels and stemness properties of PCa cells, resulting in suppressed clonogenicity and sphere-forming capacity, whereas loss of let-7 increased the expression of EZH2 contributing to PCa invasiveness (250). Since epigenetic mechanisms are regulated under the influence of extracellular changes, they create intratumoral heterogeneity that may promote CSC status. Several miRNAs involved in development are associated with PcG complexes and DNA methylation, and they have an active role in maintaining the balance between self-renewal, proliferation and differentiation in CSCs (52,206,250-253). Thus, epigenetic alterations boost CSC stemness and survival, and contribute to tumor initiation and progression.

Recent studies have reported that, among heterogenous cancer cell populations, those that show both CSC and EMT-like characteristics are more resistant to chemotherapy (254-256). Findings suggest that epigenetic modulations that give these cells CSC and EMT characteristics, as well as abnormal changes in their signaling pathways, such as Wnt/β-catenin or Notch that influence their response to therapy (256-259). Thus, these pathways, and their epigenetic regulations are potential candidates for overcoming drug resistance and CSC targeted therapy.

Current epigenetic treatment approaches and epi-drugs

Early diagnosis in cancer, predicting the prognosis and determining the treatment options is a very laborious and difficult process. “Epigenetic therapy” has become an emerging therapeutic approach (260-263). The fact that epigenetic changes in the genome are reversible provides a new hope for cancer treatment (264). Today, researchers are studying the epigenetic changes seen at different stages of cancer in order to develop new diagnostic and therapeutic approaches for various cancer types. There are FDA approved DNMTIs and HDAC inhibitors, and many more agents that are found to alter methylation patterns or modification of histones on DNA are currently being tested for use in clinics.

DNA methylation inhibitors

Promoter DNA methylation can be used to as a diagnostic marker to molecularly classify cancer, to predict cancer progression, as well as a therapeutic target (265-270). DNMTIs suppress tumor growth and induce apoptosis. Thus, they can restore the activity of tumor suppressor genes. The stability of first generation DNMTIs acting as cytosine analogues is inactivated by cytidine deaminase. Second generation DNMTIs are designed against degradation by cytidine deaminase in order to overcome the stabilization and toxicity problems. Currently available DNMTIs work at the enzymatic level, resulting in global DNA hypomethylation. Although this is therapeutically useful, global hypomethylation has some limitations, such as possibility of oncogene activation and/or increased genomic instability. Promotors located on the repetitive elements in oncogenes can be inactivated by DNA hypomethylation (271). The development of novel DNMTIs targeting specific genes or gene groups, as opposed to global hypomethylation, is a promising approach for more controlled and targeted therapy. Another issue is that DNMTIs are usually activated during the S-phase of the cell cycle. This feature affects fast growing cells, therefore works on highly proliferative cancer cells. However, it does not provide enough clinical benefit in the treatment of diseases that do not have rapid cell cycle. In addition, DNA methylation levels were shown to return to pretreatment levels upon withdrawal (263). Therefore, continuous application is required. A selected list of literature on DNMTIs is given in *Table 3*. In summary, although DNMTIs are clinically successful, novel inhibitors with

Table 3 Examples of DNA methylation inhibitors that have been tried in different cancer types

DNMT inhibitors	Class	Generation	Function	Cancer types
5-azacitidine	Nucleoside analogs	First	Sensitizes tumor cells to T-cell-mediated cytotoxicity, enhances efficacy of multiple chemotherapy drugs	Myelomonocytic leukemia (272); lung cancer (273); pancreatic adenocarcinoma (274)
5-aza-2-deoxycytidine (decitabine)			Anti-cancer effect, modulates EMT	Ovarian cancer (275); breast cancer (276); pancreatic cancer (277)
5-aza-fluoro-2- deoxycytidine		Second	Inhibits cancer cell proliferation	Colon cancer (278)
4-deoxyuridine (zebularine)			Inhibits DNA methylation by getting incorporated into DNA	Lung cancer (279); colorectal cancer (280)
RG108	Non-nucleoside analogs	First	Induces radio sensitivity, inhibits cell proliferation	Esophageal cancer (281); endometrial cancer (282)
EGCG			Suppresses tumor growth, inhibiting NF-κB activation and cell proliferation	Cervical cancer (136); colorectal cancer (137); lung cancer (283)
Psammaplin			Induces cell cycle arrest, inhibits growth and metastasis	Endometrial cancer (284); lung and glioblastoma (285); breast cancer (286)
Hydralazine			Induces radio sensitivity	Prostate cancer (287); cervical cancer (288,289)

DNMT, DNA methyltransferase; EMT, epithelial mesenchymal transition; EGCG, epigallocatechin gallate; NF-κB, nuclear factor kappa B.

higher specificity and cell cycle independence need to be developed to overcome their limitations.

HDAC inhibitors

Histone modifications are more unstable than DNA methylation due to the imbalance between histone modifying enzymes (290). So, natural balance can be achieved by correcting the enzyme level in the affected cells. In cancer, it is seen that HMT and histone demethylase enzymes are imbalanced, and there is a global decrease in HDACs (291-296).

Currently, studies are underway to find novel molecules that can minimize the problems with HDACIs by selectively inhibiting specific HDACs, such as HDAC6 and HDAC8 (297-299). A selected list of literature on HDAC inhibitors is given in *Table 4*. Better exploration of novel and target specific HDACIs will result in more potent therapy options.

