ANNUAL REVIEWS

Annual Review of Public Health

Environmental Influences on the Epigenome: Exposure-Associated DNA Methylation in Human Populations

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Annu. Rev. Public Health 2018. 39:309–33

First published as a Review in Advance on January 12, 2018

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

https://doi.org/10.1146/annurev-publhealth-040617-014629

Keywords

environment, epigenetics, human studies, molecular epidemiology

Abstract

DNA methylation is the most well studied of the epigenetic regulators in relation to environmental exposures. To date, numerous studies have detailed the manner by which DNA methylation is influenced by the environment, resulting in altered global and gene-specific DNA methylation. These studies have focused on prenatal, early-life, and adult exposure scenarios. The present review summarizes currently available literature that demonstrates a relationship between DNA methylation and environmental exposures. It includes studies on aflatoxin B_1, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke, and nutritional factors. It also addresses gaps in the literature and future directions for research. These gaps include studies of mixtures, sexual dimorphisms with respect to environmentally associated methylation changes, tissue specificity, and temporal stability of the methylation marks.

INTRODUCTION

The Epigenome: An Overview

Epigenetic machinery influences gene expression [messenger RNA (mRNA)] and subsequent protein expression levels but does not alter primary DNA sequence (83). In this way, epigenetic regulation allows for an immediate organism-level adaptation to the environment (176). Three major epigenetic regulators have been described. These include histone modifications, cytosine-phosphate-guanine (CpG) DNA methylation, and noncoding RNA expression (83). This review details studies on DNA methylation alterations in humans assessed in relation to prenatal environmental exposures, as well as studies of chronic adult exposure. We describe the state of the literature on environmental triggers for CpG methylation in human populations. We also highlight current gaps in research and future areas for study (see the sidebar titled Terms and Definitions for further explanation of terms used throughout this article).

DNA Methylation

DNA methylation is the addition of a methyl group at the fifth carbon position of the cytosine base (**Figure 1**). Typically, 5-methylcyotine (5-mC) bases are often proximal to guanine,

TERMS AND DEFINITIONS

Alu methylation: a measure of global methylation at Alu transposable elements
CpG: cytosine-phosphate-guanine
CpG methylation: addition of a methyl group to a cytosine at the 5′ position
mC: a methyl (-CH3) mark added to the 5′ position of cytosine
hmC: a hydroxymethyl (-HOCH3) mark added to the 5′ position of cytosine; the first step in the active demethylation process
fmC: a formylmethyl mark added to the 5′ position of cytosine; the second step of the active demethylation process
cmC: a carboxymethyl mark added to the 5′ position of cytosine; the final step of the active demethylation process
CpG loci: specific locations within the genome at which methylation of cytosine is altered
DNA: deoxyribonucleic acid; the carrier of the genetic code
DNA methylation: an epigenetic mark where a methyl group is added to the 5′ position of cytosine
DNMT: DNA methyltransferase; the enzyme family responsible for DNA methylation
In utero: prenatal
In vitro: experiments conducted in cell culture
In vivo: experiments conducted in live animals
LC/MS methylation: a measure of global methylation using liquid chromatography/mass spectrometry
LINE-1 methylation: a measure of global methylation utilizing methylation patterning at long interspersed nuclear elements (LINEs)
mRNA: messenger RNA, also called transcript or gene expression
RNA: ribonucleic acid; the copy of DNA that is used to create proteins
SAM: S-adenosylmethionine; the substrate needed for DNA methylation
TDG: thymine-DNA glycosylase; the primary enzyme responsible for removal of fmC and cmC
TET: ten-eleven translocation protein; the enzyme family responsible for active DNA demethylation

