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REVIEW

Environmental pollution and DNA methylation: carcinogenesis, clinical significance, and practical applications

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Abstract **Environmental pollution is one of the main causes of human cancer. Exposures to environmental carcinogens result in genetic and epigenetic alterations which induce cell transformation. Epigenetic changes caused by environmental pollution play important roles in the development and progression of environmental pollution-related cancers. Studies on DNA methylation are among the earliest and most conducted epigenetic research linked to cancer. In this review, the roles of DNA methylation in carcinogenesis and their significance in clinical medicine were summarized, and the effects of environmental pollutants, particularly air pollutants, on DNA methylation were introduced. Furthermore, prospective applications of DNA methylation to environmental pollution detection and cancer prevention were discussed.**

Keywords environmental pollution; DNA methylation; cancer; biomarker; diagnosis; therapy; prevention

Introduction

The World Health Organization estimates that a quarter of all diseases are attributed to environmental exposure. In China, diseases caused by environmental pollution have led to a serious health problem. For example, air pollution contributes to direct damaging effects on public health; about 350 000–500 000 people in China died prematurely each year as a result of air pollution [1]. Cancer is one of the major diseases caused by environmental pollution. Carcinogenesis is a multi-factor and multi-stage process. Accumulating genetic mutations had traditionally been considered the major causes of tumor [2]. However, this paradigm has been expanded, and research revealed that epigenetics also participates in carcinogenesis [3–7].

Both genetic and epigenetic mechanisms regulate gene expression and functions. The term "epigenetics" refers to all heritable changes in a cellular phenotype that are independent of alterations in the DNA sequence [8]. However, this definition of epigenetics remains debatable. Sometimes, "epigenetics" is only used to describe chromatin-based events regulating DNA-templated processes [6]. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodeling, non-coding RNA, and nuclear organization. DNA methylation, primarily referred to as the methylation of the 5-carbon on cytosine residues (5mC) in dinucleotides, is one of the most extensively characterized modification of chromatin. Emerging evidence has demonstrated that carcinogenesis caused by environmental pollution is associated with genetic and epigenetic changes. In this review, several aspects involving environmental pollution, DNA methylation, and carcinogenesis were systematically discussed.

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Environmental pollution and carcinogenesis

Polluted air, water, and soil contain a wide range of contaminants, including polycyclic aromatic hydrocarbons (PAHs), heavy metals, arsenic, benzene, sulfur dioxide, carbon monoxide, carbon dioxide, and nitrogen dioxide. The International Agency for Research on Cancer (IARC) has developed approaches to evaluate the carcinogenicity of various contaminants (http://monographs.iarc.fr/ENG/Classification/). Some important pollutants related to carcinogenesis are listed in Table 1. Exposures to these environmental carcinogens can result in genetic and epigenetic alterations, which induce cell transformation. Numerous studies have demonstrated a strong link between air pollution and lung cancer. Moreover, water and soil pollution are closely related to cancers of the

digestive tract and liver, as well as leukemia. Relationships between air pollution and lung cancer were further discussed in this paper.

Although smoking is the most important cause of lung cancer, about a quarter of lung cancer cases worldwide are not associated with smoking. A study estimated that air pollution induced more than 200 000 lung cancer deaths globally [9]. If lung cancer in never-smokers was

