REVIEW

Dynamic changes of DNA methylation induced by benzo(a)pyrene in cancer

Huizeng Wang[1†], Bingchun Liu[2†], Hong Chen[1], Peixin Xu[1], Huiting Xue[3*] and Jianlong Yuan[1*]

Abstract

Benzo(a)pyrene (BaP), the earliest and most significant carcinogen among polycyclic aromatic hydrocarbons (PAHs), has been found in foods, tobacco smoke, and automobiles exhaust, etc. Exposure to BaP induced DNA damage directly, or oxidative stress-related damage, resulting in cell apoptosis and carcinogenesis in human respiratory system, digestive system, reproductive system, etc. Moreover, BaP triggered genome-wide epigenetic alterations by methylation, which might cause disturbances in regulation of gene expression, and thereby induced cancer. It has been proved that BaP reduced genome-wide DNA methylation, and activated proto-oncogene by hypomethylation in the promoter region, but silenced tumor suppressor genes by promoter hypermethylation, resulting in cancer initiation and progression. Here we summarized the changes in DNA methylation in BaP exposure, and revealed the methylation of DNA plays a role in cancer development.

Keywords Benzo(a)pyrene, Cancer, DNA methylation, Tumor suppressor gene, Proto-oncogene

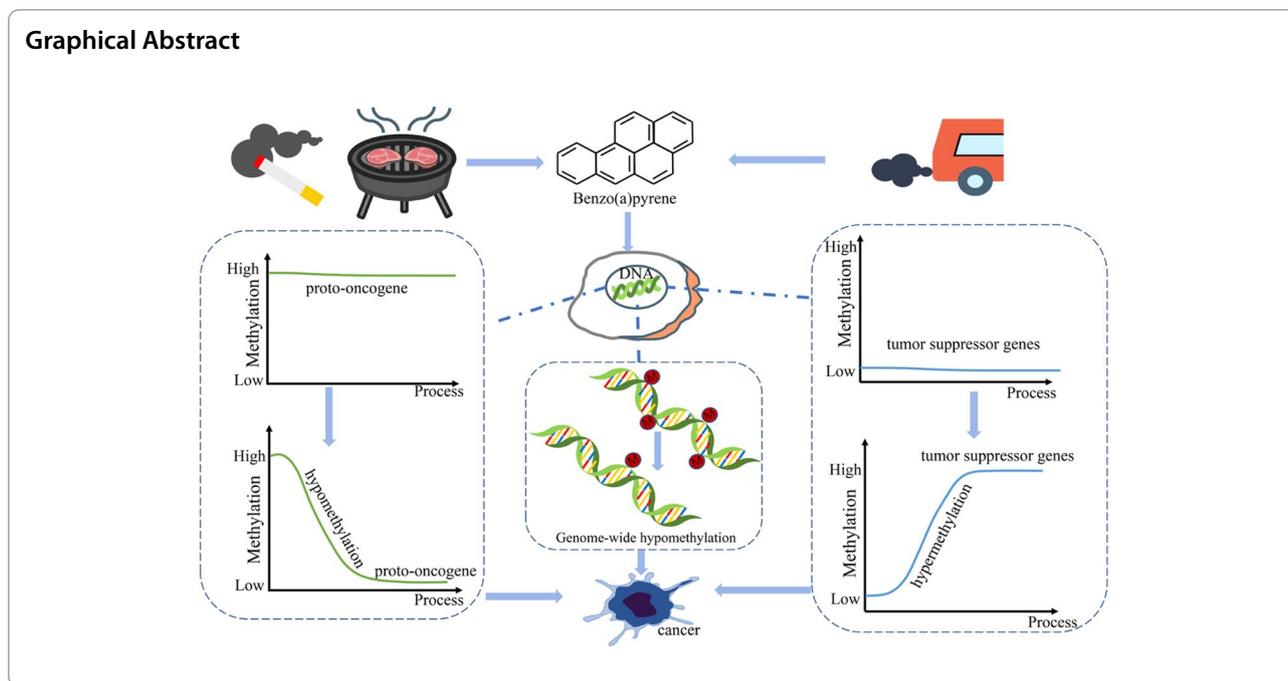†Huizeng Wang and Bingchun Liu contributed equally to this work.

*Correspondence:
Huiting Xue
huiting410@hotmail.com
Jianlong Yuan
jianlongyuan@immu.edu.cn
Full list of author information is available at the end of the article


Graphical Abstract

Introduction

Benzo(a)pyrene (BaP) is the first recognized and most prototypical environ mental pollutants and carcinogens [6, 12, 63], Bukowska, Mokra et al. [14]. It comprises five fused aromatic rings, and derived from organic materials that has not been completely burned, including fossil fuels [73, 74] and timber [17]. Thus, BaP widely exists in automobile exhaust [111], deep-fried food [45], coal chemical combustion smoke and waste, etc.[68]. BaP can be stable in the environment due to its hydrophobicity [52] and chemical stability [101], while the collection of BaP in aquatic organisms is associated to its lipophilicity [2, 30], and it can accumulate along the food chain and enter the human body. Therefore, BaP can be detected in air (Schreiberová, Vlasáková et al. [123]), soil [108], water sources [53] and foods [159].

As a byproduct of the development of science and technology, BaP is a great threat to human health. The International Agency for Research on Cancer (IARC) of the World Health Organization has listed BaP as a class I human carcinogen [92, 143], Goedtke, Sprenger et al. [46], and accumulated studies have revealed a close relationship between BaP and cancers in respiratory system [120], digestive system [44], reproductive system [121] etc. The toxicity of BaP to cells is mainly causing DNA damage [84] and oxidative stress [64, 65] by an increase in reactive oxygen species (ROS) production. BaP requires metabolic activation before reaction with DNA, and its metabolite benzo(a)pyrene-trans-7,8-dihydrodiol-9,10-epoxide (BPDE) induced genotoxicity by forming BPDE-DNA adduct [80, 106], which showing mutagenic and carcinogenic potential in cells [85]. Aryl hydrocarbon receptor (AHR) is a transcription factor [41], Gargaro, Manni et al. [43], when activated by BaP, AHR translocates to nucleus, and forms a heterodimer with the aromatic receptor nuclear transporter (Arnt) [61], which binds to the downstream target gene and activates the abnormal expression of cytochrome P450. P450 is one of the major ROS generators [96], Duan, Chen et al. [34], and ROS is a crucial factor of oxidative stress, which can induce oxidative DNA damage (Fig. 1) [91], cell apoptosis and even canceration [58, 102].

The initiation of cancer shares intimate links with genome epigenetic changes [29, 132], Hatano, Ideta et al. [54], in which DNA methylation and demethylation have been shown to be vital ways to cause carcinogenesis [47, 110, 155]. DNA methylation is the formation of 5-methylcytosine (5mC) by S-Adenosylmethionine (SAM) -dependent methyltransferases (DNMTs) (Martisova, Holcakova et al. [93], [149]. Baylin et al. suggested that the relationship between carcinogenesis and methylation was mainly through the following ways: firstly, the hypomethylation of the oncogene promoter. Secondly, the locally hypermethylation of the tumor suppressor gene promoter, and thirdly, 5mC-containing-DNA sequences or direct mutations exposed to ultraviolet light or other carcinogens [9]. DNA demethylation can either be passive or active [11], which is regulated by ten-eleven translocation (TET) family enzymes [113]. TET proteins belong to α-ketoglutarate- and Fe^{2+}-dependent

Wang *et al. Genes and Environment*   (2023) 45:21

Page 3 of 15
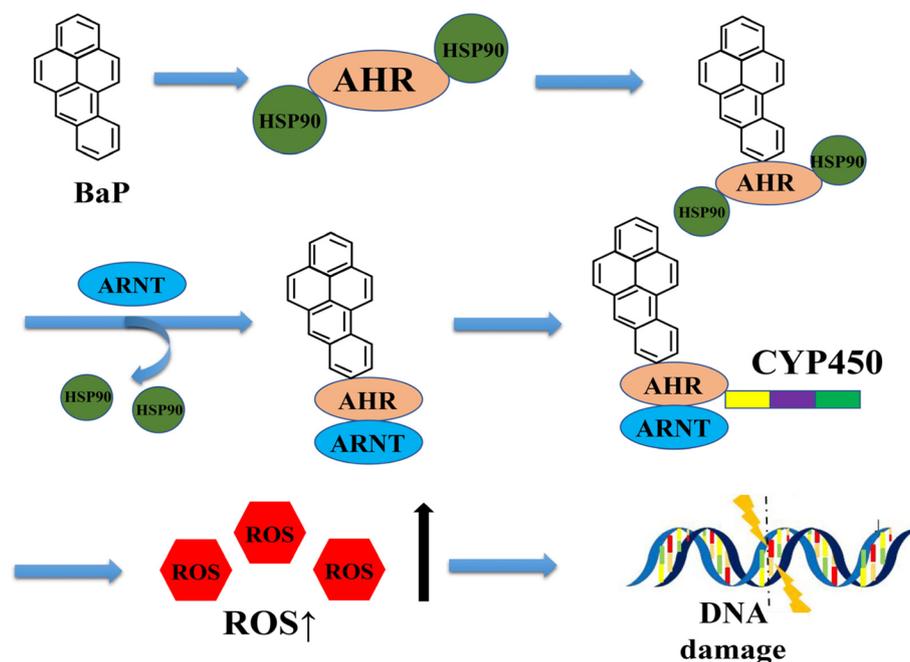
Fig. 1 Oxidative stress of benzo(a)pyrene

dioxygenases, and Tet1, Tet2 and Tet3 involved in this family [26]. Tet1 and Tet2 mainly regulates the level of 5-hydroxymethylcytosine (5hmC) in the promoter region of primordial germ cell (PGCs) genes or 5hmC inside PGCs gene, while Tet3-mediates paternal active DNA demethylation [7, 64, 65, 89, 94, 134, 161]. Active DNA demethylation occurs under the catalysis by TET proteins, which sequentially oxidize 5-methylcytosine (5mC) to 5hmC, then to 5-formylcytosine (5fC) and 5-carboxyl-cytosine (5caC) [38, 104, 126, 147]. In vivo experiments demonstrated that when the deletion of thymidine DNA glycosylase (TDG), which was pivotal in DNA demethylation, adult mice would develop delayed hepatocellular carcinoma (HCC) and hepatoblastoma (HB) (Onabote, Hassan et al. [103]). Thus, when DNA methylation and demethylation are abnormal, cells are likely to become cancerous.

It is general for cells to undergo epigenetic alterations after toxic treatment, but these changes include different trends and mechanisms. For example, NaAsO2 treatment of human bronchial epithelial (HBE) cells inhibits TET-mediated DNA demethylation and induces promoter hypermethylation of 8-oxoguanine DNA glycosylase (OGG1) and glutathione stransferase Pi 1(GSTP1) [139]. Hoang et al. found that pesticides can also cause DNA methylation changes [60]. Researchers have found that BaP changed genomic methylation levels in cells. In recent years, it has become a hot spot to reveal the carcinogenicity of BaP by changing genomic DNA

methylation. Then how BaP as a carcinogen causes cancer through the regulation of epigenetics is worthy of consideration. Exploring the effects and mechanisms of BaP on genomic methylation will help understand BaP-induced carcinogenic mechanism, evaluate the risk of environmental pollutants, and provide an important theoretical basis for prevention of BaP from human health. In this review, we discuss the effects of BaP on DNA methylation and its correlation with carcinogenesis and provide future directions for researchers to reveal the mechanisms in these biological processes.

