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Environmental chemical exposures and human epigenetics

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Abstract

Every year more than 13 million deaths worldwide are due to environmental pollutants, and approximately 24% of diseases are caused by environmental exposures that might be averted through preventive measures. Rapidly growing evidence has linked environmental pollutants with epigenetic variations, including changes in DNA methylation, histone modifications and microRNAs.

Environ mental chemicals and epigenetic changes All of these mechanisms are likely to play important roles in disease aetiology, and their modifications due to environmental pollutants might provide further understanding of disease aetiology, as well as biomarkers reflecting exposures to environmental pollutants and/or predicting the risk of future disease. We summarize the findings on epigenetic alterations related to environmental chemical exposures, and propose mechanisms of action by means of which the exposures may cause such epigenetic changes. We discuss opportunities, challenges and future directions for future epidemiology research in environmental epigenomics. Future investigations are needed to solve methodological and practical challenges, including uncertainties about stability over time of epigenomic changes induced by the environment, tissue specificity of epigenetic alterations, validation of laboratory methods, and adaptation of bioinformatic and biostatistical methods to high-throughput epigenomics. In addition, there are numerous reports of epigenetic modifications arising following exposure to environmental toxicants, but most have not been directly linked to disease endpoints. To complete our discussion, we also briefly summarize the diseases that have been linked to environmental chemicals-related epigenetic changes.

Key words Environmental chemicals epigenetics disease susceptibility

Background

More than 13 million deaths every year are due to environmental pollutants, and as much as 24% of diseases are estimated to be caused by environmental exposures that can be averted.[1] In a screening promoted by the United States Center for Disease Control and Prevention, 148 different environmental chemicals were found in the blood and urine from the US population, indicating the extent of our exposure to environmental chemicals.[2] Growing evidence suggests that environmental pollutants may cause diseases via epigenetic mechanism-regulated gene expression changes.[3,4] Dynamic chromatin remodelling is required for the initial steps in gene transcription, which can be achieved by altering the accessibility of gene promoters and regulatory regions.[5] Epigenetic

factors, including DNA methylation, histone modifications and microRNAs (miRNAs) (Figure 1), participate in these regulatory processes, thus controlling gene expressions.[6,7] Changes in these epigenetic factors have been shown to be induced by exposure to various environmental pollutants, and some of them were linked with different diseases.[8–10] In this review, we summarize the findings linking environmental chemical exposures with epigenetic alterations, provide some evidence linking such epigenetic changes with diseases (Table 1), and discuss the challenges and opportunities of environmental epigenomics in epidemiologic studies.

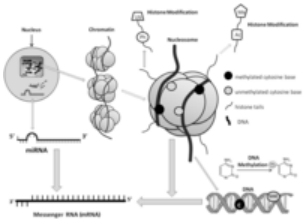

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Figure 1
Transcriptional regulation at the epigenetic level. Epigenetic mechanisms, including DNA methylation, histone modifications and miRNAs, regulate chromatin compaction and gene expression. DNA methylation at CpG sites usually suppresses gene expression. Histones are globular proteins that undergo posttranslational modifications, such as Ac, methylation and phosphorylation, thus influencing chromatin structure and gene expression. Active genes are usually characterized by low DNA methylation and highly acetylated chromatin configuration that allow access to transcription factors. miRNAs are a set of small, non-protein-coding RNAs that negatively regulate expression of target genes at the posttranscriptional level by binding to 3′-untranslated regions of target mRNAs

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Table 1
Effects of environmental chemicals on epigenetic changes

Epigenetic factors

DNA methylation

DNA methylation, a naturally occurring modification that involves the addition of a methyl group to the 5′ position of the cytosine ring, is the most commonly studied and best understood epigenetic mechanism.[11] In the human genome, it predominantly occurs at cytosine–guanine dinucleotide (CpG) sites, and serves to regulate gene expression and maintain genome stability.[12]