Table 1 Some pollutants related to human carcinogenesis

Agent	Group*	Main sources	Main objects of pollution or main modes of entry
Polycyclic aromatic hydrocarbons (PAHs)	1/2A/2B/3	Coal and oil combustion products	Air, soil
Nitro-polycyclic aromatic hydrocarbons	3	Coal and oil combustion products	Air, soil
Coal tar	1	Coal and oil combustion products	Air, soil
Coke productions	1	Coal coking	Air, water, soil
Carbon black	2B	Coal and oil combustion products	Air
Sulfur dioxide (SO_2)	3	Coal and oil combustion products	Air
$PM_{2.5}$	1	Multi-source, e.g., coal and oil combustion products, etc.	Air
Arsenic and its compounds	1	Coal and oil combustion products, mining, smelting, etc.	Air, water, soil
Formaldehyde	1	Industry, medicine, agriculture, etc.	Air, water, food
Asbestos	1	Construction industry, building materials	Inhalation, contact
Bitumen	2B/3	Petrochemical industry, construction industry, etc.	Inhalation, contact
Radon and its decay products	1	Mining, smelting	Inhalation, radioactive contamination
Benzene	1	Chemical industry	Air, water
Styrene	2B	Chemical industry	Air, water, soil
Trichloroethylene	1	Pharmaceutical and chemical industry	Air, water
1,3-butadiene	1	Chemical industry	Inhalation, contact
4,4'-diaminobiphenyl ether	2B	Synthetic dyes	Inhalation, contact
Bis-chloromethyl	1	Chemical industry	Inhalation
Carbon tetrachloride	2B	Chemical industry	Inhalation
Epoxyethane	1	Detergents, fungicides, etc.	Inhalation
Dimethylsulfate	2A	Synthetic dyes, chemical industry	Inhalation
Polychlorophends and their sodium salts	2B	Chemical industry	Inhalation, contact, ingestion
Dimethylcarbamyl chloride	2A	Pharmaceutical and pesticide industry	Inhalation, contact, ingestion
Auramine	2B/1	Dyes	Inhalation, contact, ingestion
Epichlorohydrin	2A	Chemical industry	Inhalation, contact, ingestion
Polychloroprene	3	Chemical industry	Inhalation, contact
Amitrole	3	Herbicide	Water, soil, air
Hexachlorocyclohexane	2B	Insecticide	Water, soil, air
Dichlorodiphenyltrichloroethane (DDT)	2B	Insecticide	Water, soil, air
Heptachlor	2B	Insecticide	Water, soil, air
Chlordane	2B	Insecticide	Water, soil, air
Hematite (Fe_2O_3)	3	Mining, smelting	Air, soil
Lead compounds	2B/3	Mining, smelting (lead dust), industry, etc.	Air, water, soil
Titanium dioxide	2B	Mining, smelting	Inhalation
Chromium (VI) compounds	1	Smelting (chromium residue), metal processing, electroplating, tanning, etc.	Water, soil, air
Cadmium and its compounds	1	Mining, smelting, metal processing, dyes, chemical industry, etc.	Water, soil
Nickel compounds	1/2B	Mining, smelting, metal processing	Air, water, soil
Beryllium and its compounds	1	Mining, smelting	Air, water, soil

* Grouping based on the Agents Classified by the IARC Monographs (Volumes 1–111; last update 18 February 2015; http://monographs.iarc.fr/ENG/Classification/). Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.

considered a separate disease, this malignancy would be the seventh cancer killer worldwide [10]. IARC proposed outdoor air pollution as carcinogenic in 2013 [11]. Air pollution is a complicated cocktail of chemicals that waft from sources from factories to lawnmowers [12]. PAHs and arsenic are the most important carcinogens of air pollution for lung cancer. Fine particulate matter (up to 2.5 μm in diameter, $PM_{2.5}$) and particulate matter (up to 10 μm in diameter, PM_{10}) are major components of air pollution. $PM_{2.5}$ has become the fourth largest threat to the health of people in China [13]. A recent research has established a link between lung cancer and fine particulate matter ($PM_{2.5}$) [12]. $PM_{2.5}$ contained many components, including PAHs and heavy metals. IARC has also defined $PM_{2.5}$ as a carcinogen (http://monographs.iarc.fr/ENG/Classification/).

The morbidity and mortality of air pollution-related lung cancer vary significantly in different regions. The risk of lung cancer correlated with average pollution levels (PM_{10}) [14]. Notably, high rates of air pollution-related lung cancer often occurred in special regions. Generally, air pollution was more serious in these special regions. The lung cancer cases in these special regions serve as good models to study the relationship between environmental factors and this fatal disease. A good example of air pollution-related lung cancer was found in Xuanwei City and Fuyuan County, Yunnan Province, China [15–17]. More non-smoking women suffered from lung cancer in Xuanwei and Fuyuan than in other areas. Air pollution (indoor, outdoor) by burning "smoky coal" was the main reason for lung cancer in Xuanwei and Fuyuan. Burning "smoky coal" releases numerous cancer-causing substances, such as PAHs [18].