DNA methylation in the presence of benzo(a) pyrene

Benzo(a)pyrene and DNA methyltransferases

DNA methylation occurs when a methyl group is covalently attached to the 5th carbon position of CpG dinucleotides to form a product 5mC by DNA methyltransferase (DNMTs) (Martisova, Holcakova et al. [93]). DNMTs are mainly constituted of three structures: a C-terminal catalytic domain, an N-terminal regulatory domain and the central junction region [135]. Within the family of DNMTs, DNMT1, DNMT3a, and DNMT3b have DNA methyltransferase activities [20, 112]. DNMT1 sustains DNA methylation (Svedružić Ž [128]), DNMT3a and DNMT3b are responsible for de novo DNA methylation [76], Veiga, Lawrence et al. [136]). BaP induces DNA methylation through dysregulating the expression of DNA methyltransferases. It was reported that,

Wang *et al. Genes and Environment*   (2023) 45:21

Page 4 of 15

the expression of DNMT3a was down-regulated when exposure of mouse embryonic fibroblasts to BaP for 2 weeks, while the expression of DNMT1 up-regulated after 4 weeks of exposure, and DNA methylation levels was elevated [152]. Moreover, BaP metabolite BPDE could induce DNMT3a binding to the promoters of related tumor suppressor genes, which resulted in the aberrant methylation of retinoic acid receptor-β2 (RAR-β2) in human esophageal cancer cells, and BPDE reduced DNMT3b expression [153].

However, in rainbow salmon liver, Bap was shown to inhibit the activity of DNA methyltransferase and decrease DNMT3a expression, which leading to DNA methylation globally reduce [77]. Moreover, compared with non-smokers, DNMT1 expression was apparently higher among smokers, and the level of methylated metabolites was also increased, which was associated with BaP in cigarette [71]. In human hepatic L02 cells, BaP at 0.1, 1 and 10 nmol induced the expression of DNMT1, DNMT3a and DNMT3b, resulting in glutathione-S-transferase-pi (GSTP) promoter region hypermethylation [131]. The above results demonstrated that the level of DNMTs could be modulated by BaP, which was one of the important ways to cause DNA abnormal methylation.

Benzo(a)pyrene and gene methylation

BaP induces DNA methylation by targeting DNMTs, on the other hand, BaP can directly reduce the level of genome-wide methylation, and alter the methylation levels of specific genes, including tumor suppressor genes and proto-oncogenes, resulting in activation of proto-oncogenes or inactivation of tumor suppressor genes, and tumorigenesis [9].

Benzo(a)pyrene and genome-wide DNA methylation

As an epigenetic modifier, Bukowska et al. proposed that BaP reduces genomic DNA methylation by binding to DNA [15] the mechanism may be as follows: 1. BaP enters the human body through a series of reactions to form BPDE, which binds to DNA to inhibit the expression of DNMTs, thereby reducing the process of 5mC production and eventually causing a decrease in genome-wide methylation levels [160, 15]; 2. ROS generated by BaP can lead to oxidative DNA damage, which further affects the interaction between DNMTs and methyl CpG-binding proteins, thereby inhibiting the transcription of DNMTs, reducing the role of DNMTs in methylation, and ultimately reducing genome-wide methylation levels [57, 160], 3. BaP induces the conversion of SAM to SAH by increasing Glycine N-methyltransferase (GNMT) activity, reduces the covalent binding of SAM to a methyl group mediated by DNMTs to form 5mC, further

reduces the production of 5mC, and causes a reduction in genome-wide methylation levels [37]. It was found that different concentrations of BaP (0.24, 2.4 and 24 μg/L) reduced the global levels of 5mC in Zebrafish embryonic cells, and BaP at 24 μg/L had the strongest activity [37]. In 16HBE, BaP was found significantly diminishing DNA methylation level throughout the genome in a time- and dose- dependent manner [62]. Similarly, when BaP was administrated at a dose of 600 mg/kg to the male ICR mice, the genome-wide DNA methylation level in blood and liver followed a downward trend along with the treatment time increasing [160]. Immunofluorescence staining results showed that the DNA methylation level of 16HBE cell treated with gradient concentration of BaP (2.5, 5, 10, 20 and 40 mmol/L) decreased by 3.43%, 9.27%, 23.76%, 32.55% and 43.15%, respectively [148], indicating that BaP inhibited genome-wide DNA methylation. Moreover, compared with normal tissue, genome-wide DNA in tumor tissue was found in a markly hypomethylated status (Ili, Buchegger et al. [66]). These results provide a theoretical foundation for illuminating the mechanism of carcinogenesis induced by BaP, which decreases the level of genome-wide DNA methylation, disturbs cell growth and apoptosis, and enables canceration.

Benzo(a)pyrene and specific gene methylation

Five to ten gene promoters hypermethylation when human immortalized bronchial epithelial cell treated with BPDE, including E-cadherin and Protocadherin-10 [28], which was related to breast cancer invasion [49]. Corrales et al. found that when Zebrafish embryos (during 96hpf) exposed to BaP, significant changes in methylation levels were observed in the promoters of 10 genes, including cancer-associated genes, metabolic genes, developmental and reproductive genes. Among them, six genes were hypermethylated including cancer-associated genes c-fos and MutL Homolog 1 (MLH1) [24], and four genes were hypomethylated. The results were consistent with the previous studies that cancer tissues expressed high level of hypermethylation in c-fos gene and MLH1 promoter [21, 86]. C57BL mice were treated with BaP at different concentrations (1.0, 2.5, 6.25 mg/kg), and DNA methylation in the promoter region of the N-methyl-d-aspartate receptor subunit 2B (NR2B) gene was up-regulated, and NR2B expression in prefrontal cortex and hippocampal part decreased by qPCR analysis, resulting in the diminishment of NR2B expression and abnormal behavior among mice [158]. By observing the different stages of 16HBE transformation induced by BaP, there were some correlations between the hypermethylation of the FMS-like tyrosine kinase-1 (FLT1) promoter and carcinogenesis of PAHs

Wang *et al. Genes and Environment*   (2023) 45:21

Page 5 of 15

[56]. Liu et al. treated 16HBE with different concentrations of BaP (1, 2, 5 mmol/L) for 24 h, and related genes were measured by methylation-specific PCR. They found that GSTP1promoter methylation level was in negative correlation with BaP concentrations; BaP prohibited the methylation in the promoter of CYP1A1, which was the major members of the cytochromeP450 (CYP450) family [88]. BaP (5 µg/L) not only induced hypermethylation in the promoter region of tumor suppressor gene APC, but also induced demethylation in the proto-oncogene promoters of cyclooxygenase-2 (COX-2) and mutS homolog 2(MSH2) in normal peripheral blood mononuclear cells (PBMC) [156].

The above analyses show that BaP may induce a decrease in DNA methylation level accompanied by abnormal methylation patterns of some certain genes (Table 1), and the hypermethylation of tumor suppressor genes by Bap contributes to the occurrence and development of cancer.

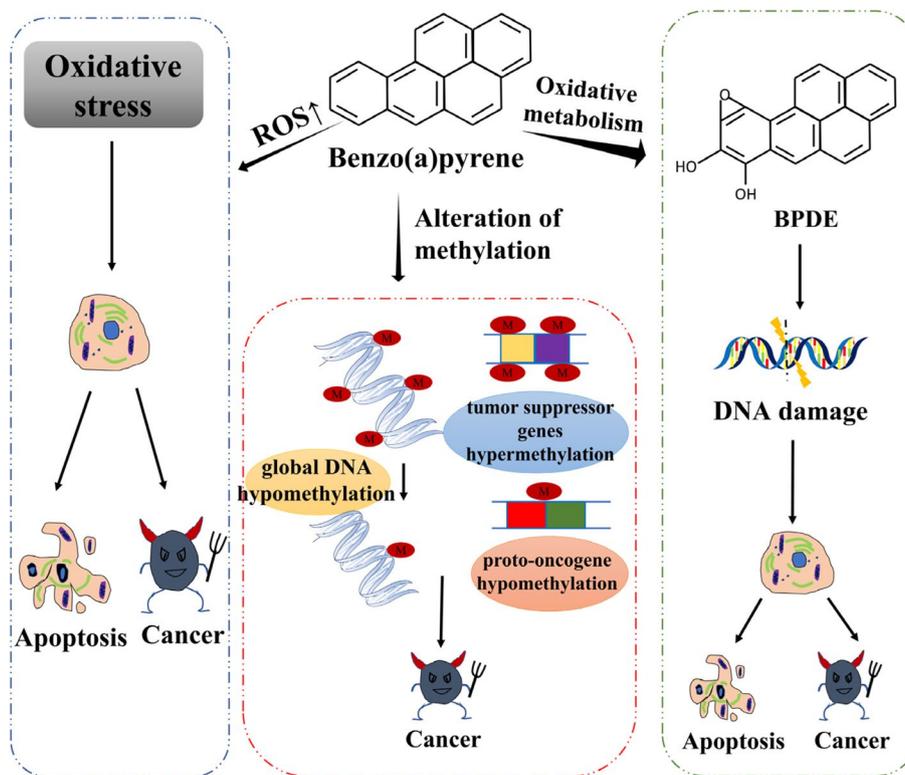## Carcinogenesis of benzo(a)pyrene by DNA methylation

Alteration of DNA methylation is the most representative epigenetic feature in cancer progression [47, 48, 72]. Silencing of tumor suppressor gene expression is caused by hypermethylation in gene promoter region, and genome-wide hypomethylation can lead to genome instability and proto-oncogene activation [146], eventually inducing the development of cancer [156]. The mechanisms of BaP can be summarized in two aspects: inducing hypomethylation of proto-oncogenes and activating them; and inhibiting tumor suppressor gene expression by hypermethylating them, both of which promote cancer initiation (Fig. 2).