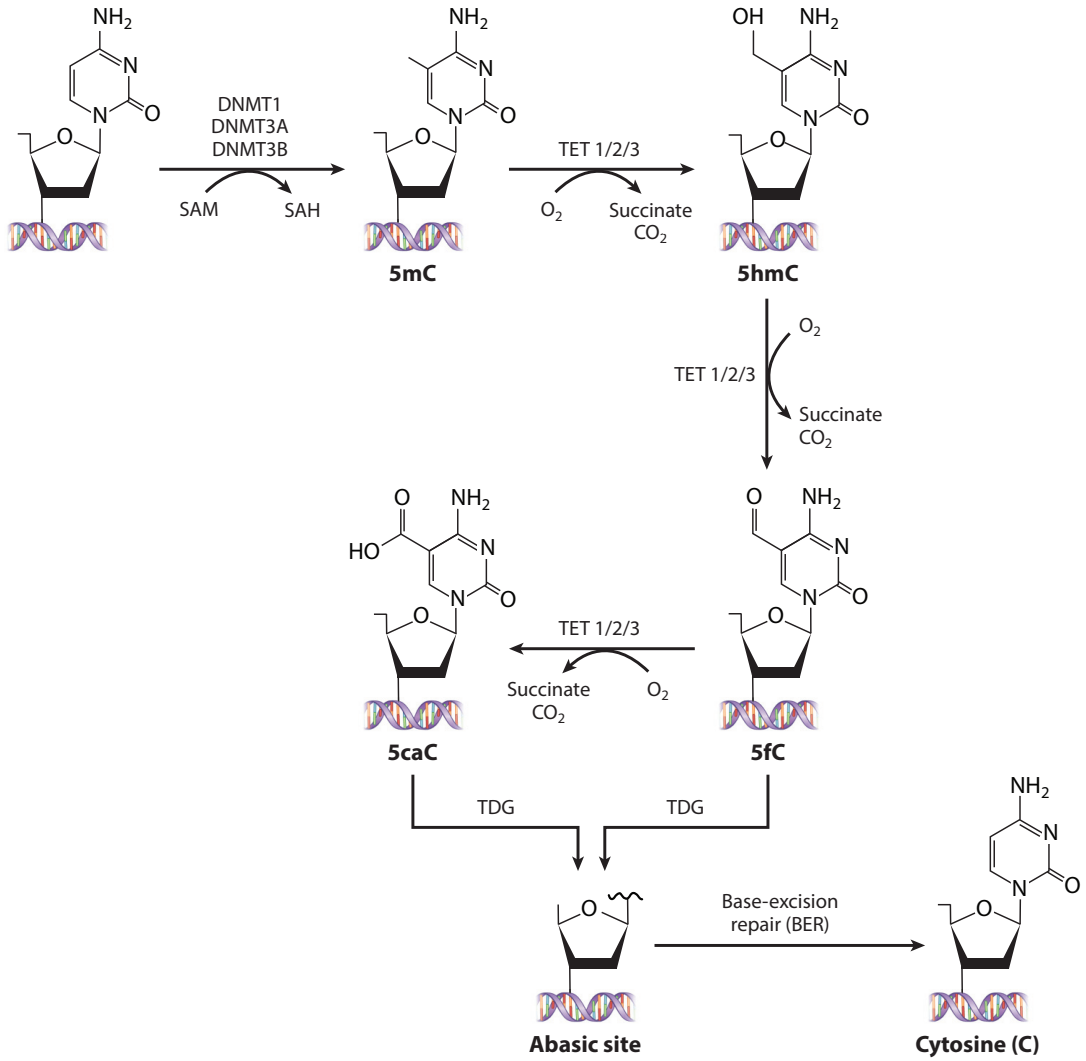

Figure 1

The diagram depicts the process of DNA methylation, namely the addition of a methyl group at the fifth carbon position of the cytosine base. The process of adding methyl groups to cytosine is carried out by the DNA methyltransferase (DNMT) enzyme family. As well as the process of the addition of methyl groups to DNA, there is also a process of active demethylation. This process is mediated by the ten eleven translocation (TET) enzyme family. Active demethylation is a multistep process whereby 5-methylcytosine is converted to 5-hydroxymethylcytosine (5-hmC), which is converted to 5-formylcytosine (5-fC) and finally 5-carboxylcytosine (5-caC). This process readies the sites for thymine-DNA glycosylase (TDG) to remove both 5-fC and 5-caC. Additional abbreviations: BER, base excision repair; OG, oxoglutarate; SAH, S-adenosyl-L-homocysteine; SAM, S-adenosyl-L-methionine.

i.e., CpG methylation, and occur within regions of the genome with a high cytosine-guanine (CG) content. These high CG content regions are often referred to as CpG islands. Sequences immediately flanking and up to two kilobases away from the islands are known as shores. The process of adding methyl groups to cytosine is carried out by the DNA methyltransferase (DNMT) enzyme family. This addition requires the cofactor S-adenosylmethionine (SAM). Within this family of enzymes, three are responsible for catalyzing the reactions of CpG methylation, namely DNMT3A, DNMT3B, and DNMT1 (92). DNMT3A and DNMT3B are responsible for de novo

methylation, e.g., methylation at sites that were not previously methylated (92). DNMT1 is primarily a maintenance methyltransferase, responsible for maintaining methyl marks during the mitotic process (92). In this way, the DNMT enzyme family adds and maintains CpG methylation across the genome.

Methyl groups can be actively removed (demethylated) from DNA, as well as added (**Figure 1**). The process of demethylation is mediated by the ten-eleven translocation (TET) enzyme family (106). Active demethylation is a multistep process characterized first by the conversion of 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) (106). Subsequently, 5-hmC is converted to 5-formylcytosine (5-fmC) and finally 5-carboxylcytosine (5-CmC) (106). This process readies the sites for thymine-DNA glycosylase (TDG) to remove both 5-fmC and 5-CmC (106). Active demethylation of the genome has been implicated as a regulatory feature that is responsible for fine-tuning CpG regulatory methylation marks.

Global DNA Methylation

Both active methylation and demethylation are responsible for creating and maintaining the CpG methylation patterns across the genome. The TET and DNMT enzymes are active during early development and also remain active throughout the life course (92, 106). Large-scale alterations of processes governing methylation, due to environmental exposure, nutritional status, or disease, are generally associated with global losses or gains of methylation particularly in early development (92). Specifically, alterations of methylation have been associated with differences in functional consequences on chromatin structure and gene expression (92). Global measures of methylation are often assessed using technologies such as LINE1, liquid chromatography–mass spectrometry (LC/MS), and Alu methylation (92). Global loss of methylation is generally associated with genomic instability and is a common phenotype of aging and cancer (56, 196). Conversely, gains in global levels of methylation, specifically in the placenta, have been associated with developmental defects, including down syndrome and gestational diabetes (91, 156). Together these show the importance of the balance of DNA methylation as it pertains to human health.

Gene-Specific Methylation

Current technologies enable the assessment of site-specific methylation, in addition to global methylation. Results of these studies have provided key insights into disease development and susceptibility because they allow for a focused study of potentially causal marks (92). For example, in the landmark Agouti mouse study that examined the effects of environmental contaminants and nutritional supplementation on methylation profiles, investigators demonstrated that methylation of the agouti coat color gene, as well as nine other CpG loci, are linked to adult health and disease susceptibility (46). Similar to global methylation, gene-specific alterations in methylation patterning have been linked to environmental exposures, especially those that occur during the prenatal period (125, 161, 189). The study by Heijmans et al. (71) was the first in a human population to show that alteration of methylation at a single gene locus resulted in changes to disease susceptibility and adult outcomes. The researchers investigated the impacts of prenatal exposure to famine during the Dutch Hunger Winter on insulin growth factor 2 (*IGF2*) methylation. This methylation was associated with lowered birth weight and a predisposition to obesity and adverse metabolic health outcomes later in life (189). These data suggest that alterations to DNA methylation that occur during the prenatal window result in later-life disease, supporting the underlying developmental origins of health and disease hypothesis (189).