Environmental studies have shown distinct DNA methylation abnormalities. One commonly reported alteration is an overall genome-wide reduction in DNA methylation content (global hypomethylation) that may lead to reactivation of transposable elements and alter the transcription of otherwise silenced adjacent genes.[13,14] Global hypomethylation is associated with genomic instability and an increased number of mutational events.[15–18] There are approximately 1.4 million Alu repetitive elements (sequences containing a recognition site for the restriction enzyme *Alu*I)[19] and a half a million long interspersed nucleotide (LINE-1) elements in the human genome that are normally heavily methylated.[20] More than one-third of DNA methylation occurs in repetitive elements.[20] Because of their high representation throughout the genome, LINE-1 and Alu have been used as global surrogate markers for estimating the genomic DNA methylation level in cancer tissues,[20–22] although recent data show lack of correlation with global methylation in normal tissues, such as peripheral blood.[23] Other types of abnormalities that can be induced by environmental pollutants are hyper- or hypo-methylation of specific genes or regions, potentially associated with aberrant gene transcription.[24–27] DNA methylation alterations that directly affect gene expression often

occur in the CpG sites located in the promoter regions of the genes. Recent evidence has shown that differentially methylated sites in various cancer tissues are enriched in sequences, termed 'CpG island shores', up to 2 kb distant from the transcription start site.[28] However, to date, gene-specific DNA methylation alterations induced by environmental exposures have been mostly investigated in gene promoter regions. CpG island shores are clearly worthy of further investigation in relation to environmental exposures, but whether they hold such importance in a non-cancer setting remains to be determined.

Histone modifications

In humans, protection and packaging of the genetic material are largely performed by histone proteins, which also offer a mechanism for regulating DNA transcription, replication and repair.[29] Histones are nuclear globular proteins that can be covalently modified by acetylation (Ac), methylation, phosphorylation, glycosylation, sumoylation, ubiquitination and adenosine diphosphate (ADP) ribosylation,[30,31] thus influencing chromatin structure and gene expression.[32,33] The most common histone modifications that have been shown to be modified by environmental chemicals are Ac and methylation of lysine residues in the amino terminal of histone 3 (H3) and H4. Histone Ac, with only a single acetyl group added to each amino acid residue usually, increases gene transcriptional activity;[34–37] whereas histone methylation (Me), found as mono (Me), di-methyl (Me2), and tri-methyl (Me3) group states[38] can inhibit or increase gene expression depending on the amino acid position that is modified.[39–41]

miRNAs

miRNAs are short single-stranded RNAs of approximately 20–24 nucleotides in length that are transcribed from DNA but not translated into proteins. miRNAs negatively regulate expression of target genes at the post-transcriptional level by binding to 3′-untranslated regions of target mRNAs.[42] Each mature miRNA is partially complementary to multiple target mRNAs and directs the RNA-induced silencing complex (RISC) to identify the target mRNAs for inactivation.[43] miRNAs are initially transcribed as longer primary transcripts (pri-miRNAs) and processed first by the RNase enzyme complex, and then by Dicer, leading to incorporation of a single strand into the RISC. miRNAs guide RISC to interact with mRNAs and determine post-transcriptional repression. miRNAs are involved in the regulation of gene expression through the targeting of mRNAs during cell proliferation, apoptosis, control of stem cell self renewal, differentiation, metabolism, development and tumour metastasis.[44,45] Compared with other mechanisms involved in gene expression, miRNAs act directly before protein synthesis and may be more directly involved in fine-tuning of gene expression or quantitative regulation.[46,47] Moreover, miRNAs also play key roles in modifying chromatin structure and participating in the maintenance of genome stability.[48] miRNAs can regulate various physiological and pathological processes, such as cell growth, differentiation, proliferation, apoptosis and metabolism.[42,49] More than 10 000 miRNAs have been reported in animals, plants and viruses by using computational and experimental methods in miRNA-related public databases. The aberrant expression of miRNAs has been linked to various human diseases, including Alzheimer's disease, cardiac hypertrophy, altered heart repolarization, lymphomas, leukaemias, and cancer at several sites.[50–66]

Environmental pollutants and epigenetic alterations

Metals

Heavy metals are widespread environmental contaminants and have been associated with a number of diseases, such as cancer, cardiovascular diseases, neurological disorders and autoimmune diseases.[67,68] In recent years, there has been an increasing appreciation of the roles of molecular factors in the aetiology of heavy metal-associated diseases.[69–71] Several studies showed that metals act as catalysts in the oxidative deterioration of biological macromolecules.[72] Metal ions induce reactive oxygen species (ROS), and thus lead to the generation of free radicals.[72,73] ROS

accumulation can affect epigenetic factors.[74–79] Growing data have linked epigenetic alterations with heavy metal exposure.