Combining epigenetic treatment approaches to increase therapy efficacy has been tried since 1990's (336). The combined use of DNMT and HDAC inhibition has shown clinical benefits (296,337). Epigenetic drugs can also be combined with conventional treatment options to obtain a stronger response and/or overcome resistance to chemotherapy or radiotherapy. It should be noted that the success of the combination of epigenetic modulations and chemotherapeutic drugs depends on the epigenetic profile of the particular patient and particular cancer type.

Conclusions and future perspectives

Epigenetics plays an important role in cancer development and progression. Early detection of certain epigenetic changes may have predictive and prognostic value in certain cancers. Botanical compounds and pharmaceuticals may be used to modify epigenetic changes to prevent and treat cancer. Integrative oncology includes the use of botanicals, mind-body practices, psychological stress reduction techniques and healthy lifestyle, including physical activity, healthy diet and stress reduction, which have profound epigenetic effects through reduction of oxidative stress and inflammation. Integrative oncology interventions focusing on physical activity, diet and stress reduction may have a role in prevention of cancer development and progression.

Table 4 Effects of HDAC Inhibitors of different classes on cancer types

HDAC inhibitors	Class	Function	Cancer types
Trichostatin A	Hydroxamic acids	Inhibits cancer cell viability and displays anti-tumor activity	Lung, breast cancer and skin cancer (300); breast cancer (301)
SAHA		Inhibits tumor cell growth	Breast cancer (302); pancreatic cancer (303)
Belinostat		Inhibits growth and displays anti-tumor activity	Pancreatic cancer (304)
Resminostat		Blocks platelet-induced HCC cell invasion	Hepatocellular carcinoma (305); pancreatic cancer (306); lung cancer (307)
Abexinostat		Induces CSC differentiation	Breast cancer (308)
Ricolinostat		Increases cancer cell apoptosis	Prostate cancer (309)
Givinostat		Shows anti-proliferative and pro-apoptotic efficacy	Glioblastoma (310)
Valproic acid	Short chain fatty acids	Inhibits cancer cell proliferation by modulating multiple signaling pathways.	Breast cancer (311); thyroid cancer (312); bladder cancer (313)
Butyric acid		Displays anti-cancer effect	Gastric cancer (314) colorectal cancer (315); bladder cancer and breast cancer (316)
Entinostat	Benzamides	Displays anti-cancer effect targeting SALL4	Lung cancer (317); ovarian cancer (318,319)
Tacedinaline		Increases cell death	Breast cancer (320)
Mocetinostat		Shows anti-tumor effects	Chondrosarcoma (321); lung cancer (322); breast cancer (323)
4SC-202		Inhibits survival and proliferation of cancer cells	Medulloblastoma (324); colorectal cancer (325)
Romidepsin	Cyclic tetrapeptides	Enhances anti-tumor effect, regulates PD-L1	Bladder cancer (326,327); colon cancer (328)
Nicotinamide	Sirtuins inhibitors	Enhances DNA repair and reduces UVR's immunosuppressive effects	Skin cancer (329,330); cervical cancer (331)
Sirtinol		Induces apoptotic effect	Breast cancer (332); lung cancer (333)
Cambinol		Induces antiproliferative effect	Bladder cancer (334)
EX-527		Increases cell death	Ovarian cancer (335)

CSC, cancer stem cell; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; SAHA, suberoylanilide hydroxamic acid; UVR, ultraviolet radiation.

Combined treatment options of standard chemotherapeutic drugs with epigenetic approaches can make it possible to reactivate genes sensitive to chemotherapy. Coexistence of multiple epigenetic modifications and the development of drug resistance reveals the necessity of combination therapy in cancer treatment. Chemotherapy resistance may also be overcome by reversing the epigenetic changes that lead to it. Epigenetic therapy approaches further allows for the personalization of the treatment considering the patient's own history, as well as his/her own lifestyle and health history.

In addition to all its advantages, it can be difficult

to work with epigenetic modifications. When DNA methylation biomarkers are analyzed, cell heterogeneity found in tissues from clinical specimens may yield variable, dynamic and complex profiling results. These variable results have to be interpreted in the context of real time changes in the tissues which may in turn influence the epigenetic modifications, which are highly susceptible to local factors, such as cell metabolism, oxygenation, free radical formation and inflammation. In addition, normal cell density is low in body fluids like serum, plasma, urine and sputum, which may make it difficult to detect epigenetic biomarkers in rare cancer cells. However, new highly sensitive cell identification and imaging technologies allow for accurate analysis of single cancer cells found in tissues and circulation, as well as different cell populations in the microenvironment. New methodologies also allow for "liquid biopsies" by identifying cell free DNA in the circulation. It is now possible to get multiple blood and tissues samples during the course of cancer treatment to evaluate genetic and epigenetic changes, which may influence the selection of different anti-cancer treatments.

Heterogeneity in differentiation status in cancerous cells and changes in the histological grade of the tumor over the course of the disease may cause ambiguous results in the correlation of clinical status. While the treatment processes of the disease are being followed, uncertain results may be obtained in patient samples Therefore, clinicians may have to obtain serial blood and tissues samples to understand the changes in genetic and epigenetic profile of the disease, and make necessary treatment changes accordingly. For example, due to the working principle of miRNAs, a miRNA has hundreds of targets. This may cause irregular treatment responses and different pathological processes that appear as a complex network.

In order to overcome the possible problems mentioned above, it is necessary to work in tissues and body fluids with high stability, to purify them at the DNA methylation stage, to create large patient groups, and to use biomarker panels approved by different regulatory agencies, such as FDA or European Medicines Agency (EMA). Also, a good epigenetic biomarker should be more cost-effective than some of the existing markers.

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