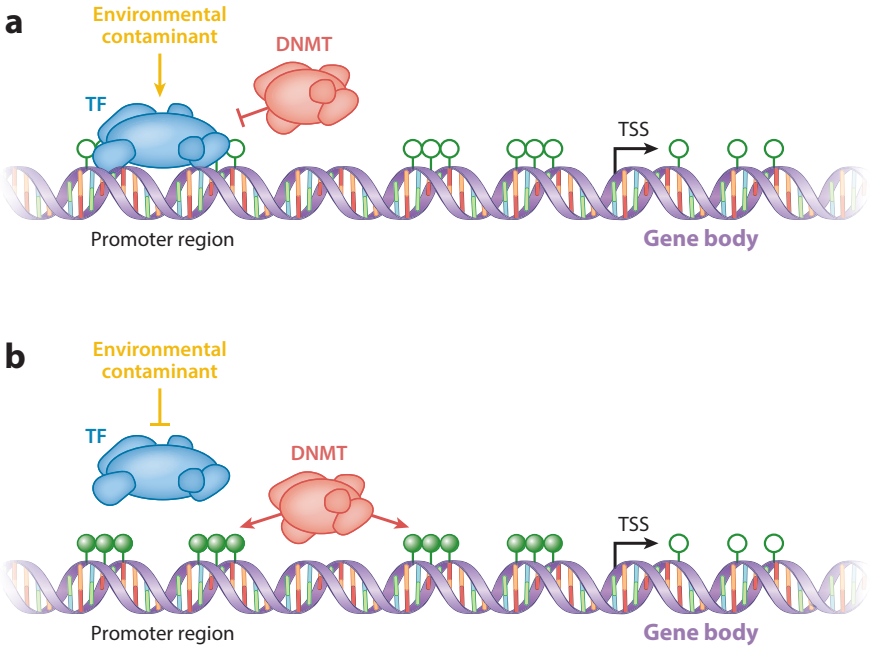

Figure 2

Diagram of the transcription factor occupancy theory. This hypothesis posits that presence or absence of transcription factors on the DNA denies or allows access to the DNA methylation machinery. In this way, transcription factors triggered by environmental exposure may influence the observed site-specific patterns of methylation. (*a*) Activation of transcription factors in response to an environmental contaminant as a mechanism of cellular defense/adaptation. The binding of the transcription factor may inhibit DNA methyltransferase (DNMT) from accessing the DNA for methylation of a particular gene, resulting in gene-specific hypomethylation. (*b*) Repression of transcription factors in response to an environmental contaminant. The lack of the transcription factor binding may allow DNMT access to particular genomic locations, resulting in gene-specific hypermethylation. Adapted from Martin & Fry 2016 (125). Additional abbreviations: TF, transcription factor; TSS, transcription start site.

Mechanisms Underlying Gene-Specific Alterations

Two often described hypotheses have been proposed to underlie environmental-induced effects on the global changes in DNA methylation. First, evidence has demonstrated the direct action of environmental chemicals on the function of DNMT and TET enzyme families. Second, evidence has also shown that chemicals may change the availability of SAM. Still, what drives gene-specific DNA methylation patterns is less clear. One hypothesis is the transcription factor occupancy theory, which proposes that presence or absence of transcription factors on the DNA denies or allows access to the DNA methylation machinery (125, 202). In this way, transcription factors triggered by environmental exposure may influence the observed site-specific patterns of methylation (**Figure 2**).

ENVIRONMENTAL TRIGGERS FOR DNA METHYLATION ALTERATIONS

Here, we detail numerous environmental triggers that have been associated with either global or site-specific DNA methylation alterations. Chemical exposures are the most widely studied class of environmental triggers of methylation, but nutritional status is another important factor. The studies summarized here represent currently available evidence demonstrating a relationship

between exposure to a contaminant and alteration of methylation. The studies have assessed both global and gene-specific alterations to methylation and assessed the impacts of exposure during the prenatal period and chronic exposure. In addition, many of the exposures described result in alterations of genes related to specific biological pathways of interest. They include aflatoxin B_1, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke, nutritional factors, and nonchemical stressors (**Table 1**).

Table 1 Summary of exposures assessed within this review

Exposures	Global methylation	Gene-specific methylation	Exposure-associated health impact	Relevant citations
Aflatoxin B1	Hypomethylation associated with exposure	71 CpG sites associated with prenatal exposure	Hepatocellular carcinomas, reduced growth, immune deficiencies	73, 75, 185, 197
Air pollution	Hypomethylation typically associated with exposure in adults, prenatal exposure is associated with both hypo- and hypermethylation	*MAPK* pathway members, *ACE*, *iNOS*, *ICAM-1*, *TLR2*, *IL-6*, *TET1*	Accelerated lung aging, loss of lung capacity, asthma, bronchitis, emphysema, and cancer	19, 20, 28, 31, 32, 36, 39, 44, 45, 63, 69, 79, 87, 88, 98, 112, 120, 165, 168, 183
Arsenic	Hypomethylation associated with exposure with sex-specific directionality shown as well	*KCNQ1*, *SQSTM1*, sex-specific profiles	Cancer lung conditions and diabetes in adults; prenatal exposure is associated with increased incidence of infection, neurocognitive effects, and increased neonatal mortality	2, 6, 9, 13, 15, 29, 33, 34, 47, 50, 54, 65, 76, 77, 84, 97, 105, 110, 121, 136, 137, 151–153, 155, 159, 177, 184, 199
Bisphenol A	Hypomethylation associated with exposure in females, potential nonmonotonic dose responses	*SNORD*, *SULT2A1*, *COMT*	Neurocognitive effects, increased incidence of cancer, and heart conditions from prenatal exposure	52, 53, 70, 99, 133, 134
Cadmium	Hypomethylation associated with exposure	*DNMT1*	Cancer, lung, bone, and kidney disease, developmental toxicity	51, 70, 78, 103, 129, 169, 170, 187, 188
Chromium	Hypermethylation associated with exposure	Not assessed at present	Cancer	3, 192
Lead	Not assessed at present	Alterations in imprinted genes, sex-specific response	Neurotoxicity, developmental toxicity	64, 70, 114, 138, 172–174
Mercury	Not assessed at present	*EMID2*, sex-specific profiles	Neurotoxicity	14, 34, 35, 62, 70, 119
Polycyclic aromatic hydrocarbons	Hypomethylation associated with exposure	*HIN1*, *ESR1*, *TWIST1*	Cancer	48, 72, 74, 101, 112, 146, 149, 194, 195, 198