Arsenic

Evidence has been rapidly increasing that exposure to arsenic (As) alters DNA methylation both globally and in the promoter regions of certain genes. Upon entering the human body, inorganic As is methylated for detoxification. This detoxification process uses *S*-adenosyl methionine (SAM), which is a universal methyl donor for methyltransferases including DNA methyltransferases (DNMTs) that determine DNA methylation. Thus, it has been shown that As exposure leads to SAM insufficiency and decreases the activity of DNMTs due to the reduction of their substrate. In addition, As has also been shown to decrease *DNMT* gene expression.[80] These As-induced processes may all contribute to global DNA hypomethylation. Arsenic exposure was shown to induce global hypomethylation in a dose-dependent manner in several *in vitro* studies.[80–83] Further, rats and mice exposed to As for several weeks exhibited global hypomethylation in hepatic DNA.[84–87] Nonetheless, evidence in humans is still limited and not completely consistent. In a cross-sectional study of 64 subjects, As level in contaminated water was associated with global DNA hypermethylation in blood mononuclear cells.[88] A global dose-dependent hypermethylation of blood DNA was observed in Bangladeshi adults with chronic As exposure.[89]

Arsenic exposure has also been associated with gene-specific hyper- or hypo-methylation in both experimental settings and human studies.[85,90–101] As exposure has been shown to induce dose-dependent promoter hypermethylation of several tumour suppressor genes, such as *p15*, *p16*, *p53* and *DAPK*, *in vitro* and *in vivo*.[91,93,98,101,102] Furthermore, As exposure-related up-regulation of *ER-alpha*, *c-myc* and *Ha-ras1* gene expression was linked to their promoter hypomethylation in cell lines[94,95] and animal studies.[84,85,97] Evidence in humans is rapidly growing. Toenail As concentration was positively associated with *RASSF1A* and *PRSS3* promoter methylation levels in bladder tumours.[100] Promoter hypermethylation in these two genes was associated with As-induced invasive lung tumours compared with non-invasive tumours.[100] Promoter hypermethylation of *DAPK* was observed in human uroepithelial cells exposed to As,[90] as well as in tumours from 13 of 17 patients living in As-contaminated areas relative to 8 of 21 patients living in As non-contaminated areas.[99] Increased DNA methylation of the *p16* promoter was observed in arseniasis patients when compared with people with no history of As exposure.[101]

Arsenic exposure has also been shown to cause alterations in histone modifications. The earliest evidence on As-induced histone acetylation reductions was in Drosophila.[103] Trivalent As has recently been linked to reduced H3 and H4 lysine 16 (H4K16) acetylation in human bladder epithelial cells.[104] On the other hand, trivalent As exposure has also been shown to increase histone acetylation, which was shown to up-regulate genes related to apoptosis or cell stress response.[105,106] Ramirez *et al.* have reported that As could cause global histone acetylation by inhibiting the activity of histone deacetylases (HDACs).[107] Together, these studies provide evidence that histone acetylation can be dysregulated by As exposure. Early in 1983, As was also shown to induce methylation changes in H3 and H4 in Drosophila.[103] Similar results on H3 were seen in Drosophila Kc 111 cell several years later.[108,109] In recent years, in mammalian cells, arsenite (AsIII) exposure has been associated with increased H3 lysine 9 dimethylation (H3K9me2) and H3 lysine 4 trimethylation (H3K4me3), and decreased H3 lysine 27 trimethylation (H3K27me3).[110,111] As was shown to induce apoptosis by up-regulation of phosphorylated H2AX[112] and cause H3 phosphorylation, which may play important roles in the up-regulation of the oncogenes.[106]

Exposure of human lymphoblast cell line TK-6 to arsenite exhibited global increases in miRNA expression.[113] Arsenic trioxide (As_2O_3) has been used as a pharmacological treatment in acute promyelocytic leukaemia.[114] Cao *et al.*[115] demonstrated that numerous miRNAs were up-regulated or down-regulated in T24 human bladder carcinoma cells exposed to As_2O_3.

In particular, miRNA-19a was substantially decreased, resulting in cell growth arrest and apoptosis. The As-related changes in miRNA expression were shown to be reversible when the exposure was removed.[115]

Nickel

Nickel has been proposed to increase chromatin condensation and trigger *de novo* DNA methylation of critical tumour suppressor or senescence genes.[116] In Chinese hamster G12 cells transfected with the *Escherichia coli* guanine phosphoribosyl transferase (*gpt*) gene, nickel was shown to induce hypermethylation and inhibit the expression of the transfected *gpt* gene.[117] An animal study has further shown that nickel induced DNA hypermethylation, altered heterochromatin states and caused gene inactivation, eventually leading to malignant transformation.[118] Govindarajan *et al.*[119] have observed DNA hypermethylation of *p16* in nickel-induced tumours of wild-type C57BL/6 mice, as well as in mice heterozygous for the tumour suppressor *p53* gene injected with nickel compound.