Association of benzo(a)pyrene methylation levels with multiple cancers

BaP as a Class I carcinogen, can cause a variety of cancers [44, 120]. When BaP enters the human body, it undergoes a series of chemical reactions, and affects DNA methylation levels, which contributes to carcinogenesis of human

Table 1 Methylation changes induced by benzo(a)pyrene

Changes in methylation		Sample type	Treatment dose / time	Correlation between dose / time and methylation	Reference
Changes in DNMTs	DNMT3a↓	Mouse embryonic fibroblasts	0.25 µmol 2 weeks, 4 weeks	Negative correlation	[152]
	DNMT1↑			positive correlation	
	DNMT1↑	Smokers	Not stated	Not stated	[71]
Global methylation	Whole genome↑	Mouse embryonic fibroblasts	0.25 µmol 2 weeks, 4 weeks	positive correlation	[152]
	Whole liver genome↓	Rainbow salmon liver	(1 ng/L), (10 ng/L) 24 h and 14 days	negatively correlated with time and dose	[77]
	Whole genome↓	Zebrafish embryos	0.24, 2.4, 24 µg/L	Negative correlation	[37]
		16HBE	10, 20, 40 µmol 24 h, 72 h	Negative correlation	[62]
		ICR mice	600 mg/kg	Negative correlation	[160]
Hypermethylation of specific genes	RAR-β2↑	Human esophageal cancer cells	24 h	Not stated	[153]
	GSTP↑	Human hepatic L02 cells	0.1, 1, 10 nmol	Positive correlation	[131]
	E-cadherin↑	Human Immortalized bronchial epithelial cells	0.05, 0.1, 0.25 µmol/L	Positive correlation	[28]
	Protocadherin-10↑			Positive correlation	
	c-fos↑	Zebrafish embryos	50 µg/L	Not stated	[24]
	MLH1↑			Not stated	
	NR2B↑	C57BL mice	1.0, 2.5, 6.25 mg/kg	Positive correlation	[158]
	FLT1↑	16HBE	20 mmol	Not stated	[56]
	APC↑	Human HCT116	5 µg/L	Not stated	[156]
Hypomethylation of specific genes	GSTP1↓	16HBE	1, 2, 5 mmol/L	Negative correlation	[88]
	CYP1A1↓			Negative correlation	
	COX-2↓	Human PBMC	5 µg/L	Not stated	[156]
	MSH2↓			Not stated	

Wang *et al. Genes and Environment*   (2023) 45:21

Page 6 of 15

Fig. 2 The mechanism of carcinogenesis of benzo(a)pyrene

respiratory system, digestive system and reproductive system, and eventually results in the occurrence of a variety of cancers (Fig. 3, Table 2).

Respiratory system cancer
Lung Cancer is one of the most common malignant tumors worldwide, with a highest mortality rate and morbidity rate [83, 133]. The occurrence of lung cancer is closely related to smoking [31, 67] and air pollution [122, 150], which are rich in BaP. Daily BaP concentrations were collected from 8 traffic stations in Barcelona during the severely cold period from 2013 to 2015. on the basis of Lung Cancer Risk (LCR) equation for BaP inhalation, the LCR values of the 8 stations exceeded the 10^{-6} threshold. It is concluded that chronic exposure to BaP increased the incidence of lung cancer [32]. Comparative study was
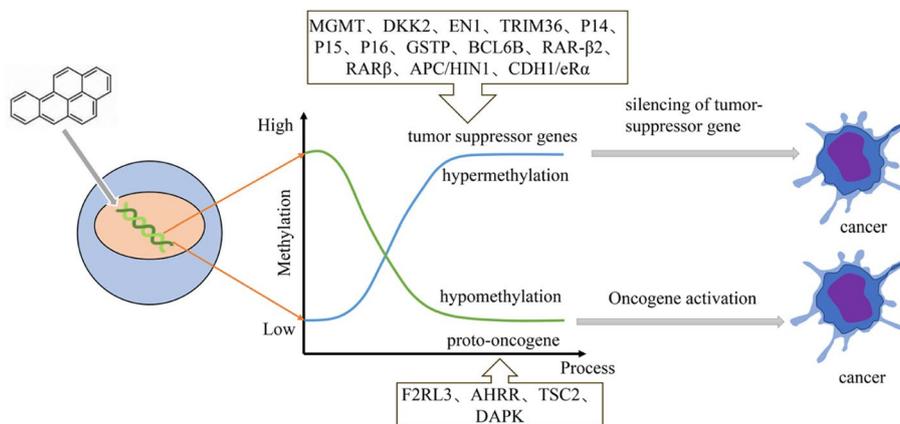
Fig. 3 Benzo(a)pyrene alters gene methylation levels leading to cancer

Wang *et al. Genes and Environment*   (2023) 45:21

Page 7 of 15

Table 2 Carcinogenic epigenetic changes of benzo(a)pyrene

Changes in methylation		Objects exposed to BaP	Reference
Genome-wide hypomethylation		16HBE	[62, 148]
		zebrafish embryo	[37],
		ICR mouse	[160]
		colorectal cancer tumor tissue	[66]
Hypermethylation of specific genes	APC	human HCT116	[156]
	c-fos, MLH1	zebrafish embryo	[24]
	FLT1	16HBE	[56]
	DKK2, EN1	16HBE	[69]
	TRIM36	HBE	[55]
	P14, P15, P16	coke oven workers	[157]
	GSTP	lung Cancer Patients	[131]
	BCL6B	mice	[16]
	RAR-β2	human esophageal cancer cells	[127, 153]
	RARβ, APC	Breast cancer patients	[144]
	HIN1, CDH1	breast cancer patients	[145]
	eRα	mice	[117]
Hypomethylation of specific genes	GSTP1, CYP1A1	16HBE	[88]
	LINE-1, MGMT	workers exposed to PAHs	[33]
	F2RL3, AHRR	creosote-exposed workers, chimney sweeps	[3]
	TSC2	human MCF-7, human HCC1806	[115]
	DAPK-1	breast cancer cells	[145]

conducted on lung cancer cases, and the results showed that the plasma BPDE-Alb adduct per SD (26.85 ng/mL) increased, the risk of lung cancer expanded by 46%. Meta-analysis determined that 15 CpG was interrelated with the plasma BPDE-Alb adducts, including Ubiquitin-conjugating enzyme E2 O (UBE2O), Sterile alpha motif domain containing protein 4A (SAMD4A), Acyl-CoA binding domain-containing 6 (ACBD6), Diacylglycerol kinase 2 (DGK2) and Schlafen 13 (SLFN13), which mediated the association between BaP exposure and 30%-60% lung cancer risk. These results highlighted the change of DNA methylation by BaP might be a contributing factor for lung cancer [95]. Some scholars believed that that BPDE, a metabolite of BaP, affected DNA methylation by binding to CpG, which was one of potential mechanisms of lung cancer induced by BaP [15]. The above studies indicated that BaP induced lung carcinogenesis by altering methylation of genes.

Long interspersed nucleotide element 1 (LINE-1) is the biggest family of long interspersed nucleotide elements, and some studies have shown that LINE-1 is an indicator of methylation levels in the genome [119]. Numerous tumors have been reported to exhibit the hypomethylation of LINE-1 [105]. The methylation levels of LINE-1 and O6-methylguanine-DNA methyltransferase

(MGMT) in PAHs exposure group and control group were detected by pyrosequencing (PSQ) technology, and the results demonstrated that PAHs induced LINE-1 hypomethylation, and genome-wide hypomethylation might promote genomic instability, eventually contributed tumor progression; MGMT promoter hypomethylation resulted in the abnormal expression in gene level, which reduced its ability to repair damaged genes, further exacerbating the stability of the chromosomes. According to these findings, PAH-induced carcinogenesis seemed to be mediated by specific methylation in the CpG island region of the MGMT [33]. These results were consistent with the situation of LINE-1 hypomethylation [107] and MGMT promoter hypomethylation [59] in lung cancer cells. A comparative study was utilized to detect DNA methylation in 16HBE cells treated with BaP and in lung cancer Xuanwei lung cancer (XWLC) cells without any treatment. The results showed that low levels of 5mC and high levels of 5-hmC were found in XWLC cells, and lower global 5-mC level and higher 5-hmC level were found in BaP-treated 16HBE cells, which suggested that BaP treatment led to cell demethylation and BaP-induced alterations in DNA methylation might be a contributing factor to aberrant DNA methylation in XWLC. Moreover, Bisulfite sequencing PCR (BSP) analyzed the

Wang *et al. Genes and Environment*　　(2023) 45:21

Page 8 of 15

state of methylation of 25 CpG dinucleotides located in the promoter region of Dickkopf-2 (DKK2) and 20 CpG dinucleotides in the Engrailed 1 (EN1) promoter region after 16HBE cell treated with BaP, and the results showed that hypermethylation occurred at the, 1st, 2ed, 5th and 6th CpG dinucleotides in DKK2 promoter region and the 1st, 8th and 14th CpG dinucleotides in the EN1 promoter element, which were similar to those observed in XWLC cells [69]. Based on these findings, a mechanism on how BaP-induced DNA methylation changes resulting in lung cancer was explored. BaP induced significant hypermethylation of the DKK2 and EN1 gene promoter elements, and then inhibited DKK2 and EN1 gene expression, which promoted lung cancer cell proliferation and cancer development.

In 2017, He et al. observed in HBE cells that following exposure to BaP, a tumor suppressor gene, tripartite motif containing 36 (TRIM36) were hypermethylated, which may be involved in BaP-induced cell carcinogenesis. To prove this conjecture, pyrosequencing technologies were applied to detect the degree of TRIM36 methylation in non-small cell lung cancer (NSCLC) patients. The results showed that TRIM36 hypermethylation was found in 90.0% (27/30) of the NSCLC, indicating that BaP induced hypermethylation of TRIM36, then promoted lung carcinogenesis [55]. In 2019, the same study group found that hypermethylation of FLT1 promoter, a tumor suppressor gene, probably involved in the carcinogenic process of PAHs [56]. Both studies demonstrated that BaP induced part of tumor suppressor genes inactivation through hypermethylation, which was associated with the development and progression of cancer.

Studies have proven that hypermethylation in the promoter region of P14 (ARK), P16 (INK4a) gene contributed to the occurrence of lung cancer, which were considered to be an early event in lung carcinogenesis [130, 151]. Coke oven workers are at high risk of developing lung cancer, because of the high concentration of BaP in the working environment [25, 109]. By comparing the concentration of BaP in the air of coke oven workshop with control workshop, Zhang et al. found that the average concentration of BaP at the coke oven top (1286.5 ng/ m^3) was 147 times higher than the average concentration (8.6 ng/m^3) in control workshop, which suggested that BaP played a major role in lung cancer development in coke-oven workers. To explore the mechanism of carcinogenesis in BaP, the author chose 74 coke-oven workers long-time exposing to BaP as experimental group, and 47 plumbers who had less opportunity exposing to BaP as control group, and genomic DNA methylation from workers' PBMC were measured. The results showed that CpG island in the promoter regions of tumor suppressor genes P14 (Ark), P15 (INK4b) and P16 (INK4a)

were significantly higher in experimental group [157]. It is well known that silencing of tumor-suppressor genes is associated with the promoter-region hypermethylation, which can induce cell proliferation and over-growth, and ultimately lead to tumorigenesis. Thus, it may be the main reason for coke-oven workers at high prevalence rate of lung cancer.

DNA hypomethylation in factor II receptor-like 3 (F2RL3) and aryl hydrocarbon receptor repressor (AHRR) gene is smoking-related biomarker in blood, which closely correlated with lung cancer incidence and mortality. Alhamdow et al. [3] compared the DNA methylation of lung cancer-related genes F2RL3 and AHRR between the workers occupationally exposed to PAHs and the control group. The CpG methylation levels of AHRR and F2RL3 in the exposed group were significantly lower than those in the control group, which was consistent with the above expression.