(*Continued*)

Table 1 (*Continued*)

Exposures	Global methylation	Gene-specific methylation	Exposure-associated health impact	Relevant citations
Persistent organic pollutants	Nonmonotonic association with exposure	*IGF2*, *TNF-α*, *NR3C1*	Various health effects	40, 71, 82, 100, 116, 128, 141, 162, 201
Tobacco smoke	Hypomethylation associated with exposure	*AHRR*, *CNTNAP2*, *MYO1G*	Cancer, developmental toxicity, cardiovascular disease, chronic respiratory conditions	26, 27, 37, 55, 67, 86, 89, 94, 118, 148, 157, 175, 181, 182
Nutritional factors	Hypermethylation associated with exposure	*IGF2*, *RXR-α*, *PLAG1*	Proper development	1, 17, 22, 23, 71, 93, 126, 131, 142, 154
Nonchemical stressors	Not assessed at present	*BDNF*, *IGF2*	Various health effects	7, 24, 66, 102, 117, 135, 139, 180

Abbreviations: *ACE*, angiotensin-converting enzyme; *AHRR*, aryl hydrocarbon receptor repressor; *BDNF*, brain-derived neurotrophic factor; *CNTNAP2*, contactin-associated protein-like 2; *COMT*, catechol-*O*-methyltransferase; CpG, cytosine-phosphate-guanine; *DNMT1*, DNA methyltransferase; EMID2, collagen type XXVI alpha 1 chain; *ESR1*, estrogen receptor 1; HIN1, high in normal-1; *ICAM-1*, intercellular adhesion molecule 1; *IGF2*, insulin growth factor 2; *IL-6*, interleukin 6; *iNOS*, nitric oxide synthase; *KCNQ1*, potassium voltage-gated channel subfamily Q member 1; *MAPK*, mitogen-activated protein kinase; *MYO1G*, myosin IG; *NR3C1*, nuclear receptor subfamily 3 group C member 1; *PLAG1*, PLAG1 Zinc Finger; *RXR-α*, retinoid X receptor alpha; *SNORD*, small nucleolar RNA; *SQSTM1*, sequestosome 1; *SULT2A1*, sulfotransferase family 2A member 1; *TET1*, tet methylcytosine dioxygenase; *TLR2*, toll-like receptor 2; *TNF-α*, tumor necrosis factor alpha; *TWIST1*, twist family BHLH transcription factor 1.

Aflatoxin B_1

Aflatoxin B_1 (AFB_1) is a mycotoxin that can contaminate foods such as peanuts, grain, and corn (185). It is one of the most potent hepatic carcinogens and is known to induce specific DNA lesions leading to subsequent mutation and resulting in hepatocellular carcinoma (197, 200). Interestingly, hepatocellular carcinomas are known to have altered DNA methylation profiles, so investigation of AFB_1 as an epimutagen has been of interest (197, 200). To this end, studies showed that adults in two separate Taiwanese populations who were exposed to AFB_1 had lower levels of methylation in white blood cells (197, 200). These results are consistent with broader findings in cancer biology that suggest that genomic instability is a hallmark of cancer. In line with this proposition, the authors suggest that epigenetic alterations may provide an accurate way to assess cancer risk in AFB_1-exposed populations. In addition to chronic exposure and global measures, researchers have assessed gene-specific alterations in DNA methylation in response to prenatal AFB_1 exposure in Gambia. A total of 71 CpG sites related to immune response and growth factors were identified to be altered in association with AFB_1 in white blood cells (73). These data suggest that reduced growth and immune deficiencies associated with prenatal AFB_1 exposure could be mediated by methylation (185), but more research is needed to understand the impacts of AFB_1-associated methylation on a wider range of health effects.

Air Pollution

Air pollutants include a broad array of different environmental exposures, including particulate matter (PM) of various sizes and composition, ozone, nitrogen oxides, sulfur oxides, carbon monoxide, diesel exhaust fumes, and a wide variety of toxic chemicals such as benzene. In addition to these specific contaminants, broader descriptors such as urban development and traffic-related air pollution are commonly used to classify exposure in the field. These studies emphasize the effects of toxic air pollutant mixtures on the epigenome. For example, Carmona et al. (36) showed that

alterations in blood DNA methylation levels of the mitogen-activated protein kinase (MAPK) pathway are associated with exposure to generalized measures of air pollution in human populations. Furthermore, Bind et al. (19) demonstrated that exposure to air pollutants can result in functional changes to blood-based measures of protein expression and that altered DNA methylation may be indicative of susceptibility to these changes.