More importantly, industrial developments are heightening levels of outdoor air pollution in some regions, cities, and countries, particularly in developing countries. Air pollution is becoming increasingly serious in some regions of developing countries. Therefore, air pollution-related lung cancer in developing countries is more severe than that in developed countries. However, the control of air pollution is a significant challenge for developing countries because of technical and financial problems. A very long time is needed to control environmental pollution and thereby save numerous lives worldwide.

DNA methylation and carcinogenesis

Studies on DNA methylation are among the earliest and most conducted epigenetic research linked to cancer. Multiple alterations in DNA methylation, including loss of DNA methylation (hypomethylation) and increases in DNA methylation (hypermethylation), were observed in malignant cells. In the cancer field, some people use "epimutation" to define a heritable change in gene activity that is not associated with a DNA mutation but rather with gain or loss of DNA methylation or other heritable modifications of chromatin [19]. Numerous studies have provided comprehensive data and highlighted a potential connection between DNA methylation alterations (epimutation) and cancer.

Global hypomethylation and carcinogenesis

DNA repeat elements, including long interspersed nuclear element (LINE), moderately repeated DNA sequences, satellite repeats, short interspersed nuclear element, and Alu repeats, are heavily methylated in normal human cells. Genome-wide hypomethylation is largely attributed to the loss of methylation at DNA repeat elements, such as LINE, moderately repeated DNA sequences, and satellite repeats in cancer cells [6,7,20]. Global hypomethylation can also induce genomic instability [5,6], loss of imprinting [7], and activation of oncogenes [5–7], which contribute to the development and progression of cancer. Although genome-wide hypomethylation was studied to link epigenetics to cancer, the functional roles and significance of global hypomethylation in carcinogenesis remain largely unknown.

Hypomethylation of gene promoters and carcinogenesis

Apart from the loss of methylation at DNA repeat elements, DNA hypomethylation of individual genes may also occur. Unlike hypermethylation of gene promoters, promoter hypomethylation of genes resulted in upregulation of genes [21,22]. Moreover, highly prevalent regions of hypomethylation have correlated with increased gene expression [22]. A study found that the expression of MAGFA11 (a cancer germline antigen) was associated with promoter and global DNA hypomethylation, and MAGFA11 promoter activity was directly repressed by DNA methylation through influencing nucleosome occupancy at the MAGFA11 promoter [23]. Thus, DNA hypomethylation of gene promoters may activate oncogenes and participate in carcinogenesis.

CpG hypermethylation of gene promoters and carcinogenesis

In mammalian cells, DNA methylation occurs almost exclusively at cytosines located at 5′ to a guanine in a cytosine-phosphate-guanine (CpG) dinucleotide; however, some studies observed the presence of non-CpG methylation in embryonic stem cells [24,25]. CpG islands in the gene promoters are generally protected from methylation. CpG islands methylated in the gene promoters play an important role in transcriptional regulation, and the hypermethylation of promoters can lead to transcriptional

silencing. Altered methylation in CpG promoter islands is common in various cancers [4,6,7]. (1) CpG hypermethylation of promoters affects the expression of protein-coding genes. The relationship between CpG island methylation and gene expression is mostly studied in cancer epigenetics. Numerous studies have demonstrated that CpG hypermethylation of gene promoters may lead to aberrant silencing of importantly functional genes, such as *RB*, *BRCA1/2*, *PTEN*, *MGMT*, *CDKN2B*, *P16*, *RASSF1A*, *MLH1*, *GSTP1*, *APC*, and E-cadherin [3,7,20]. These genes are involved in cell cycle, DNA repair, key signaling pathways, genomic stability, detoxication, and cell adhesion, among others. These alterations in gene expression demonstrate functional roles in the development and progression of cancer. (2) CpG island hypermethylation of promoters has deregulated the expression of tumor-suppressor microRNA (miRNA) and contributed to tumorigenesis [26,27]. Although many genes were found to be silenced by promoter hypermethylation, the underlying mechanisms remain largely unknown. Promoter hypermethylation may establish a molecular environment to inhibit gene expression. For example, promoter hypermethylation prevented the binding of transcription factors [28]. DNA hypermethylation can also create binding sites for methyl-binding proteins and complexes and then form a repressive chromatin configuration [29]. In a recent study, functional genome analysis indicated that the classical notion of gene silencing through promoter hypermethylation was not a prominent feature, and many genes with differentially methylated promoters did not show distinct expression [22]. This finding suggested that the promoter methylation cooperates with other factors to regulate gene expression.