Digestive system cancer

Gastric cancer (GC) is one of the most commonly malignant cancers [19, 82]. The common causes of GC are H. pylori infection [23], chronic atrophic gastritis [78], unhealthy diets [129] and inheritance [22] et al. China has a high incidence rate of liver cancer [36], and viral infection [79], chronic alcoholism [50], eating moldy and deteriorate foods [116] can lead to hepatic cancer. Moreover, BaP can also induce gastric and hepatic cancer [44, 140]. It has been shown that the promoter region in GSTP gene (a tumor suppressor gene) was significantly hypermethylated in HCC patients, and BPDE-Alb adducts were remarkably correlated with GSTP methylation level. In addition, there was a higher risk of developing HCC in those individuals with higher levels of BPDE-Alb adducts and GSTP hypermethylation. Tian et al. further evaluated the association between epigenetic alterations caused by BaP and the risk factors in HCC. The results showed that BaP induced the hypermethylation of promoter regions in the detoxification gene GSTP, leading to a loss of protective function owing to gene silencing, which triggered the accumulation of poisons in liver, increased oxidative stress, DNA damage and hepatocarcinogenesis [131]. B-cell CLL/lymphoma 6 member B (BCL6B) is a tumor suppressor. Once the promoter regions of BCL6B is excessively methylated, gene expression is suppressed or silenced, leading to colonic carcinoma [51], and gastric carcinogenesis [16, 87]. To explore how BCL6B functions as a tumor suppressor gene during gastric carcinogenesis, Cai et al. used Bcl6b-deficient mice and wild type mice to investigate Bcl6b's role in the development of gastritis and GC caused by BaP. The results showed in wild mice that during gastric carcinogenesis induced by BaP, Bcl6b expression was gradually decreased by its promoter

Wang *et al. Genes and Environment*   (2023) 45:21

Page 9 of 15

CpG islands hypermethylation, alongside an increased in inflammatory response. In addition, in BCL6B gene knockout mice, BaP induced inflammatory response and promoted gastric carcinogenesis [16]. Thus, BaP regulated the expression and function of BCL6B through promoter hypermethylation, then triggered an elevated inflammatory response which promoted the occurrence and development of tumors.

At present, absent expression of Retinoic Acid Receptor-β2 (RAR-β2) and hypermethylation in its promoter region have been used as diagnostic markers of oncogenesis [98]. RAR-β2 promoter hypermethylation is an early event during esophageal cancer progression [142]. It was found that RAR-β2 promoter hypermethylation was induced by BPDE, and then its expression was decreased by recruiting DNMT3A in combination with RAR-β2, which promoted the occurrence and development of esophageal cancer [153]. The inhibition of RAR-β2 expression by BPDE induced COX-2 highly expression [127], and overexpression of COX-2 was linked to esophageal cancer [4, 18]. There are some similarities between the mechanisms on lung cancer and digestive system cancer induced by BaP. BaP modulates aberrant DNA methylation or promoter hypermethylation in various tumor suppressor genes, which alters gene expression and contributes carcinogenesis.

Reproductive system cancer

breast cancer is a common malignancy in women (Sethi, Shanmugam et al. [125], Velloso, Trombetta-Lima et al. [137]). Its etiology is related to genetic factors [97], endocrine hormones [1], and exposure to environmental pollutants such as BaP [5]. There is evidence that aberrant methylation of genomic DNA contributes to breast cancer development [39], Lubecka, Kaufman-Szymczyk et al. [90], [35]. Therefore, BaP inducing breast cancer through abnormal DNA methylation is worth investigating.

In 2004, Sadikovic et al. treated MCF-7 and MDA-MB 231 cell lines by 5 mol/L of BaP, and found that the level of global genome methylation was reduced by 12% in BaP-treated cells [114]. Previous studies have shown that genome-wide hypomethylation was observed in breast cancer [100], which was consistent with Sadikovic's study. In 2006, the authors tested the growth dynamics of four breast cancer cell lines exposed to BaP, and found that BaP exposure reduced cell proliferation via accumulation of cell cycle at S and G2/M phases, and induced p53-dependent cellular apoptosis. Amplification of inter-methylated sites (AIMS) analysis showed that BaP induced the hypomethylation of tumor suppressor gene subunit 2 (TSC2) in human MCF-7 and HCC1806 cells [115], which also could be detected in breast cancer [70]. All the results indicated that p53-specific cell

cycle interruption and DNA methylation disruption were resulted from BaP exposure, and short interspersed nucleotide elements (SINEs) acted as specific targets on the association of Bap exposure with DNA methylation, which contributed to genomic instability and breast carcinogenesis.

It is suggested that exposure to environmental contaminants correlated with DNA methylation and breast cancer progression. A study on the relationship among DNA methylation, PAH-DNA adducts, and breast cancer was carried out in 2015 by White et al. Thirteen genes were identified associated with breast cancer occurrence, and that the tumor suppressor gene retinoic acid receptor beta (RARβ) and the adenomatous polyposis coli (APC) promoter specific methylation interacted with PAH-DNA adducts, which affected the hormone receptor expression, and increased the risk for developing breast cancer [144]. It is more likely to express the hypermethylation of RARβ and APC in the promoter regions in breast cancer tissue in comparison to normal breast tissue [81].

The changes of promoter methylation in death-associated protein kinase (DAPK) [27], harpin-induced 1(HIN1) [99]and Cadherin 1 (CDH1) [138] genes can be acted as biomarkers for carcinogenesis. In 2016, White et al. discussed methylation in the promoter region of cancer-related genes and global methylation in the peripheral blood of breast cancer patients with long-time exposing to PAHs. They found that the expression level of the tumor suppressors HIN1 and CDH1 were elevated, and the methylation level of death-associated protein kinase 1 (DAPK-1), a breast tumorigenic gene, was decreased. Moreover, an increased frequency of chromosomal mutations and instability were observed in peripheral blood with LINE-1 hypomethylation [145]. The results indicated that air pollutants such PAHs induced mammary tumor formation by altering the methylation of oncogenes [118]. In 2021, Sahay proved that prenatal exposure to PAHs induced the hypermethylation of CpG-2012 and CpG-2138 in estrogen receptors α (ERα) gene promoter region, reducing the expression of eRα at gene and protein levels in mouse mammary gland. Moreover, PAHs could inhibit the expression of tumor suppressor gene Brca, and eventually induced mammary carcinogenesis [117]. As the most representative carcinogen in PAHs [8, 42, 124], BaP contributed to breast cancer occurrence by changing tumor suppressor genes methylation.

Discussion

Overall, BaP as the product of combustion of organic matter including fossil fuels, can pollute the environment. Generally, BaP can be found in soil [154], air [75] and water sources [141].Because of its chemical properties [2, 52, 101], BaP can enter human body and cause the

Wang *et al. Genes and Environment*   (2023) 45:21

Page 10 of 15

incidence of disease in human. As a common toxicant, BaP triggers cell damage and cancerization by forming DNA-adduct, oxidative stress, or in the epigenetic aspect. In this review, the changes of cellular genomic methylation levels modulated by BaP were summarized. It is commonly believed that BaP reduced genome-wide methylation levels. However, Yauk et al. [152] study found that BaP induced genome-wide hypermethylation by cytosine extension assay in 2008, which might be related to the insufficient techniques. Cytosine extension assay is mainly used for testing the overall level of methylation of CpG, CpHpG, CNpG and asymmetric sites in plant tissues [10, 13], but the research objects of Yauk are animal cells, which may contribute to the sharp contrast results.

BaP as a PAHs carcinogen, enters human body through diet, cigarette smoke and gasoline exhaust, and promotes carcinogenesis in human organs and tissues. In this review, mechanisms of BaP-induced carcinogenicity were discussed at the epigenetic level. GSTP is a member of the tumor suppressor gene family, the studies of Tian et al. and Liu et al. gained different results. Tian et al. found that BaP induced hypermethylation of GSTP, but Liu et al. showed that BaP caused hypomethylation of GSTP1. The differences on the dosage of BaP and exposure time might contribute to these different results. The epigenetic toxicity of BaP was not limited to methylation and demethylation, studies have shown that BaP promoted histone acetylation and deacetylation [15, 40], which could in turn lead to abnormal chromatin structure and aberrant gene expression. The different results from Tian and Liu could be caused via other epigenetic mechanisms. It is still not well-known that BaP inducing abnormal DNA methylation associated with digestive system cancer and reproductive system cancer, but there is certain correlation between BaP exposure and tumor suppressor gene methylation in these two cancers. The epigenetic changes of genes induced by BaP and the mechanisms of carcinogenesis have not been fully elucidated, and needed a deeper understanding.

BaP is a carcinogen and can cause epigenetic changes such as DNA methylation and histone acetylation [15], in addition, BaP can affect DNA methylation and demethylation, the most important part of epigenetics, by influencing DNMTs and thus DNA methylation [77, 152]. Based on the above, it is known that DNMTs with DNA methyltransferase activity mainly include DNMT1, DNMT3a and DNMT3b, and BaP further affects genome-wide or specific gene methylation levels by increasing DNMT1 expression or decreasing DNMT3a expression [71, 152]. However, the mechanism of how BaP affects gene methylation changes by altering DNMTs is still unclear, and the enzymes involved in the methylation and demethylation process include, in addition to DNMTs, the TET protein family, which can mediate the DNA demethylation process [147]. Whether BaP causes DNA methylation changes with the involvement of TET proteins is less reported in the relevant literature. Therefore, it is important to further explore the mechanism of BaP-induced genome-wide methylation level reduction, proto-oncogene hypermethylation and oncogene hypomethylation, to discover the cause of cancer at the molecular level, to solve this puzzle by scientific means, and to provide treatment options for patients who develop cancer due to BaP exposure, and to make a significant contribution to human health. Therefore, it is urgent to explore the mechanism of how BaP affects gene methylation changes by affecting DNMTs.

Nowadays, with the development and progress of industrialization, air pollution caused by atmosphere BaP has become a problem and demands prompt solution. Cancer caused by BaP has also become one of the threatening factors for human health. Governments should not only reduce the emission of BaP to the atmosphere, but also demand further study the mechanisms on the carcinogenesis by epigenetic modification. Folic acid plays an extremely important role in human health. In addition to effectively preventing diseases such as neonatal neural tube defects and megaloblastic anemia, folic acid can provide methyl donors to participate in the transfer of one carbon unit. DNA methylation is a process in which DNMT catalyzes the covalent binding of SAM with a methyl to form 5mC. According to the above, we know that BaP can reduce the level of methylation of the whole genome, and then cause cancer, so whether folic acid, as a methyl donor, can further promote the occurrence of DNA methylation, effectively alleviate the decrease of the level of methylation of the whole genome, and then reduce the incidence of cancer is worthy of further exploration in the future. Whether 5-azacytidine (5-Aza), as an inhibitor of DNA methyltransferase, can inhibit cancer caused by the activation of BaP-induced hypomethylation of proto-oncogenes has not been reported, which is also the direction that scientists will study in the future. Finding suitable drugs to act on specific targets to reduce the incidence of cancer caused by exposure to environmental poisons, is the significance of scientific existence, but also the direction of researchers' efforts. In order to provide new insights on reducing or even eradicating the harm of BaP to public health, better maintenance of general public health should be devoted to the development of prevention.