In addition to studies of general air pollutants, specific air pollutants have been a subject of interest. The constituents of the different types of air pollution, such as the composition of PM or ozone content, likely impact the observed relationship with gene-specific methylation patterns (31, 79). However, in adults, different constituents and pollution types are generally associated with global hypomethylation (12, 18, 44, 45, 69, 120). More recent studies have sought to differentiate the effects of hmC from mC and found that PM smaller than or equal to 10 microns in length (PM_{10}), PM smaller than or equal to 2.5 microns in diameter ($PM_{2.5}$), and elemental composition of PM are associated with 5hmC but not with 5mC (168). $PM_{2.5}$ exposure is associated with decreased methylation of the angiotensin-converting enzyme (*ACE*) gene (190), the nitric oxide synthase (*iNOS*) gene (98, 166), and hypermethylation of the mitochondrial genome (32), providing a potential mechanistic link between elevated blood pressure and PM exposure. Additionally, coagulation factor II (*F2*), intercellular adhesion molecule 1 (*ICAM-1*), and toll-like receptor 2 (*TLR-2*) display hypomethylation in association with air pollution constituents, and interferon gamma (*IFN-γ*) and interleukin 6 (*IL-6*) are associated with hypermethylation (20). Of great interest is the finding that traffic-related air pollution can influence methylation at the tet methylcytosine dioxygenase 1 (*TET1*) gene, a key enzyme in DNA demethylation, resulting in changes to gene expression (178).

Prenatal exposure to air pollution appears to differentially affect methylation patterns depending on the developmental window of exposure. Specifically, exposure during the first trimester is associated with decreased LINE-1 methylation, whereas exposure later in pregnancy is associated with increased LINE-1 methylation (28, 88). In addition to these global measures, researchers have investigated the relationship between pollutants and gene-specific methylation. For example, prenatal exposure to airborne vanadium has been linked to alteration of DNA methylation in genes interleukin 4 (*IL-4*) and *INF-γ* (95). Prenatal exposure to $PM_{2.5}$ has been associated with hypomethylation of the leptin gene (165), sites around poly(ADP-ribose) polymerase 1 (*PARP1*) promoter (4), and the mitochondrial genome (87). In addition to these findings, untargeted analyses of the genome have revealed associations between prenatal air exposure and CpG methylation related to xenobiotic metabolism and oxygen and gas transport (63). In utero exposure to diesel exhaust and allergens has been linked to alterations in CpG methylation related to cell adhesion, protein metabolism, and vascular development (39). DNA methylation alterations accumulated later in life that are associated with air pollution found in peripheral blood do not appear to be stable, as compared with those accumulated during the prenatal period and during childhood, which do appear to be stable (183). Taken together, these data suggest the potential for developmental reprogramming of the epigenome with respect to in utero air pollution.

Arsenic

Arsenic exposure is currently impacting the lives of hundreds of millions around the globe (38). Arsenic has been associated with altered methylation patterns in both chronically exposed adults and prenatally exposed infants. Global measures of methylation in blood samples from adults, children, and infants exposed in utero have been negatively associated with increased arsenic exposure. These data support the role of arsenic in global hypomethylation (15, 76, 84, 97, 110). In contrast with these studies, some have demonstrated that arsenic exposure is associated with

global hypermethylation (121, 136, 153), including one study conducted in children (2), and another focused on CD-4-positive T cell profiling (50). More recent studies have demonstrated that arsenic is associated with global methylation changes in a sex-dependent manner. Two studies of cord blood from prenatally exposed infants in Bangladesh found a positive association between methylation and arsenic exposure in male infants and a negative relationship between methylation and arsenic exposure in female infants (137, 152). Furthermore, studies in adults have shown that female adults display an inverse relationship between exposure and LINE-1 methylation, but males display a nonsignificant relationship (76). In addition to sex dependence, emerging research is focusing on differentiating the effects of arsenic on hmC and mC. At present, a single study from a US-based cohort found that both blood profiles of hmC and mC displayed negative correlations in association with arsenic (184).

In addition to studies of global methylation, numerous studies have been conducted on gene-specific DNA methylation alterations in adults chronically exposed to arsenic (9, 13, 155, 177, 199), as well as infants exposed to arsenic in utero (29, 33, 34, 65, 105, 159). The majority of these studies have assessed methylation patterns in blood; however, two studies have assessed the relationship between exposure and methylation in potential target tissues: placenta (33, 65) and exfoliated urothelial cells (155). In addition, one study has examined the relationship between methylation and gene expression, suggesting that not all methylation marks have functional consequences (159). Additionally, there is no overlap among the genes that have been identified as targets of arsenic exposure in utero (8, 125) and those identified in adults (8). The majority of these studies have found that most of the loci are hypermethylated in association with arsenic (6). These studies have implicated genes that influence arsenic-associated birth and health outcomes. As a specific example, methylation of potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) has been associated with lower birth weight (159). Methylation of *p16* and *p53* has been associated with various cancers (77, 84), and altered sequestosome 1 (*SQSTM1*) methylation has been associated with diabetes (9). As detailed in this section, the current body of epigenetic literature focused on arsenic exposure includes assessment of the impacts of sex, functional consequence, and tissue specificity on DNA methylation response. Taken together these studies suggest that arsenic-associated methylation may result in genomic instability and may play a role in arsenic-associated disease development in the context of both prenatal and chronic exposure.

Bisphenol-A

Bisphenol A (BPA) is an endocrine-disrupting chemical of public health concern because of its ubiquitous exposure and accumulation in the environment (42). Given the unclear nature of the health effects and dose–response relationship, BPA has been an area of active investigation. In studies of blood-based methylation alterations, it appears that BPA induces hypomethylation in women (70) and in young girls (99); however, its effects in males are unclear. Further complicating the study of DNA methylation and BPA exposure, fetal liver methylation alterations associated with prenatal exposure to BPA display a nonmonotonic association with BPA level (53). In gene-specific analyses of CpG methylation as it relates to prenatal BPA exposure, altered methylation patterns were observed in diverse tissues, including placenta, fetal liver and fetal kidney. Among the differentially methylated loci associated with BPA were the small nucleolar RNA (*SNORD*) complex of genes (53), sulfotransferase family 2A member 1 (*SULT2A1*), and catechol-*O*-methyltransferase (*COMT*) (133). Methylation patterning associated with BPA may be specific to different tissue types (134). Generally, BPA has also been shown to induce hypomethylation of CpG targets on the X chromosome (99) and alter methylation associated with immune function, transport activity, and metabolism (52, 53, 99, 133, 134). Taken together, the present evidence supports sexual

dimorphism and a nonmonotonic dose response of DNA methylation associated with BPA, resulting in a need for more research to understand the complicated functional consequences of BPA-associated DNA methylation alterations.