Nickel may cause diseases also via affecting histone modifications. Evidence on nickel-induced histone modifications includes increases of H3K9 dimethylation, loss of histone acetylation in H2A, H2B, H3 and H4, and increases of the ubiquitination in H2A and H2B.[116,120–127] An increase in H3K9 dimethylation and a decrease in H3K4 methylation and histone acetylation was found in the promoter of the *gpt* transgene in G12 cells exposed to nickel.[116,123,128] In mouse PW cells and human cells treated with the HDAC inhibitor trichostatin A, nickel showed a lower capacity to induce malignant transformation.[129] This finding suggested that gene silencing mediated by histone deacetylation may play a critical role in nickel-induced cell transformation.[129] In addition, nickel has also been shown to induce a loss of histone methylation *in vivo* and decreased activity of histone H3K9 demethylase *in vitro.*[123] Nickel also suppresses histone H4 acetylation *in vitro* in both yeast and mammalian cells.[130,131] Nickel can induce H3 phosphorylation, specifically in serine 10 (H3S10) via activation of the c-jun N-terminal kinase/stress-activated protein kinase pathway.[132]

Cadmium

Cadmium (Cd) has been shown to alter global DNA methylation.[133] Takiguchi *et al.*[134] demonstrated that Cd inhibits DNMTs and initially induces global DNA hypomethylation *in vitro* (TRL1215 rat liver cells). However, prolonged exposure was shown to lead to DNA hypermethylation and enhanced DNMTs activity in the same experiment.[134] Cd can also decrease DNA methylation in proto-oncogenes and promote oncogenes expression that can result in cell proliferation.[133,134]

Transcriptional and post-transcriptional gene regulation is critical in responses to Cd exposure, in which miRNAs may play an important role.[135,136] Bollati *et al.*[137] have recently demonstrated that increased expression of miR-146a in peripheral blood leucocytes from steel workers was related to inhalation of Cd-rich air particles. miRNA-146a expression is regulated by the transcription factor nuclear factor-kappa B, which represents an important causal link between inflammation and carcinogenesis.[138]

Other metals

Mercury (Hg) is widely present in various environmental media and foods at levels that can adversely affect humans and animals. Exposure to Hg has been associated with brain tissue DNA hypomethylation in the polar bear.[139] Arai *et al.*[140] have studied the effects of Hg on DNA methylation status in mouse embryonic stem cells. After 48 or 96 h of exposure to the chemical, they observed hypermethylation of *Rnd2* gene in Hg-treated mouse embryonic stem cells.

Lead is among the most prevalent toxic environmental metals, and has substantial oxidative properties. Long-term exposure to lead was shown to alter epigenetic marks. In the Normative Aging Study, LINE-1 methylation levels were examined in association with patella and tibia lead levels, measured by K-X-Ray fluorescence. Patella lead levels were

associated with reduced LINE-1 DNA methylation. The association between lead exposure and LINE-1 DNA methylation may have implications for the mechanisms of action of lead on health outcomes, and also suggests that changes in DNA methylation may represent a biomarker of past lead exposure.[141] In addition, Pilsner *et al.*[142] characterized genomic DNA methylation in the lower brain stem region from 47 polar bears hunted in central East Greenland between 1999 and 2001. They have reported an inverse association between cumulative lead measures and genomic DNA methylation level.