Abbreviations

BaP   Benzo(a)pyrene
PAHs   Polycyclic aromatic hydrocarbons

Wang *et al. Genes and Environment*   (2023) 45:21

Page 11 of 15

IARC	The International Agency for Research on Cancer
ROS	Reactive oxygen species
BPDE	Benzo(a)pyrene-trans-7,8-dihydrodiol-9,10-epoxide
AHR	Aryl hydrocarbon receptor
Arnt	Aromatic receptor nuclear transporter
TET	Ten-eleven translocation
5mC	5-Methylcytosine
5hmC	5-Hydroxymethylcytosine
5fC	5-Formylcytosine
5caC	5-Carboxylcytosine
PGCs	Primordial germ cell
TDG	Thymidine DNA glycosylase
HCC	Hepatocellular carcinoma
HB	Hepatoblastoma
DNMTs	DNA methyltransferase
SAM	S-Adenosylmethionine
16HBE	Human bronchial epithelial cells
OGG1	8-Oxoguanine DNA glycosylase
RAR-β2	Retinoic acid receptor-β2
MLH1	MutL Homolog 1
NR2B	N-methyl-d-aspartate receptor subunit 2B
FLT1	FMS-like tyrosine kinase-1
CYP450	CytochromeP450
GSTP	Glutathione-S-transferase-pi
GNMT	Glycine N-methyltransferase
GSTP1	Glutathione S-transferase P1
COX-2	Cyclooxygenase-2
MSH2	MutS homolog 2
PBMC	Peripheral blood mononuclear cells
LCR	Lung Cancer Risk
UBE2O	Ubiquitin-conjugating enzyme E2 O
SAMD4A	Sterile alpha motif domain containing protein 4A
ACBD6	Acyl-CoA binding domain-containing 6
DGK2	Diacylglycerol kinase 2
SLFN13	Schlafen 13
LINE-1	Long interspersed nucleotide element 1
MGMT	O6-methylguanine-DNA methyltransferase
PSQ	Pyrosequencing
XWLC	Xuanwei lung cancer
BSP	Bisulfite sequencing PCR
DKK2	Dickkopf-2
EN1	Engrailed 1
TRIM36	Tripartite motif containing 36
NSCLC	Non-small cell lung cancer
F2RL3	Factor II receptor-like
AHRR	Aryl hydrocarbon receptor repressor
GC	Gastric cancer
BCL6B	B-cell CLL/lymphoma 6 member B
AIMS	Amplification of inter-methylated sites
SINEs	Short interspersed nucleotide elements
TSC2	Subunit 2
RARβ	Retinoic acid receptor β
APC	Adenomatous polyposis coli
DAPK	Death-associated protein kinase
HIN1	Harpin-induced
CDH1	Cadherin 1
DAPK-1	Death-associated protein kinase 1
Erα	Estrogen receptors α
5-Aza	5-Azacytidine

Authors' contributions

Huizeng Wang and Bingchun Liu: Conceptualization, Methodology. Writing—Original Draft, Hong Chen, Peixin Xu and Huiting Xue: Methodology, Writing—Review & Editing, Funding acquisition. Jianlong yuan: Conceptualization, Writing—Review & Editing, Funding acquisition.

Funding

Availability of data and materials

Not applicable because of no datasets and materials were generated or used during the current study.

Declarations

Ethics approval and consent to participate

Not applicable in this review study.

Competing interests

The authors declare no conflict of interest.

Author details

[1]Department of Laboratory Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010050, China. [2]Stem Cell Research Center, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010050, China. [3]College of Basic Medicine, Inner Mongolia Medical University, Hohhot 010010, China.

References

1. Africander D, Storbeck KH. Steroid metabolism in breast cancer: Where are we and what are we missing? Mol Cell Endocrinol. 2018;466:86–97.
2. Albornoz-Abud NA, Canul-Marín GF, Chan-Cuá I, Hernández-Núñez E, Cañizares-Martínez MA, Valdés-Lozano D, Rodríguez-Canul R, Albores-Medina A, Colli-Dula RC. Gene expression analysis on growth, development and toxicity pathways of male Nile tilapia (Oreochromis niloticus), after acute and sub-chronic benzo (α) pyrene exposures. Comp Biochem Physiol C Toxicol Pharmacol. 2021;250:109160.
3. Alhamdow A, Lindh C, Hagberg J, Graff P, Westberg H, Krais AM, Albin M, Gustavsson P, Tinnerberg H, Broberg K. DNA methylation of the cancer-related genes F2RL3 and AHRR is associated with occupational exposure to polycyclic aromatic hydrocarbons. Carcinogenesis. 2018;39(7):869–78.
4. Altorki N. COX-2: a target for prevention and treatment of esophageal cancer. J Surg Res. 2004;117(1):114–20.
5. Amadou A, Praud D, Coudon T, Deygas F, Grassot L, Faure E, Couvidat F, Caudeville J, Bessagnet B, Salizzoni P, Gulliver J, Leffondré K, Severi G, Mancini FR, Fervers B. Risk of breast cancer associated with long-term exposure to benzo[a]pyrene (BaP) air pollution: Evidence from the French E3N cohort study. Environ Int. 2021;149:106399.
6. An L, Shi Q, Fan M, Huang G, Zhu M, Zhang M, Liu Y, Weng Y. Benzo[a] pyrene injures BMP2-induced osteogenic differentiation of mesenchymal stem cells through AhR reducing BMPRII. Ecotoxicol Environ Saf. 2020;203:110930.
7. Antunes C, Sousa N, Pinto L, Marques CJ. TET enzymes in neurophysiology and brain function. Neurosci Biobehav Rev. 2019;102:337–44.
8. Baiken Y, Kanayeva D, Taipakova S, Groisman R, Ishchenko AA, Begimbetova D, Matkarimov B, Saparbaev M. Role of Base Excision Repair Pathway in the Processing of Complex DNA Damage Generated by Oxidative Stress and Anticancer Drugs. Front Cell Dev Biol. 2020;8:617884.
9. Baylin SB, Jones PA. "Epigenetic Determinants of Cancer." Cold Spring Harb Perspect Biol. 2016;8(9):a019505.
10. Bilichak A, Kovalchuk I. Analysis of Global Genome Methylation Using the Cytosine-Extension Assay. Methods Mol Biol. 2017;1456:73–9.
11. Bochtler M, Kolano A, Xu GL. DNA demethylation pathways: Additional players and regulators. BioEssays. 2017;39(1):1–13.
12. Boente C, Baragaño D, Gallego JR. Benzo[a]pyrene sourcing and abundance in a coal region in transition reveals historical pollution, rendering soil screening levels impractical. Environ Pollut. 2020;266(Pt 1):115341.

Wang *et al. Genes and Environment* (2023) 45:21

Page 12 of 15

13. Boyko A, Kovalchuk I. Detection of changes in global genome methylation using the cytosine-extension assay. Methods Mol Biol. 2010;631:33–9.

14. Bukowska B, Mokra K, Michałowicz J. "Benzo[a]pyrene-Environmental Occurrence, Human Exposure, and Mechanisms of Toxicity." Int J Mol Sci. 2022;23(11):6348.

15. Bukowska B, Sicinska P. "Influence of Benzo(a)pyrene on Different Epigenetic Processes." Int J Mol Sci. 2021;22(24):13453.

16. Cai WY, Lin LY, Wang L, Yang L, Ye GD, Zeng Q, Cheng J, Xie YY, Chen ML, Luo QC. Inhibition of Bcl6b promotes gastric cancer by amplifying inflammation in mice. Cell Commun Signal. 2019;17(1):72.

17. Campbell J, Franzen A, Van Landingham C, Lumpkin M, Crowell S, Meredith C, Loccisano A, Gentry R, Clewell H. Predicting lung dosimetry of inhaled particleborne benzo[a]pyrene using physiologically based pharmacokinetic modeling. Inhal Toxicol. 2016;28(11):520–35.

18. Chen J, Wu F, Pei HL, Gu WD, Ning ZH, Shao YJ, Huang J. Analysis of the correlation between P53 and Cox-2 expression and prognosis in esophageal cancer. Oncol Lett. 2015;10(4):2197–203.

19. Chen S, Dong H, Yang S, Guo H. Cathepsins in digestive cancers. Oncotarget. 2017;8(25):41690–700.

20. Chen Z, Zhang Y. Role of Mammalian DNA Methyltransferases in Development. Annu Rev Biochem. 2020;89:135–58.

21. Choi EK, Uyeno S, Nishida N, Okumoto T, Fujimura S, Aoki Y, Nata M, Sagisaka K, Fukuda Y, Nakao K, Yoshimoto T, Kim YS, Ono T. Alterations of c-fos gene methylation in the processes of aging and tumorigenesis in human liver. Mutat Res. 1996;354(1):123–8.

22. Choi YJ, Kim N. Gastric cancer and family history. Korean J Intern Med. 2016;31(6):1042–53.

23. Collatuzzo G, Pelucchi C, Negri E, López-Carrillo L, Tsugane S, Hidaka A, Shigueaki Hamada G, Hernández-Ramírez RU, López-Cervantes M, Malekzadeh R, Pourfarzi F, Mu L, Zhang ZF, Lunet N, La Vecchia C, Boffetta P. Exploring the interactions between Helicobacter pylori (Hp) infection and other risk factors of gastric cancer: A pooled analysis in the Stomach cancer Pooling (StoP) Project. Int J Cancer. 2021;149(6):1228–38.

24. Corrales J, Fang X, Thornton C, Mei W, Barbazuk WB, Duke M, Scheffler BE, Willett KL. Effects on specific promoter DNA methylation in zebrafish embryos and larvae following benzo[a]pyrene exposure. Comp Biochem Physiol C Toxicol Pharmacol. 2014;163:37–46.

25. Costantino JP, Redmond CK, Bearden A. Occupationally related cancer risk among coke oven workers: 30 years of follow-up. J Occup Environ Med. 1995;37(5):597–604.

26. Crake RLI, Burgess ER, Royds JA, Phillips E, Vissers MCM, Dachs GU. The Role of 2-Oxoglutarate Dependent Dioxygenases in Gliomas and Glioblastomas: A Review of Epigenetic Reprogramming and Hypoxic Response. Front Oncol. 2021;11:619300.

27. Dai L, Ma C, Zhang Z, Zeng S, Liu A, Tang S, Ren Q, Sun Y, Xu C. DAPK Promoter Methylation and Bladder Cancer Risk: A Systematic Review and Meta-Analysis. PLoS ONE. 2016;11(12):e0167228.

28. Damiani LA, Yingling CM, Leng S, Romo PE, Nakamura J, Belinsky SA. Carcinogen-induced gene promoter hypermethylation is mediated by DNMT1 and causal for transformation of immortalized bronchial epithelial cells. Cancer Res. 2008;68(21):9005–14.

29. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. Cell. 2012;150(1):12–27.

30. de Gelder S, Bakke MJ, Vos J, Rasinger JD, Ingebrigtsen K, Grung M, Ruus A, Flik G, Klaren PHM, Berntssen MHG. The effect of dietary lipid composition on the intestinal uptake and tissue distribution of benzo[a]pyrene and phenanthrene in Atlantic salmon (Salmo salar). Comp Biochem Physiol C Toxicol Pharmacol. 2016;185–186:65–76.

31. de Groot PM, Wu CC, Carter BW, Munden RF. The epidemiology of lung cancer. Transl Lung Cancer Res. 2018;7(3):220–33.