Cadmium

Cadmium exposure is of concern because it has a long half-life, ranging up to three decades, and is associated with numerous health effects, including kidney dysfunction, pregnancy and reproductive disorders, developmental toxicity, and cancer (170). Additionally, exposure is of concern because it accumulates in the bones over an individual's life course and is released during pregnancy. This phenomenon magnifies prenatal exposure to cadmium and increases risk for cadmium-associated pregnancy disorders (170). In general, cadmium has been inversely associated with blood-based measures of LINE-1 methylation in women from the Argentinean Andes (78) and in prenatally exposed infants from the United States (22). More specifically, cadmium has been linked to blood-based methylation alterations in key genes related to DNA methylation machinery, including *DNMT1*, observed in adult cohorts in Thailand and Argentina (78, 188). Prenatal cadmium exposure in a US-based cohort has been associated with alterations in placental methylation that could drive observed differences in fetal growth (51). Exposure to cadmium has also been associated with sex-specific differences in methylation alterations, and a subset of the marks are associated with alterations in birth size (103, 129, 187). In addition to focusing on either maternal or fetal outcomes, one US-based study looked at cadmium-associated DNA methylation patterns in both infants and their mothers. The study found that cadmium-associated methylation profiles in the infants differed from those in the mother (169). Taken together, specific gene targets of epigenetic dysregulation by cadmium could provide a basis for understanding cadmium-associated reproductive effects.

Chromium

Chromium, specifically hexavalent chromium, is a known carcinogen (30). Unlike most toxic metals, it is known to form mutagenic lesions (30). In addition, in contrast with most metals whereby the carcinogenic effects are derived primarily from exposure through ingestion, chromium is primarily an inhaled carcinogen; limited evidence suggests carcinogenicity through ingestion routes (30). A study of workers occupationally exposed to chromate showed increased accumulation in peripheral red blood cells (192). Chromate was also associated with DNA hypomethylation, a hallmark of cancer (192). The authors suggest that this association may be due to an interplay between chromate and folate, a donor to the SAM pool (192). The study suggests that chromate may also be able to induce folate deficiency in conjunction with its action as a direct mutagen, increasing its carcinogenic properties. In a separate cohort, lung cells from chromate-exposed workers who developed lung cancer were associated with aberrant methylation patterns that differed from methylation profiles of lung cancers from individuals who were not exposed to chromate (3). Chromium-associated methylation remains an understudied area, and further research is needed to investigate these relationships.

Lead

Lead is a known neurotoxicant, impacting the growth and development of children (138). Both 5-mC and 5-hmC are altered in response to prenatal lead exposure. There is a clear sex-specific response, where a unique set of loci are differentially methylated in males and females in response

to lead (64, 172, 173). Studies have also found that a core set of loci is changed in both males and females who were exposed to lead in utero (64, 172, 173). In addition, children who were prenatally exposed to lead in US-based cohorts display variable methylation patterns in imprinted genes, suggesting an increased risk of childhood obesity and cardiometabolic disease in adulthood (64, 138). A recent US-based study that utilized dried blood spots suggested that a grandmother's exposure to lead could leave imprints on her grandchild's methylome, suggesting a role for transgenerational inheritance of human epigenetic marks (174). Among adults, a general loss of methylation in blood has been correlated with increased blood lead levels (114). Among women undergoing in vitro fertilization, hypomethylation of collagen type I alpha 2 chain (*COL1A2*) has been observed (70). In general, lead has been associated with an altered methylation pattern that has the potential to explain lead-associated health effects, particularly in the context of prenatal and early-life exposures.

Mercury

As with lead, mercury exposure is of concern because it is a known neurotoxicant (35, 119). Prenatal exposure to mercury can modulate methylation patterns in both infants (14, 34) and the placenta (119). The alterations observed in blood are indicative of shifts in immune cell proportions (14, 34), emphasizing the importance of controlling blood-based methylation for white blood cell populations. In contrast, placental DNA methylation alterations associated with mercury have been associated with adverse neurological outcomes, a relationship that is potentially mediated through collagen type XXVI alpha 1 chain (*EMID2*). A recent study has similarly found that mercury-associated alterations in methylation that persisted throughout childhood were also related to cognitive performance during childhood (35). This study identified sex-specific differences in altered methylation profiles as well as methylation changes that persisted into early childhood (35). The sex specificity of methylation alterations associated with mercury has also been identified in adults (62). The studies of mercury-associated alterations of CpG methylation are among the first studies to assess the stability of epigenetic marks longitudinally, and they have also assessed sex specificity. The present findings suggest a need for further investigation because a potential role for methylation as a mediator of mercury-associated neurotoxicity has been identified.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are persistent organic pollutants (POPs) and known genotoxicants that have been associated with numerous adverse health outcomes. Prenatal exposures to PAHs have been associated with decreased global methylation in China and the United States (72, 112), as have adult exposures in China, Poland, and the United States (48, 140, 146, 147). In addition, methylation of key genes related to breast cancer, including retinoic acid receptor beta (RARβ) and adenomatosis polyposis coli tumor suppressor (*APC*), has been associated with the presence of PAH adducts in breast and breast tumor tissue as well as with various sources of PAH exposure (194, 195). Specifically, synthetic log use has been associated with secretoglobin family 3A member 1 (*HIN1*), environmental tobacco smoke was associated with estrogen receptor 1 (*ESR1*), and current smoking status was associated with twist family BHLH transcription factor 1 (*TWIST1*) (195). PAHs from tobacco smoke were also shown to alter methylation patterns of genes associated with cardiovascular disease and cancer in a Chinese population (203). Additional genes that display altered methylation in association with more general measures of PAH exposures are associated with insulin resistance (101), childhood asthma status (74, 149), and cancer (198). All the genes described above display hypermethylation in relationship with PAHs,

suggesting a potential role for PAHs as an environmental factor that can silence gene expression through epigenetic regulation at site-specific loci. The studies of PAH-associated modifications of DNA methylation highlight the impact of hydrocarbon mixtures and suggest a role for the epigenome in PAH-associated carcinogenicity.