Other alterations in DNA methylation and carcinogenesis

Besides DNA methylation in promoters, methylation within the gene body also affects gene expression [25,30–32]. Generally, gene body methylation is positively correlated with gene expression. Alterations in methylation of the gene body may demonstrate functional and clinical implications in carcinogenesis [30]. Furthermore, the demethylation of gene bodies caused by 5-Aza-2'-deoxycytidine (5-Aza-CdR) treatment can induce gene downregulation, indicating that gene body methylation is a therapeutic target in cancer [33].

Genome-wide DNA methylation studies also found that DNA hypermethylation occurred at "CpG island shores." CpG island shores are conserved sequences of upstream and downstream CpG islands. Interestingly, cancer-related changes in DNA methylation also involve CpG island shores [6,34]. Methylation of CpG island shores is strongly related to gene expression, and most genes downregulated in association with shore hypermethylation are activated by 5-Aza-CdR and DNA methyltransferase knockout [34]. Another recent study used DNA methylation sequencing and found that non-CpG methylation was low in tumor but high in normal adult tissue [22]. However, the pathological functions of these regional alterations in methylation remain unclear.

Interrelationships of DNA methylation and genetic alterations in carcinogenesis

Epigenetic and genetic alterations contribute to crosstalk in carcinogenesis [5]. On the one hand, some inactivating mutations in genes, particularly in DNA methyltransferase (DNMT) genes, can disrupt DNA methylation patterns [35,36]. On the other hand, alterations in DNA methylation facilitate genetic mutation and disable DNA repair functions. The hypermethylation of DNMT3 exons potentially leads to genetic mutation via the hydrolytic deamination of 5mC to form a C-to-T transition mutation [5]. Additionally, chromatin organization, which is regulated by DNA and histone modifications, exerts a major influence on regional mutation rates in human cancer cells [37–40]. A genome-wide DNA methylation study also found that partially methylated domains affecting up to one-third of the genome showed increased mutation rates [22]. Several DNA repair genes, such as MGMT and MLH1, are regulated by promoter methylation. The hypermethylation of MGMT enhances susceptibility of genetic mutations in p53 and KRAS [3]. The loss of function of MLH1 by promoter hypermethylation results in microsatellite instability [41]. Interestingly, some tumor suppressor genes are deregulated by simultaneous promoter methylation and somatic mutations [42]. Tomasetti and Vogelstein thought that the majority of cancers are ascribed to random mutations arising during DNA replication in normal stem cells [43]. Given that alterations in DNA methylation can increase the incidence of random mutations arising during DNA replication, interrelationships of DNA methylation and genetic alterations should be further studied.

Interrelationships of DNA methylation and other epigenetic in carcinogenesis

Epigenetic mechanisms, such as histone modifications and chromatin remodeling, are closely related to DNA methylation [44]. Other epigenetic alterations can affect DNA methylation. Histone modifications (acetylation and methylation) are correlated with DNA methylation status [45,46]. For example, genetic reactivation of long interspersed element-1 (LINE-1 or L1) by benzo(a)pyrene (BaP) carcinogen involves an ordered cascade of epigenetic events beginning with nucleosomal histone modifications and is completed with alterations in DNA methyltransferase-1 recruitment to the L1 promoter and

reduced DNA methylation of CpG islands [47]. Moreover, DNA methylation provides binding sites for some methyl binding proteins, such as MBD1, MBD2, MBD3, and McGP2, and these proteins recruit histone-modifying enzymes to coordinate the chromatin-templated processes [48]. A relationship also exists between DNA methylation and miRNA. On the one hand, miR-29b resulted in global hypomethylation and promoter hypomethylation of some genes through downregulation of DNMTs (i.e., DNMT1, DNMT3A, and DNMT3B) [21]. On the other hand, DNA methylation downregulates miRNA transcription and then affects gene expression [26,27].