32. Dimitriou K, Kassomenos P. The influence of specific atmospheric circulation types on PM10-bound benzo(a)pyrene inhalation related lung cancer risk in Barcelona, Spain. Environ Int. 2018;112:107–14.

33. Duan H, He Z, Ma J, Zhang B, Sheng Z, Bin P, Cheng J, Niu Y, Dong H, Lin H, Dai Y, Zhu B, Chen W, Xiao Y, Zheng Y. Global and MGMT promoter hypomethylation independently associated with genomic instability of lymphocytes in subjects exposed to high-dose polycyclic aromatic hydrocarbon. Arch Toxicol. 2013;87(11):2013–22.

34. Duan J, Chen C, Li H, Ju G, Gao A, Sun Y, Zhang W. "Multifaceted Protective Effects of Hesperidin by Aromatic Hydrocarbon Receptor in Endothelial Cell Injury Induced by Benzo[a]Pyrene." Nutrients. 2022;14(3):574.

35. Elashi AA, Sasidharan Nair V, Taha RZ, Shaath H, Elkord E. DNA methylation of immune checkpoints in the peripheral blood of breast and colorectal cancer patients. Oncoimmunology. 2019;8(2):e1542918.

36. Fan Z, Zong J, Lau WY, Zhang Y. Indocyanine green and its nanosynthetic particles for the diagnosis and treatment of hepatocellular carcinoma. Am J Transl Res. 2020;12(6):2344–52.

37. Fang X, Thornton C, Scheffler BE, Willett KL. Benzo[a]pyrene decreases global and gene specific DNA methylation during zebrafish development. Environ Toxicol Pharmacol. 2013;36(1):40–50.

38. Feng Y, Chen JJ, Xie NB, Ding JH, You XJ, Tao WB, Zhang X, Yi C, Zhou X, Yuan BF, Feng YQ. Direct decarboxylation of ten-eleven translocation-produced 5-carboxylcytosine in mammalian genomes forms a new mechanism for active DNA demethylation. Chem Sci. 2021;12(34):11322–9.

39. Fleischer T, Tekpli X, Mathelier A, Wang S, Nebdal D, Dhakal HP, Sahlberg KK, Schlichting E, Børresen-Dale AL, Borgen E, Naume B, Eskeland R, Frigessi A, Tost J, Hurtado A, Kristensen VN. DNA methylation at enhancers identifies distinct breast cancer lineages. Nat Commun. 2017;8(1):1379.

40. Fu I, Cai Y, Geacintov NE, Zhang Y, Broyde S. Nucleosome Histone Tail Conformation and Dynamics: Impacts of Lysine Acetylation and a Nearby Minor Groove Benzo[a]pyrene-Derived Lesion. Biochemistry. 2017;56(14):1963–73.

41. Fujii-Kuriyama Y, Mimura J. Molecular mechanisms of AhR functions in the regulation of cytochrome P450 genes. Biochem Biophys Res Commun. 2005;338(1):311–7.

42. Gao M, Zheng A, Chen L, Dang F, Liu X, Gao J. Benzo(a)pyrene affects proliferation with reference to metabolic genes and ROS/HIF-1α/HO-1 signaling in A549 and MCF-7 cancer cells. Drug Chem Toxicol. 2022;45(2):741–9.

43. Gargaro M, Manni G, Scalisi G, Puccetti P, Fallarino F. "Tryptophan Metabolites at the Crossroad of Immune-Cell Interaction via the Aryl Hydrocarbon Receptor: Implications for Tumor Immunotherapy." Int J Mol Sci. 2021;22(9):4644.

44. Ge Y, Gu P, Wang W, Cao L, Zhang L, Li J, Mu W, Wang H. Benzo[a]pyrene stimulates miR-650 expression to promote the pathogenesis of fatty liver disease and hepatocellular carcinoma via SOCS3/JAK/STAT3 cascades. J Mol Cell Biol. 2021;13(8):556–64.

45. Gholizadah S, Mohammadi R, Soleimani D, Rezaei M, Ahanikamangar S, Mosalmanzadeh N, Nachvak SM, Fattahi N. Polycyclic aromatic hydrocarbons in grilled foods from Kermanshah province. Food Addit Contam Part B Surveill. 2021;14(4):287–94.

46. Goedtke L, Sprenger H, Hofmann U, Schmidt FF, Hammer HS, Zanger UM, Poetz O, Seidel A, Braeuning A, Hessel-Pras S. "Polycyclic Aromatic Hydrocarbons Activate the Aryl Hydrocarbon Receptor and the Constitutive Androstane Receptor to Regulate Xenobiotic Metabolism in Human Liver Cells." Int J Mol Sci. 2020;22(1):372.

47. Gokul G, Khosla S. DNA methylation and cancer. Subcell Biochem. 2013;61:597–625.

48. Gonzalo V, Castellví-Bel S, Balaguer F, Pellisé M, Ocaña T, Castells A. Epigenetics of cancer. Gastroenterol Hepatol. 2008;31(1):37–45.

49. Graff JR, Gabrielson E, Fujii H, Baylin SB, Herman JG. Methylation patterns of the E-cadherin 5′CpG island are unstable and reflect the dynamic, heterogeneous loss of E-cadherin expression during metastatic progression. J Biol Chem. 2000;275(4):2727–32.

50. Grewal P, Viswanathen VA. Liver cancer and alcohol. Clin Liver Dis. 2012;16(4):839–50.

51. Gu Y, Li A, Sun H, Li X, Zha H, Zhao J, Xie J, Zeng Z, Zhou L. BCL6B suppresses proliferation and migration of colorectal carcinoma cells through inhibition of the PI3K/AKT signaling pathway. Int J Mol Med. 2018;41(5):2660–8.

52. Guo J, Wen X. Performance and kinetics of benzo(a)pyrene biodegradation in contaminated water and soil and improvement of soil properties by biosurfactant amendment. Ecotoxicol Environ Saf. 2021;207:111292.

53. Gutierrez-Urbano I, Villen-Guzman M, Perez-Recuerda R, Rodriguez-Maroto JM. Removal of polycyclic aromatic hydrocarbons (PAHs) in conventional drinking water treatment processes. J Contam Hydrol. 2021;243:103888.

Wang *et al. Genes and Environment*   (2023) 45:21

Page 13 of 15

54. Hatano Y, Ideta T, Hirata A, Hatano K, Tomita H, Okada H, Shimizu M, Tanaka T, Hara A. "Virus-Driven Carcinogenesis." Cancers (Basel). 2021;13(11):2625.

55. He Z, Li D, Ma J, Chen L, Duan H, Zhang B, Gao C, Li J, Xing X, Zhao J, Wang S, Wang F, Zhang H, Li H, Chen S, Zeng X, Wang Q, Xiao Y, Zheng Y, Chen W. TRIM36 hypermethylation is involved in polycyclic aromatic hydrocarbons-induced cell transformation. Environ Pollut. 2017;225:93–103.

56. He Z, Zhang R, Chen S, Chen L, Li H, Ye L, Li Q, Wang Z, Wang Q, Duan H, Niu Y, Xiao Y, Dong G, Li D, Yu D, Zheng Y, Xing X, Chen W. FLT1 hypermethylation is involved in polycyclic aromatic hydrocarbons-induced cell transformation. Environ Pollut. 2019;252(Pt A):607–15.

57. Hermann A, Gowher H, Jeltsch A. Biochemistry and biology of mammalian DNA methyltransferases. Cell Mol Life Sci. 2004;61(19–20):2571–87.

58. Hidaka T, Fujimura T, Aiba S. Aryl Hydrocarbon Receptor Modulates Carcinogenesis and Maintenance of Skin Cancers. Front Med (Lausanne). 2019;6:194.

59. Hiddinga BI, Pauwels P, Janssens A, van Meerbeeck JP. O(6)-Methylguanine-DNA methyltransferase (MGMT): A drugable target in lung cancer? Lung Cancer. 2017;107:91–9.

60. Hoang TT, Qi C, Paul KC, Lee M, White JD, Richards M, Auerbach SS, Long S, Shrestha S, Wang T, Beane Freeman LE, Hofmann JN, Parks C, Xu CJ, Ritz B, Koppelman GH, London SJ. Epigenome-Wide DNA Methylation and Pesticide Use in the Agricultural Lung Health Study. Environ Health Perspect. 2021;129(4):97008.

61. Hoffman EC, Reyes H, Chu FF, Sander F, Conley LH, Brooks BA, Hankinson O. Cloning of a factor required for activity of the Ah (dioxin) receptor. Science. 1991;252(5008):954–8.

62. Huang H, Hu G, Cai J, Xia B, Liu J, Li X, Gao W, Zhang J, Liu Y, Zhuang Z. Role of poly(ADP-ribose) glycohydrolase silencing in DNA hypomethylation induced by benzo(a)pyrene. Biochem Biophys Res Commun. 2014;452(3):708–14.

63. Huang L, Xiao X, Yao Y, Yu J, Chen Q, Liang P, Zhang Y. Benzo[a]pyrene promotes progression in tongue squamous cell carcinoma. Oral Dis. 2020;26(8):1649–58.

64. Huang Y, Zhang J, Tao Y, Ji C, Aniagu S, Jiang Y, Chen T. AHR/ROS-mediated mitochondria apoptosis contributes to benzo[a]pyrene-induced heart defects and the protective effects of resveratrol. Toxicology. 2021;462:152965.

65. Huang Z, Yu J, Johnson J, Jin SG, Pfeifer GP. Purification of TET Proteins. Methods Mol Biol. 2021;2272:225–37.

66. Ili C, Buchegger K, Demond H, Castillo-Fernandez J, Kelsey G, Zanella L, Abanto M, Riquelme I, López J, Viscarra T, García P, Bellolio E, Saavedra D, Brebi P. "Landscape of Genome-Wide DNA Methylation of Colorectal Cancer Metastasis." Cancers (Basel). 2020;12(9):2710.

67. Jassem E, Szymanowska A, Sieminska A, Jassem J. Smoking and lung cancer. Pneumonol Alergol Pol. 2009;77(5):469–73.

68. Ji Y, Wang Y, Shen D, Kang Q, Ma J, Chen L. Revisiting the cellular toxicity of benzo[a]pyrene from the view of nanoclusters: size- and nanoplastic adsorption-dependent bioavailability. Nanoscale. 2021;13(2):1016–28.

69. Jiang CL, He SW, Zhang YD, Duan HX, Huang T, Huang YC, Li GF, Wang P, Ma LJ, Zhou GB, Cao Y. Air pollution and DNA methylation alterations in lung cancer: A systematic and comparative study. Oncotarget. 2017;8(1):1369–91.

70. Jiang WG, Sampson J, Martin TA, Lee-Jones L, Watkins G, Douglas-Jones A, Mokbel K, Mansel RE. Tuberin and hamartin are aberrantly expressed and linked to clinical outcome in human breast cancer: the role of promoter methylation of TSC genes. Eur J Cancer. 2005;41(11):1628–36.