Persistent Organic Pollutants

POPs are a class of compounds that persist long after their introduction into the environment. Many of these chemicals are known to have toxic effects on wildlife and ecosystems, leading to questions about effects on human health. Examples of these compounds include dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE), as well as polybrominated diphenyl (PBDEs), polychlorinated biphenyl (PBCs), perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Exposure to POPs impacts global measures of methylation, specifically Alu and LINE-1 elements. Prenatal, early-life, and later-life exposure to these compounds may be associated with a global hypomethylation (82, 85, 100, 162), DNA hypermethylation (40, 116, 193), and nonmonotonic associations (100, 141) in populations from the United States, Korea, Europe, and the Arctic. Specifically, PBDEs have been linked to hypomethylation of tumor necrosis factor alpha (*TNF-α*) in cord blood from a US-based cohort (43), *IGF2* in placenta from both a US-based cohort and a Chinese-based cohort (96, 201), and nuclear receptor subfamily 3 group C member 1 (*NR3C1*) in placentas from a Chinese-based cohort (201). Exposure is also associated with hypomethylation in sperm cells with exposure to POPs and PFOAs, suggesting that POPs are potential germline epimutagens and could be tied to preconception exposure (40, 113). In utero PFOA exposures also induce global hypomethylation in cord blood from a US-based population (67) as well as induce hypomethylation of *IGF2* in cord blood from a Japanese cohort (104). Researchers found associations between methylation alterations associated with POPs and neurological development in children (104). Supporting this finding, PCBs and PBDEs have been associated with hypomethylation of genes associated with autism (49, 128). Taken together, the existing literature supports the role of POPs-associated methylation as a potential mediator of POP-associated health effects in humans.

Tobacco Smoke

Tobacco smoke is an exposure of concern because it is a known carcinogen, in addition to being associated with cardiovascular disease and other chronic respiratory conditions. One of the means of carcinogenicity is genomic instability and dysregulation of the epigenome. Specifically, tobacco smoke has been associated with global hypomethylation for both in utero exposures (26, 55, 67, 89) and adult exposures (41). Of the methylation targets of tobacco smoke, aryl hydrocarbon receptor repressor (*AHRR*) has been identified as a reproducible biomarker of exposure across studies (68, 150, 157, 158, 175). The locus cg05575921 was shown to be hypomethylated across populations and altered in response to prenatal tobacco smoke exposure (16, 68, 94, 150, 157, 158, 160, 175). Additional targets include cancer, cell cycle, and metabolism-related genes (37, 59, 90, 115, 148, 167, 203). Prenatal exposure to tobacco smoke has been associated with alterations of genes related to fetal growth restriction (86, 118), development (94, 123, 171), cancer and cell growth (160), and other processes (26, 27, 181, 182, 191). Among these genes, contactin-associated protein-like 2 (*CNTNAP2*), cytochrome P450, family 1, member A1 (*CYP1A1*), and myosin IG (*MYO1G*) are common across numerous studies (125). Further support for the effect of tobacco smoke on DNA methylation comes from recent work that has demonstrated the stability of methylation patterns at a subset of the genes identified as differentially methylated in response to prenatal exposure

(27, 164). Of the assessed contaminants, the most overlap in gene-specific methylation patterns was observed for tobacco smoke (108, 125), which suggests that the observed blood modifications may be useful biomarkers in the future. Taken together, the data corroborate that tobacco smoke has a strong effect on DNA methylation that is potentially related to exposure-associated health outcomes.

Nutritional Factors

Among other environmental factors that alter CpG methylation, in addition to chemicals in the environment, nutrition should be considered. Alterations of early-life and prenatal nutritional status have been associated with developmental programming, resulting in later-life health outcomes (16, 126). In addition, given the direct relationship between one-carbon metabolism and the process of DNA methylation described earlier, it is highly likely that alterations to nutritional status could directly impact the amount and patterns of DNA methylation. Specifically, methyl donor nutrients such as methionine, folate, betaine, and choline have been implicated in alterations in methylation patterns. These nutrients are directly related to one-carbon metabolism, the process that generates SAM, the major substrate for DNA methylation.

In general, supplementation with methyl donors appears to increase global methylation levels (154), and deficiency is associated with global hypomethylation (1). Similarly, intermediates of one-carbon metabolism are also associated with decreased SAM levels (22, 58). Of these nutrients, folate is a commonly added dietary supplement because it is important for fetal development. Folate has been associated with global measures of methylation in infants (93), children (130), and adults (17, 21). Similarly, a positive relationship exists between 5-hmC and methyl donors. This effect appears to be limited to the third trimester of pregnancy (142). Meanwhile, increased paternal intake of methyl donor nutrients has been associated with increased global methylation in the cord blood of offspring (145), whereas increases in maternal methyl donors influence methylation patterns related to infant metabolism and growth (143, 144). A key mediator of this relationship may be the *H19/IGF2* locus (57, 81, 179). This same locus was shown to be altered by exposure to prenatal famine (71) and has been implicated in later-life obesity and diabetes. In addition to *H19/IGF2*, retinoid X receptor alpha (*RXR-α*) appears to be modified in association with maternal folate intake during the prenatal period (60), which is of key interest because RXR-α is known to play a role in later-life obesity and metabolic disorders. Among the genes altered by folate in adult pathways are those related to cancer (61, 107), inflammation (23), and fetal growth and development (5, 80). Folate intake also appears to moderate the effects of environmental contaminant exposure, including arsenic (153), chromium (192), hormonal markers (186), tobacco smoke (16) and pesticides (163).