Mechanisms of DNA methylation regulation in carcinogenesis

Although alterations in DNA methylation in cancers have been observed for a long time, the mechanisms of alterations in DNA methylation during malignant transformation have not been completely elucidated. DNA methylation status is regulated by both DNA methylation (the methylation of the C5 position of cytosine, 5mC) and DNA demethylation. The 5-carbon of cytosine nucleotides is methylated by DNMTs. DNA demethylation includes a stepwise process, i.e., hydroxylation of 5mC catalyzed by the ten-11 translocation (TET) family of proteins and then deamination by activation-induced cytidine deaminase or carboxylation [49]. Mutations of several DNMTs have been observed in cancer tissue, and these mutations were related to the alterations in DNA methylation, as well as the development and progression of cancer [35,36]. Additionally, overexpression of DNMT1, DNMT3A, and DNMT3B possibly contributed to hypermethylation in various cancers [50]. Mutations in TET family members were found in myeloproliferative neoplasms [51]. Besides DNMTs and TETs, isocitrate dehydrogenase (IDH)1 and IDH2, which induce DNA hypermethylation, also exhibited mutations in cancers [52]. The mechanisms of DNA methylation regulation are complex, and those of DNA methylation alterations may vary in different cancers.

Environmental pollution and DNA methylation

Environmental carcinogens and DNA methylation alterations

Environmental carcinogens include a wide range of contaminants. This article focuses on environmental pollution-related carcinogens. Other environmental factors, such as diet, smoke, and alcohol, were not discussed in this review. The main carcinogens of environmental pollution include PAHs, heavy metals, arsenic, benzene, and air particles. Substantial research has revealed relationships between DNA methylation and environmental carcinogens [53–125]. The major findings and references are summarized in Table 2. Some studies were not included owing to the limitation of space.

PAHs comprise one family of the most important environmental carcinogens, which are produced by burning coal, gasoline, diesel, and tobacco. PAHs widely occur in polluted air, water, and soil. The relationships between DNA methylation and PAHs have been frequently studied *in vivo* and *in vitro*. PAH exposure induced CpG site-specific hypermethylation of p16INK4α *in vivo* [54]. Prenatal PAH exposure was also associated with decreased global methylation of white blood cells in the umbilical cord [55], and transplacental exposure to airborne PAH was related to DNA methylation of 5′-CpG island of ACSL3 [56]. A study demonstrated that the maternal PAH exposure and treatment of BaP, which is a common PAH, increased promoter hypermethylation and reduced expression of IFNγ *in vivo* and *in vitro*, respectively [57]. Besides environmental exposures, alterations in DNA methylation were also detectable in lung tissue and peripheral blood DNAs from smokers [58]. *In vitro* treatment with BaP decreased global DNA methylation in zebrafish embryos [59]. Cultured human bronchial epithelial cells treated with BaP showed alterations in DNA methylation, including DNA hypomethylation and hypermethylation [60–62]. The suppressed mRNA expression of several genes agreed with the hypermethylation of these genes. Furthermore, the BaP-induced gene hypermethylation was associated with the transformation of cultured cells [62]. Apart from inducing global hypomethylation and promoter hypermethylation of specific genes, BaP reduces DNA methyltransferase levels, mediates hypomethylation of L1 promoter, and modulates L1 expression [47]. In cultured breast cancer cells, BaP exposure can also disrupt DNA methylation [63]. Thus, BaP induces changes in DNA methylation via multiple mechanisms and pathways. Similarly, alterations in DNA methylation and gene expression were observed in human bronchial epithelial cells exposed to cigarette smoke condensate [64].

Fine particulate matter ($PM_{2.5}$) and particulate matter (PM_{10}) are major air pollutants. Multiple alterations in DNA methylation, including global DNA hypomethylation and gene-specific hyper- and hypomethylation, were linked with exposure to $PM_{2.5}$ and PM_{10} [65–76]. However, the particulate matter contained several elemental components, and such components vary in different regions. Therefore, $PM_{2.5}$ and PM_{10} in various regions may demonstrate diverse biological effects, including influence on DNA methylation. Besides the exposure quantities of $PM_{2.5}$ and PM_{10}, the qualities of $PM_{2.5}$ and PM_{10} should also be noted.