71. Jin F, Thaiparambil J, Donepudi SR, Vantaku V, Piyarathna DWB, Maity S, Krishnapuram R, Putluri V, Gu F, Purwaha P, Bhowmik SK, Ambati CR, von Rundstedt FC, Roghmann F, Berg S, Noldus J, Rajapakshe K, Gödde D, Roth S, Störkel S, Degener S, Michailidis G, Kaipparettu BA, Karanam B, Terris MK, Kavuri SM, Lerner SP, Kheradmand F, Coarfa C, Sreekumar A, Lotan Y, El-Zein R, Putluri N. Tobacco-Specific Carcinogens Induce Hypermethylation, DNA Adducts, and DNA Damage in Bladder Cancer. Cancer Prev Res (Phila). 2017;10(10):588–97.

72. Jones PA, Baylin SB. The epigenomics of cancer. Cell. 2007;128(4):683–92.

73. Knecht AL, Truong L, Simonich MT, Tanguay RL. Developmental benzo[a]pyrene (B[a]P) exposure impacts larval behavior and impairs adult learning in zebrafish. Neurotoxicol Teratol. 2017;59:27–34.

74. Kodzhahinchev V, Shekh K, Weber LP, Niyogi S. Interactive effects of cadmium and Benzo[a]pyrene in adult zebrafish (Danio rerio) during short-term aqueous co-exposure. Environ Pollut. 2021;272:116027.

75. Kosińska I, Nitsch-Osuch A. Benzo(a)pyrene in atmospheric and indoor air, health hazards and possibilities of limitation. Pol Merkur Lekarski. 2020;49(286):282–8.

76. Koukoura O, Sifakis S, Spandidos DA. DNA methylation in the human placenta and fetal growth (review). Mol Med Rep. 2012;5(4):883–9.

77. Kuc C, Richard DJ, Johnson S, Bragg L, Servos MR, Doxey AC, Craig PM. Rainbow trout exposed to benzo[a]pyrene yields conserved microRNA binding sites in DNA methyltransferases across 500 million years of evolution. Sci Rep. 2017;7(1):16843.

78. Lahner E, Carabotti M, Annibale B. Treatment of Helicobacter pylori infection in atrophic gastritis. World J Gastroenterol. 2018;24(22):2373–80.

79. Lebossé F, Zoulim F. Hepatitis B vaccine and liver cancer. Bull Cancer. 2021;108(1):90–101.

80. Lee SE, Kwon K, Oh SW, Park SJ, Yu E, Kim H, Yang S, Park JY, Chung WJ, Cho JY, Lee J. Mechanisms of Resorcinol Antagonism of Benzo[a]pyrene-Induced Damage to Human Keratinocytes. Biomol Ther (Seoul). 2021;29(2):227–33.

81. Lewis CM, Cler LR, Bu DW, Zochbauer-Muller S, Milchgrub S, Naftalis EZ, Leitch AM, Minna JD, Euhus DM. Promoter hypermethylation in benign breast epithelium in relation to predicted breast cancer risk. Clin Cancer Res. 2005;11(1):166–72.

82. Li B, Chen L, Luo HL, Yi FM, Wei YP, Zhang WX. Docetaxel, cisplatin, and 5-fluorouracil compared with epirubicin, cisplatin, and 5-fluorouracil regimen for advanced gastric cancer: A systematic review and meta-analysis. World J Clin Cases. 2019;7(5):600–15.

83. Li C, Hong W. Research status and funding trends of lung cancer biomarkers. J Thorac Dis. 2013;5(5):698–705.

84. Li M, Liu J, Zhou J, Liu A, Chen E, Yang Q. DNA adduct formation and reduced EIF4A3expression contributes to benzo[a]pyrene-induced DNA damage in human bronchial epithelial BEAS-2B cells. Toxicol Lett. 2021;351:53–64.

85. Li W, Hu J, Adebali O, Adar S, Yang Y, Chiou YY, Sancar A. Human genome-wide repair map of DNA damage caused by the cigarette smoke carcinogen benzo[a]pyrene. Proc Natl Acad Sci U S A. 2017;114(26):6752–7.

86. Li X, Yao X, Wang Y, Hu F, Wang F, Jiang L, Liu Y, Wang D, Sun G, Zhao Y. MLH1 promoter methylation frequency in colorectal cancer patients and related clinicopathological and molecular features. PLoS ONE. 2013;8(3):e59064.

87. Li X, Yu J, Brock MV, Tao Q, Herman JG, Liang P, Guo M. Epigenetic silencing of BCL6B inactivates p53 signaling and causes human hepatocellular carcinoma cell resist to 5-FU. Oncotarget. 2015;6(13):11547–60.

88. Liu A, Li X, Hao Z, Cao J, Li H, Sun M, Zhang Z, Liang R, Zhang H. Alterations of DNA methylation and mRNA levels of CYP1A1, GSTP1, and GSTM1 in human bronchial epithelial cells induced by benzo[a]pyrene. Toxicol Ind Health. 2022;38(3):127–38.

89. Liu D, Li G, Zuo Y. Function determinants of TET proteins: the arrangements of sequence motifs with specific codes. Brief Bioinform. 2019;20(5):1826–35.

90. Lubecka K, Kaufman-Szymczyk A, Cebula-Obrzut B, Smolewski P, Szemraj J, Fabianowska-Majewska K. "Novel Clofarabine-Based Combinations with Polyphenols Epigenetically Reactivate Retinoic Acid Receptor Beta, Inhibit Cell Growth, and Induce Apoptosis of Breast Cancer Cells." Int J Mol Sci. 2018;19(12):3970.

91. Ma Z, Liu X, Zhang Q, Yu Z, Gao D. Carvedilol suppresses malignant proliferation of mammary epithelial cells through inhibition of the ROS-mediated PI3K/AKT signaling pathway. Oncol Rep. 2019;41(2):811–8.

92. Madeen E, Siddens LK, Uesugi S, McQuistan T, Corley RA, Smith J, Waters KM, Tilton SC, Anderson KA, Ognibene T, Turteltaub K, Williams DE. Toxicokinetics of benzo[a]pyrene in humans: Extensive metabolism as determined by UPLC-accelerator mass spectrometry following oral micro-dosing. Toxicol Appl Pharmacol. 2019;364:97–105.

93. Martisova A, Holcakova J, Izadi N, Sebuyoya R, Hrstka R, Bartosik M. "DNA Methylation in Solid Tumors: Functions and Methods of Detection." Int J Mol Sci. 2021;22(8):4247.

Wang *et al. Genes and Environment*   (2023) 45:21

Page 14 of 15

94. Melamed P, Yosefzon Y, David C, Tsukerman A, Pnueli L. Tet Enzymes, Variants, and Differential Effects on Function. Front Cell Dev Biol. 2018;6:22.

95. Meng H, Li G, Wei W, Bai Y, Feng Y, Fu M, Guan X, Li M, Li H, Wang C, Jie J, Wu X, He M, Zhang X, Wei S, Li Y, Guo H. Epigenome-wide DNA methylation signature of benzo[a]pyrene exposure and their mediation roles in benzo[a]pyrene-associated lung cancer development. J Hazard Mater. 2021;416:125839.

96. Miller KP, Ramos KS. Impact of cellular metabolism on the biological effects of benzo[a]pyrene and related hydrocarbons. Drug Metab Rev. 2001;33(1):1–35.

97. Moghbeli M. Genetic and molecular biology of breast cancer among Iranian patients. J Transl Med. 2019;17(1):218.

98. Mongan NP, Gudas LJ. Diverse actions of retinoid receptors in cancer prevention and treatment. Differentiation. 2007;75(9):853–70.

99. Moses-Fynn E, Tang W, Beyene D, Apprey V, Copeland R, Kanaan Y, Kwabi-Addo B. Correlating blood-based DNA methylation markers and prostate cancer risk in African-American men. PLoS ONE. 2018;13(9):e0203322.

100. Narayan A, Ji W, Zhang XY, Marrogi A, Graff JR, Baylin SB, Ehrlich M. Hypomethylation of pericentromeric DNA in breast adenocarcinomas. Int J Cancer. 1998;77(6):833–8.

101. Nzila A, Musa MM. "Current Status of and Future Perspectives in Bacterial Degradation of Benzo[a]pyrene." Int J Environ Res Public Health. 2020;18(1):262.

102. Omidian K, Rafiei H, Bandy B. Increased mitochondrial content and function by resveratrol and select flavonoids protects against benzo[a]pyrene-induced bioenergetic dysfunction and ROS generation in a cell model of neoplastic transformation. Free Radic Biol Med. 2020;152:767–75.

103. Onabote O, Hassan HM, Isovic M, Torchia J. "The Role of Thymine DNA Glycosylase in Transcription, Active DNA Demethylation, and Cancer." Cancers (Basel). 2022;14(3):765.

104. Onodera A, González-Avalos E, Lio CJ, Georges RO, Bellacosa A, Nakayama T, Rao A. Roles of TET and TDG in DNA demethylation in proliferating and non-proliferating immune cells. Genome Biol. 2021;22(1):186.

105. Patchsung M, Boonla C, Amnattrakul P, Dissayabutra T, Mutirangura A, Tosukhowong P. Long interspersed nuclear element-1 hypomethylation and oxidative stress: correlation and bladder cancer diagnostic potential. PLoS ONE. 2012;7(5):e37009.

106. Penning TM. Human aldo-keto reductases and the metabolic activation of polycyclic aromatic hydrocarbons. Chem Res Toxicol. 2014;27(11):1901–17.

107. Pham DAT, Le SD, Doan TM, Luu PT, Nguyen UQ, Ho SV, Vo LTT. Standardization of DNA amount for bisulfite conversion for analyzing the methylation status of LINE-1 in lung cancer. PLoS ONE. 2021;16(8): e0256254.

108. Qazi F, Shahsavari E, Prawer S, Ball AS, Tomljenovic-Hanic S. Detection and identification of polyaromatic hydrocarbons (PAHs) contamination in soil using intrinsic fluorescence. Environ Pollut. 2021;272:116010.

109. Redmond CK. Cancer mortality among coke oven workers. Environ Health Perspect. 1983;52:67–73.

110. Reiter-Brennan C, Semmler L, Klein A. The effects of 2-hydroxyglutarate on the tumorigenesis of gliomas. Contemp Oncol (Pozn). 2018;22(4):215–22.

111. Ren N, Atyah M, Chen WY, Zhou CH. The various aspects of genetic and epigenetic toxicology: testing methods and clinical applications. J Transl Med. 2017;15(1):110.

112. Rhee YY, Kim KJ, Kang GH. CpG Island Methylator Phenotype-High Colorectal Cancers and Their Prognostic Implications and Relationships with the Serrated Neoplasia Pathway. Gut Liver. 2017;11(1):38–46.

113. Ross SE, Bogdanovic O. TET enzymes, DNA demethylation and pluripotency. Biochem Soc Trans. 2019;47(3):875–85.

114. Sadikovic B, Haines TR, Butcher DT, Rodenhiser DI. Chemically induced DNA hypomethylation in breast carcinoma cells detected by the amplification of intermethylated sites. Breast Cancer Res. 2004;6(4):R329-337.

115. Sadikovic B, Rodenhiser DI. Benzopyrene exposure disrupts DNA methylation and growth dynamics in breast cancer cells. Toxicol Appl Pharmacol. 2006;216(3):458–68.

116. Saha Turna N, Wu F. Risk assessment of aflatoxin-related liver cancer in Bangladesh. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2019;36(2):320–6.