In addition to folate donor nutrients, other micronutrients are also critical for methylation status. The vitamin B family are members of one-carbon metabolism, as well as micronutrients. Homocysteine (58), choline (22), and vitamin B12 (127) are associated with alterations in global methylation during the prenatal period. Methylation differences associated with these nutrients, when investigated on a gene-specific level, are associated with differences in alterations in imprinted genes, including PLAG1 Zinc Finger (*ZAC1/PLAG1*) (11, 80). For example, increased maternal vitamin D is associated with hypermethylation tumor suppression genes in infants (131). In addition, selenium, which has a sex-specific relationship (151), has been shown to alter methylation at genes related to Keshan disease, which arises from selenium deficiency. These results suggest that micronutrients, as well as one-carbon metabolism indicators, are important to CpG methylation alterations. Thus more consideration should be given to nutritional status during the study of perturbations of CpG methylation associated with environmental exposures.

Nonchemical Environmental Exposures

The field of epigenetics has generally focused on environmental factors such as chemical contaminants and nutrients. However, other factors related to the social environment are known to play a role in alterations related to DNA methylation. For example, numerous studies have demonstrated that socioeconomic status is related to adult (24, 109, 180) and prenatal (7, 63, 102, 109) alterations of DNA methylation. Socioeconomic status is environmental in nature because it is related to social factors that affect individuals. Some research has suggested that childhood adversity/socioeconomic status, as compared with that experienced in adulthood, is more strongly tied to adult methylation patterns and health outcomes (24, 135). Additionally, it is important to consider the mother's general health/mental state, given that the mother is the environment for the developing fetus. To this end, maternal mental health can impact methylation patterns in infants. Specifically, maternal depression during the prenatal period has been linked to altered methylation of brain-derived neurotrophic factor (*BDNF*) (25), and maternal anxiety during the prenatal period is associated with hypomethylation of the *IGF2/H19* loci (122). These changes are further related to childhood anxiety and birth weight. More broadly, prenatal and early-life social/location-based CpG alterations are related to immune function and inflammatory pathways (7, 117, 135). These findings suggest the strong need to consider social and community impacts along with more tangible measures of environmental exposure to contaminants and nutrients.

FUTURE DIRECTIONS

Environmental epigenetic studies have broadly categorized the relationship between exposure and alterations in CpG methylation for numerous contaminants, nutrients, and social factors. However, there are currently four major gaps in the scientific literature, which pertain to environmental factors and the epigenome: (*a*) the assessment of mixtures and contaminant/nutrient interactions, (*b*) sex-specific responses, (*c*) tissue-specific responses, and (*d*) stability and functional consequences of CpG methylation. One of the major limitations of the field at present is the failure to consider environmental mixtures and the interactions of numerous environmental factors. Numerous hypotheses have proposed that nutrition, exposure, and hormonal signaling can all impact methylation (111). Studies have shown that the effects of numerous contaminants are modulated by one-carbon metabolism nutrients (16, 110, 153, 163, 192). Furthermore, humans are not exposed to a single contaminant. As detailed previously, only a handful of studies have examined the relationship between multiple environmental factors and their impacts on DNA methylation. In the future, nutritional assessment in conjunction with environmental assessment as well as assessment of multiple contaminants are needed to advance the field.

In addition to multi-contaminant environmental mixtures, the sex of the exposed individual may impact the relationship between environmental factors and DNA methylation. For example, baseline differences in methylation patterns have been shown between placentas derived from male pregnancies compared with those from female pregnancies (124). Given that many of these differences pertain to metabolism and transport of environmental contaminants, these could underlie some of the observed differences in health effects between males and females (124). In support of this notion, differences in methylation patterns associated with environmental contaminants have been observed in males and females (2, 29, 82, 103, 129, 137, 172). Furthermore, sex-based differences in DNA methylation should be considered because they may influence the response to environmental exposure (152). Future studies can utilize both interaction models and stratified modeling to understand the sex-specific effects of the contaminants as well as potential disease susceptibility. Although this approach has become more standard in the study of some

contaminants, such as in studies of arsenic and cadmium (29, 82, 103, 129, 137, 152), it is still not as fully considered in others.

Tissue specificity is the third area in which improved understanding of methylation is important. Many studies have focused on blood-based methylation as biomarkers for disease; however, the meaning of these methylation marks is somewhat unclear. Although it is a readily accessible biospecimen for the study of humans, it may not reflect changes in specific tissues of interest (10, 33). In the case of some specific biomarkers, such as decreased methylation of *AHRR* in smokers, it is clear that this methylation pattern is conserved across tissue types, specifically blood and lung tissue (175). In addition, some studies have shown that imprinted gene methylation is conserved across tissue types, making these genes strong targets for study, as their methylation may represent changes across tissues (132). However, future work should examine toxicological target tissues, such as the placenta as an organ of reproductive toxicity, or use banked biopsies from target organs such as livers and kidneys.

The final gap in the literature is centered around the stability of methylation marks and their functional consequences. Only a handful of studies have assessed the stability of methylation over time (35). Although more researchers are looking to understand functional consequences by assessing gene expression, protein expression, or birth outcomes (119, 159), this is not standard practice yet. Given that methylation is a mechanism for adaptation, it would be unsurprising if methylation signatures changed over an individual's life course depending on subsequent exposure. However, given that previously described studies have shown stability of specific loci, it is possible that some of the methylation patterns observed were preprogrammed during gestation. These should be targets of further studies. To close this gap, prospective cohort studies with longitudinal measures of methylation and gene expression should be established.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This research was supported by grants from the National Institute of Environmental Health Sciences (T32-ES007018, T32-ES007126, R01-ES0019315, P42-ES005948). We acknowledge Caroline Reed for the figure design.

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