Arsenic is a common environmental carcinogen. DNA methylation of gene *p53* and *p16* promoters was detected in arsenic-exposed population [77]. Arsenic treatment can

Table 2 Some environmental pollutants and DNA methylation in previous studies

Agent	Alterations in DNA methylation	References
Polycyclic aromatic hydrocarbons (PAHs)	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[47,54–63,80]
Carbon black	Gene-specific hypermethylation	[68]
$PM_{2.5}$, PM_{10}	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[65–76]
Arsenic	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[77–79]
Formaldehyde	Global DNA hypomethylation	[80,81]
Radon	Gene-specific hypermethylation	[82–84]
Asbestos	Gene-specific hyper- and hypomethylation	[85–87]
Benzene	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[80, 88–90]
Styrene	Global DNA hypomethylation	[80]
Trichloroethylene	Global DNA hypomethylation	[80]
1,3-butadiene	Global DNA hypomethylation and gene-specific hypermethylation	[91–94]
Carbon tetrachloride	Global DNA hypomethylation	[80]
Dimethylsulfate	DNA hypermethylation	[95]
Epichlorohydrin	Global DNA hypomethylation	[80]
Hexachlorocyclohexane	Global DNA hypomethylation	[96]
Dichlorodiphenyltrichloroethane (DDT)	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[97,98]
Chlordane	Global DNA hypomethylation	[96]
Lead	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[99−102]
Chromium	Global DNA hypomethylation and gene-specific hyper- and hypomethylation	[103−106]
Cadmium	Global DNA hyper- and hypomethylationand gene-specific hypermethylation	[107–119]
Nickel	Gene-specific hypermethylation	[120–125]
Beryllium	Gene-specific hypermethylation	[68]

induce alterations in DNA methylation in cultured cells [78,79]. Formaldehyde is also a common environmental carcinogen, particularly in China. Unfortunately, research on formaldehyde is very limited [80,81]. Furthermore, the relationships between DNA methylation and radon remain poorly understood, although several studies have been conducted [82–84].

Exposure to asbestos led to alterations in DNA methylation [85–87]. Such alterations can be induced by some environmental chemicals, such as benzene [80,88–90], styrene [80], trichloroethylene [80], 1,3-butadiene [91–94], carbon tetrachloride [80], dimethylsulfate [95], and epichlorohydrin [80]. Overall, knowledge on the relationships between DNA methylation and environmental chemicals is limited.

Pesticides are important environmental pollutants. Exposure to hexachlorocyclohexane [96], dichlorodiphenyltrichloroethane (DDT) [97,98], and chlordane [96] resulted in alterations in DNA methylation. However, the pathological functions and clinical significance are unclear. Thus, additional related studies are needed.

Heavy metals are involved in air, water, and soil pollution. The relationships between DNA methylation and heavy metals have been thoroughly investigated. Alterations in DNA methylation can be caused by exposure to lead [99–102], chromium [103–106], cadmium [107–119], nickel [120–125], and beryllium [68]. Paradoxically, two studies showed that cadmium reduces genome methylation [116,117], but other investigations revealed that cadmium exposure is associated with DNA hypermethylation [109,119]. More importantly, when a heavy metal enters the human body, this element can hardly be removed. Alterations in DNA methylation caused by heavy metals may be very stable. Thus, their pathological functions and clinical significance should be further noted.

Alterations in DNA methylation induced by environmental carcinogens and carcinogenesis

Exposure to environmental pollution induced various patterns of DNA methylation, such as global hypomethylation and hyper- and hypomethylation of specific genes. Alterations in DNA methylation (epimutation) may participate in carcinogenesis. Global hypomethylation correlates with genomic instability [5] and activates potential oncogenes [4,7,20]. By contrast, hypermethylation of tumor suppressor genes and DNA repair genes leads to gene silencing. Genomic instability, activation of oncogenes, silencing of tumor suppressor genes, and defects in DNA repair are implicated in virtually every step of cancer development and progression. Although environmental exposure induced numerous methylation changes, all these alterations in DNA methylation cannot