117. Sahay D, Lloyd SE, Rivera JA, Jezioro J, McDonald JD, Pitiranggon M, Yan B, Szabolcs M, Terry MB, Miller RL. Prenatal polycyclic aromatic hydrocarbons, altered ERα pathway-related methylation and expression, and mammary epithelial cell proliferation in offspring and grandoffspring adult mice. Environ Res. 2021;196: 110961.

118. Sahay D, Terry MB, Miller R. Is breast cancer a result of epigenetic responses to traffic-related air pollution? A review of the latest evidence. Epigenomics. 2019;11(6):701–14.

119. Saito K, Kawakami K, Matsumoto I, Oda M, Watanabe G, Minamoto T. Long interspersed nuclear element 1 hypomethylation is a marker of poor prognosis in stage IA non-small cell lung cancer. Clin Cancer Res. 2010;16(8):2418–26.

120. Salem ML, El-Ashmawy NE, Abd El-Fattah EE, Khedr EG. Immunosuppressive role of Benzo[a]pyrene in induction of lung cancer in mice. Chem Biol Interact. 2021;333: 109330.

121. Saunders CR, Das SK, Ramesh A, Shockley DC, Mukherjee S. Benzo(a) pyrene-induced acute neurotoxicity in the F-344 rat: role of oxidative stress. J Appl Toxicol. 2006;26(5):427–38.

122. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, Perez-Padilla R, Rice MB, Riojas-Rodriguez H, Sood A, Thurston GD, To T, Vanker A, Wuebbles DJ. Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems. Chest. 2019;155(2):417–26.

123. Schreiberová M, Vlasáková L, Vlek O, Mejdíová J, Horálek J, Bieser JJA. "Benzo[a]pyrene in the Ambient Air in the Czech Republic: Emission Sources, Current and Long-Term Monitoring Analysis and Human Exposure." Atmosphere. 2020;11(9):955.

124. Seo JS, Keum YS, Li QX. Bacterial degradation of aromatic compounds. Int J Environ Res Public Health. 2009;6(1):278–309.

125. Sethi G, Shanmugam MK, Arfuso F, Kumar AP. "Role of RNF20 in cancer development and progression - a comprehensive review." Biosci Rep. 2018;38(4):BSR20171287.

126. Shen L, Wu H, Diep D, Yamaguchi S, D'Alessio AC, Fung HL, Zhang K, Zhang Y. Genome-wide analysis reveals TET- and TDG-dependent 5-methylcytosine oxidation dynamics. Cell. 2013;153(3):692–706.

127. Song S, Lippman SM, Zou Y, Ye X, Ajani JA, Xu XC. Induction of cyclooxygenase-2 by benzo[a]pyrene diol epoxide through inhibition of retinoic acid receptor-beta 2 expression. Oncogene. 2005;24(56):8268–76.

128. Svedružić Ž, M. Dnmt1 structure and function. Prog Mol Biol Transl Sci. 2011;101:221–54.

129. Tay SW, Li JW, Fock KM. Diet and cancer of the esophagus and stomach. Curr Opin Gastroenterol. 2021;37(2):158–63.

130. Tian K, Lin L, Jia Z, Guo X, Zhang L. Promoter methylation status and protein expression of p14ARF gene in squamous cell carcinoma and adenocarcinoma of the lung. Zhongguo Fei Ai Za Zhi. 2006;9(1):40–4.

131. Tian M, Zhao B, Zhang J, Martin FL, Huang Q, Liu L, Shen H. Association of environmental benzo[a]pyrene exposure and DNA methylation alterations in hepatocellular carcinoma: A Chinese case-control study. Sci Total Environ. 2016;541:1243–52.

132. Toh TB, Lim JJ, Chow EK. Epigenetics in cancer stem cells. Mol Cancer. 2017;16(1):29.

133. Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016;893:1–19.

134. Tsagaratou A, Lio CJ, Yue X, Rao A. TET Methylcytosine Oxidases in T Cell and B Cell Development and Function. Front Immunol. 2017;8:220.

135. Uysal F, Akkoyunlu G, Ozturk S. Dynamic expression of DNA methyltransferases (DNMTs) in oocytes and early embryos. Biochimie. 2015;116:103–13.

136. Veiga CB, Lawrence EM, Murphy AJ, Herold MJ, Dragoljevic D. "Myelodysplasia Syndrome, Clonal Hematopoiesis and Cardiovascular Disease." Cancers (Basel). 2021;13(8):1968.

137. Velloso FJ, Trombetta-Lima M, Anschau V, Sogayar MC, Correa RG. "NOD-like receptors: major players (and targets) in the interface between innate immunity and cancer." Biosci Rep. 2019;39(4):BSR20181709.

138. Wang Q, Wang B, Zhang YM, Wang W. The association between CDH1 promoter methylation and patients with ovarian cancer: a systematic meta-analysis. J Ovarian Res. 2016;9:23.

Wang *et al. Genes and Environment*   (2023) 45:21

Page 15 of 15

139. Wang Q, Wang W, Zhang A. TET-mediated DNA demethylation plays an important role in arsenic-induced HBE cells oxidative stress via regulating promoter methylation of OGG1 and GSTP1. Toxicol In Vitro. 2021;72:105075.
140. Wang Q, Xue Y. Characterization of solid tumors induced by polycyclic aromatic hydrocarbons in mice. Med Sci Monit Basic Res. 2015;21:81–5.
141. Wang X, Zhang X, Wang X, Liang W, Wang J, Niu L, Zhao X, Wu F. Deriving convincing human health ambient water quality criteria for benzo[a]pyrene and providing basis for the water quality management: The impacts of national bioaccumulation factors and probabilistic modeling. Sci Total Environ. 2022;814:152523.
142. Wang Y, Fang MZ, Liao J, Yang GY, Nie Y, Song Y, So C, Xu X, Wang LD, Yang CS. Hypermethylation-associated inactivation of retinoic acid receptor beta in human esophageal squamous cell carcinoma. Clin Cancer Res. 2003;9(14):5257–63.
143. Wei Y, Zhao L, He W, Yang J, Geng C, Chen Y, Liu T, Chen H, Li Y. Benzo[a]pyrene promotes gastric cancer cell proliferation and metastasis likely through the Aryl hydrocarbon receptor and ERK-dependent induction of MMP9 and c-myc. Int J Oncol. 2016;49(5):2055–63.
144. White AJ, Chen J, McCullough LE, Xu X, Cho YH, Teitelbaum SL, Neugut AI, Terry MB, Hibshoosh H, Santella RM, Gammon MD. Polycyclic aromatic hydrocarbon (PAH)-DNA adducts and breast cancer: modification by gene promoter methylation in a population-based study. Cancer Causes Control. 2015;26(12):1791–802.
145. White AJ, Chen J, Teitelbaum SL, McCullough LE, Xu X, Hee Cho Y, Conway K, Beyea J, Stellman SD, Steck SE, Mordukhovich I, Eng SM, Beth Terry M, Engel LS, Hatch M, Neugut AI, Hibshoosh H, Santella RM, Gammon MD. Sources of polycyclic aromatic hydrocarbons are associated with gene-specific promoter methylation in women with breast cancer. Environ Res. 2016;145:93–100.
146. Wilson AS, Power BE, Molloy PL. DNA hypomethylation and human diseases. Biochim Biophys Acta. 2007;1775(1):138–62.
147. Wu X, Zhang Y. TET-mediated active DNA demethylation: mechanism, function and beyond. Nat Rev Genet. 2017;18(9):517–34.
148. Xia B, Yang LQ, Huang HY, Pang L, Yang XF, Yi YJ, Ren XH, Li J, Zhuang ZX, Liu JJ. Repression of Biotin-Related Proteins by Benzo[a]Pyrene-Induced Epigenetic Modifications in Human Bronchial Epithelial Cells. Int J Toxicol. 2016;35(3):336–43.
149. Xue Y, Nie D, Wang LJ, Qiu HC, Ma L, Dong MX, Tu WJ, Zhao J. Microglial Polarization: Novel Therapeutic Strategy against Ischemic Stroke. Aging Dis. 2021;12(2):466–79.
150. Xue Y, Wang L, Zhang Y, Zhao Y, Liu Y. Air pollution: A culprit of lung cancer. J Hazard Mater. 2022;434:128937.
151. Yang P, Ma J, Zhang B, Duan H, He Z, Zeng J, Zeng X, Li D, Wang Q, Xiao Y, Liu C, Xiao Q, Chen L, Zhu X, Xing X, Li Z, Zhang S, Zhang Z, Ma L, Wang E, Zhuang Z, Zheng Y, Chen W. CpG site-specific hypermethylation of p16INK4α in peripheral blood lymphocytes of PAH-exposed workers. Cancer Epidemiol Biomarkers Prev. 2012;21(1):182–90.
152. Yauk CL, Polyzos A, Rowan-Carroll A, Kortubash I, Williams A, Kovalchuk O. Tandem repeat mutation, global DNA methylation, and regulation of DNA methyltransferases in cultured mouse embryonic fibroblast cells chronically exposed to chemicals with different modes of action. Environ Mol Mutagen. 2008;49(1):26–35.
153. Ye F, Xu XC. Benzo[a]pyrene diol epoxide suppresses retinoic acid receptor-beta2 expression by recruiting DNA (cytosine-5-)-methyltransferase 3A. Mol Cancer. 2010;9:93.
154. Yi M, Zhang L, Li Y, Qian Y. Structural, metabolic, and functional characteristics of soil microbial communities in response to benzo[a]pyrene stress. J Hazard Mater. 2022;431: 128632.
155. Zafon C, Gil J, Pérez-González B, Jordà M. DNA methylation in thyroid cancer. Endocr Relat Cancer. 2019;26(7):R415-r439.
156. Zarei R, Moghadam D, Sarabi MM, Naghibalhossaini F. The effect of benzo[alpha]pyrene on DNA methylation and telomerase activity in human normal and cancer cells. Toxicol In Vitro. 2022;80: 105331.
157. Zhang H, Li X, Ge L, Yang J, Sun J, Niu Q. Methylation of CpG island of p14(ARK), p15(INK4b) and p16(INK4a) genes in coke oven workers. Hum Exp Toxicol. 2015;34(2):191–7.
158. Zhang W, Tian F, Zheng J, Li S, Qiang M. Chronic Administration of Benzo(a)pyrene Induces Memory Impairment and Anxiety-Like Behavior and Increases of NR2B DNA Methylation. PLoS ONE. 2016;11(2):e0149574.
159. Zhang Y, Chen X, Zhang Y. Analytical chemistry, formation, mitigation, and risk assessment of polycyclic aromatic hydrocarbons: From food processing to in vivo metabolic transformation. Compr Rev Food Sci Food Saf. 2021;20(2):1422–56.
160. Zhao L, Zhang S, Anik X, Tan W, Pang D, Ouyang H. "Toxicological effects of benzo[a]pyrene on DNA methylation of whole genome in ICR mice". Cell Mol Biol (Noisy-le-grand). 2015;61(5):115–9.
161. Zhenwei J, Shuxin G, Yongchun Z, Xianhua Z. Mechanisms of TET protein-mediated DNA demethylation and its role in the regulation of mouse development. Yi Chuan. 2015;37(1):34–40.

Publisher's Note