simultaneously play a causative role in carcinogenesis. Some of the methylation alterations ("drivers") may participate in carcinogenesis and contribute to the development and progression of cancer. These drivers may be involved in many pathological functions, such as abnormal expression of genes and noncoding RNAs, as well as genomic instability. Most of the methylation alterations ("passengers") are only consequential events of transformation. Thus, the drivers should be differentiated from the passengers to study the carcinogenesis induced by environmental exposure. A recent study also demonstrated that only one-third of the variation in cancer risk among tissue is attributable to environmental factors or inherited predispositions, and the majority is caused by random mutations arising during DNA replication in normal stem cells [43]. However, aside from directly inducing gene mutations, environmental factors can also increase the incidence of gene mutations arising during DNA replication by affecting DNA methylation. Thus, the relationships between DNA methylation induced by environmental exposure and the gene mutations arising during DNA replication should be studied.

Mechanisms of DNA methylation alterations by environmental carcinogens

The mechanisms of DNA methylation regulation involve several aspects. Various environmental carcinogens may affect DNA methylation via different mechanisms. Most studies have focused on DNMTs. For examples, BaP-induced gene hypermethylation was mediated by DNMT action [62]. A research demonstrated that BaP affected gene-specific methylation through histone modifications and alterations in DNMT1 recruitment to the promoter [47]. In workers exposed to benzene, toluene, and xylene (BTX), decreased DNMT1, DNMT3a, and DNMT3b mRNA expression was correlated with increased airborne BTX, and decreased DNMTs may be involved in global hypomethylation associated with BTX exposure [88]. Demethylation of global DNA and downregulation of DNMT1 can be observed in mice exposure to 1,3-butadiene [93]. DNMT3b overexpression can result in generalized DNA hypermethylation and gene silencing during cadmium-induced malignant transformation of human prostate cells [118]. However, another study showed that increased global DNA methylation was associated with the overexpression of *DNMT* genes, *DNMT1* and *DNMT3a*, during cadmium-induced malignant transformation [119]. Silencing of the O(6)-methylguanine DNA methyltransferase and upregulation of DNMT1 expression were specifically detected in NiS-transformed human bronchial epithelial cells [120]. Additionally, hydroquinone caused decreased levels of DNA methylation, as well as increased TET1 activity and global levels of 5-hydroxymethylcytosine (5-hmC) [126].

Although environmental carcinogens have affected DNA methylation through DNMTs and TETs, most of these environmental carcinogens have caused multiple alterations in DNA methylation, e.g., global DNA hypomethylation and gene-specific hyper- and hypomethylation. On the one hand, environmental carcinogens induced active DNMTs and DNA hypermethylation. On the other hand, they can also induce inactive DNMTs and DNA hypomethylation. The changes in DNMT activities cannot explain all the phenomena. Moreover, the mechanisms of DNA methylation alterations induced by environmental carcinogens have not been completely elucidated. To date, the mechanism by which environmental carcinogens induce gene-specific hyper- and hypomethylation remains largely unknown. Thus, further studies on this topic are necessary.

DNA methylation and cancer diagnosis and warning

Various cancers show distinct alterations in DNA methylation compared with normal cells. Thus, alterations in DNA methylation can be considered as biomarkers for cancer detection and diagnosis. As biomarkers of cancer diagnosis and warning, alterations in DNA methylation provide several advantages: (1) Growing evidence suggests that alterations in DNA methylation are very early events during transformation of normal cells into cancer cells. Thus, alterations in DNA methylation can be used in early cancer detection and diagnosis. (2) In some cancer types, alterations in DNA methylation can be detected in circulating DNA. Moreover, methylation patterns were similar in sputum, serum DNA, and tumor tissue [127]. Therefore, examination of blood and sputum samples provides the conditions for early cancer detection. (3) Specific alterations in DNA methylation may be related to particular cancer types [128]. Aside from cancer-specific changes in DNA methylation, alterations in DNA methylation also reflected tumor-type specificity. (4) In contrast to genetic changes, more dynamic alterations in DNA methylation are particularly sensitive to environmental influences. DNA methylation tests may demonstrate higher sensitivity than gene tests for cancer warning. Although DNA methylation exhibits many characteristics of powerful biomarkers, good biomarkers with high sensitivity and specificity based on DNA methylation are still lacking for clinical application.

DNA methylation and cancer therapy

Many studies attempted to influence DNA methylation with epigenetic drugs for cancer therapy [128–130]. The major targets are DNMTs. Two drugs, 5-Aza-CdR and 5-azacytidine (5-Aza-CR), have been approved by the Food

and Drug Administration in the United States for clinical application. Both 5-Aza-CdR and 5-Aza-CR, which are cytosine analogs, are incorporated into replicated DNA in place of cytosine and trap DNMTs, resulting in proteosomal degradation and heritable global demethylation upon cell division [33]. Additionally, TET1/2/3 mediating DNA demethylation are promising drug targets. In principle, both epigenetic amplifications and deletions of genes can be considered targets for cancer therapy.

DNA methylation and environmental pollution assessment

Gene mutations have been generally used as molecular biomarkers for exposure to environmental pollution. However, DNA methylation as biomarkers of exposure to environmental pollution exhibited several features: (1) Alterations in DNA methylation can be observed in cultured cells after treatment with low-dose carcinogens, such as PAHs, but gene mutations did not occur for the low-dose treatment. Thus, alterations in DNA methylation showed higher sensitivity than gene mutations for exposure to environmental pollution [67]. (2) Alterations in DNA methylation are detectable in peripheral blood. The peripheral blood is easily obtained for practical application. (3) Environmental carcinogens can induce the characteristic injury "chemical signature" in genome. Similarly, environmental carcinogens may leave a fingerprint on the epigenetic interface (epigenetic signatures) [67]. For example, MTHFR hypermethylation and reduced F2RL3 methylation intensities were associated with tobacco smoking [131,132]. Therefore, epigenetic fingerprints can be used to assess environmental carcinogens. (4) Alterations in DNA methylation are stable after exposure to tobacco smoke and environmental pollution. Thus, DNA methylation tests can be used to detect historical exposures. Several studies have demonstrated that DNA methylation can be considered a long-term biomarker of exposure to tobacco smoke [132,133]. Overall, DNA methylation may be widely used as a biomarker to examine environmental pollution and even toxicity of food and drugs *in vivo* and *in vitro*.

DNA methylation and cancer prevention

The prevention of environmental pollution-related cancer entails several aspects, such as environmental pollution detection, control of environmental pollution, screening of high-risk population, protection of high-risk population from environmental exposure, use of preventive medicine by high-risk population, and detection and/or treatment of pre-cancer diseases. Genetic and epigenetic mechanisms are crucial factors in cancer carcinogenesis. DNA methylation may be one of appropriate entrances to prevent cancers. (1) DNA methylation can be used as a sensitive marker to assess environmental carcinogens for environmental pollution detection. (2) Examination of DNA methylation patterns in healthy people exposed to strong pollution may be helpful to screen the population susceptible to environmental carcinogens, thus protecting the high-risk population. (3) Alterations in DNA methylation are believed to be responsible for early events in tumorigenesis and associated with pre-cancer lesions [20]. Therefore, alterations in DNA methylation may be powerful biomarkers for the early detection of pre-cancer lesions. Subsequently, these lesions can be treated, and tumor development can be inhibited. (4) Some chemical agents that can reduce DNA methylation alterations induced by environmental carcinogens may be used as preventive drugs for the high-risk population, including those that are very susceptible, workers exposed to high pollution, and residents living in highly polluted regions. Cancer prevention is a very challenging task, but it is extremely valuable.

Conclusions

Environmental pollution is one of the main causes of human cancer. Environmental pollution can affect DNA methylation. On the one hand, DNA methylation alterations induced by environmental pollution may participate in carcinogenesis. On the other hand, DNA methylation alterations can be used as biomarkers to diagnose, treat, and prevent cancers, as well as detect environmental pollution.

Finally, novel forms of DNA modifications, such as 5-hydroxymethylcytosine (5-hmC), are associated with carcinogenesis-like DNA methylation. Thus, the relationships between environmental carcinogens and these new forms of DNA modifications should be further studied.

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Compliance with ethics guidelines

Yi Cao declares no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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