Hexavalent chromium [Cr(VI)] is a mutagen and carcinogen that has been linked to lung cancer and other adverse health effects in occupational studies. Kondo *et al.*[143] found *p16* and *hMLH1* hypermethylation in lung cancer patients with past chromate exposure.[144] *In vitro* experiments on cells exposed to binary mixtures of benzo[a]pyrene (B[a]P) and chromium have shown that B[a]P activates Cyp1A1 transcriptional responses mediated by the aryl hydrocarbon receptor (AhR), whereas chromium represses B[a]P-inducible AhR-mediated gene expression[145,146] by inducing cross-links of histone deacetylase 1–DNA methyltransferase 1 (HDAC1–DNMT1) complexes to the Cyp1A1 promoter chromatin and inhibit histone marks, including phosphorylation of histone H3 Ser-10, trimethylation of H3 Lys-4 and various acetylation marks in histones H3 and H4. HDAC1 and DNMT1 inhibitors or depletion of HDAC1 or DNMT1 with siRNAs blocked the chromium-induced transcriptional repression by decreasing the interaction of these proteins with the Cyp1A1 promoter and allowing histone acetylation to proceed. By inhibiting Cyp1A1 expression, chromium stimulate the formation of B[a]P DNA adducts. These findings may link histone modifications to chromium-associated developmental and carcinogenic outcomes.[147] Chromate exposure of human lung A549 cells has been shown to increase the global levels of di- and tri-methylated histone H3 lysine 9 (H3K9) and lysine 4 (H3K4), but decrease tri-methylated histone H3 lysine 27 (H3K27) and di-methylated histone H3 arginine 2 (H3R2). Most interestingly, H3K9 dimethylation was enriched in the human *MLH1* gene promoter following chromate exposure, and this was correlated with decreased *MLH1* mRNA expression. Chromate exposure increased the protein as well as mRNA levels of G9a, a histone methyltransferase that specifically methylates H3K9. This Cr(VI)-induced increase in G9a may account for the global elevation of H3K9 dimethylation. Furthermore, supplementation with ascorbate, the primary reductant of Cr(VI) and also an essential cofactor for the histone demethylase activity, partially reversed the H3K9 dimethylation induced by chromate. These results suggest that Cr(VI) may target histone methyltransferases and demethylases, which in turn affect both global and gene promoter-specific histone methylation, leading to the silencing of specific tumour suppressor genes.[148]

Recent investigations have demonstrated that aluminum exposure can alter the expression of a number of miRNAs. miR-146a in human neural cells was up-regulated after treatment with aluminium sulphate. Up-regulation of miR-146a corresponded to the decreased expression of complement factor H, a repressor of inflammation.[149] In addition, a study on aluminium-sulphate-treated human neural cells in primary culture has shown increased expression of a set of miRNAs, including miR-9, miR-125b and miR-128.[150] The same miRNAs were also found to be up-regulated in brain cells of Alzheimer patients, suggesting that aluminum exposure may induce genotoxicity via miRNA-related regulatory elements.[150]

Pesticides

Growing evidence suggests that epigenetic events can be induced by pesticide exposures.[28,151–153] Animal models have shown that exposure to some pesticides, such as vinclozolin and methoxyclor, induces heritable alterations of DNA methylation in male germline associated with testis dysfunction,[154–156] or affects ovarian function via altered methylation patterns.[157] Decreased methylation in the promoter regions of *c-jun* and *c-myc* and increased levels of their mRNAs and proteins were found in livers of mice exposed to dichloro- and trichloro-acetic acid.[158,159] Dichlorvos has been demonstrated to induce DNA methylation in multiple

tissues in an animal toxicity study.[160] DNA methylation in repetitive elements in blood DNA was inversely associated with increased levels of plasma pesticide residues and other persistent organic pollutants in an Arctic population,[161] a finding later confirmed in a similar study in a Korean population.[162] Whether aberrant DNA methylation represents the link between pesticides and risks of pesticide-related disease, including the excess of cancer risk observed in some epidemiology studies,[163–168] remains to be determined.

Dieldrin, a widely used organochlorine pesticide, has been shown to increase acetylation of core histones H3 and H4 in a time-dependent manner. Histone acetylation was induced within 10 min of dieldrin exposure, suggesting that histone hyperacetylation is an early event in dieldrin-induced diseases. Treatment with anacardic acid, a histone acetyltransferase inhibitor, decreased dieldrin-induced histone acetylation.[169] Dieldrin was further shown to induce histone hyperacetylation in the striatum and substantia nigra in mouse models, suggesting the roles for histone hyperacetylation in dieldrin-induced dopaminergic neuronal degeneration.[170]

Air pollution

Exposure to particulate matter (PM) of ambient air pollution has been associated with increased morbidity and mortality related to cardiovascular and respiratory diseases.[171,172] Black carbon, a component of PM derived from vehicular traffic, has been linked to decreased DNA methylation in LINE-1 repetitive elements in 1097 blood DNA samples of elderly men in the Boston area. Additional evidence for PM effects on DNA methylation stemmed from an investigation of workers in a steel plant with well-characterized exposure to PM with diameters of <10 μm (PM_{10}). Methylation of inducible nitric oxide synthase gene promoter region was decreased in blood samples of individuals exposed to PM_{10} after 3 days of work in the foundry when compared with baseline.[173] In the same study, methylation of Alu and LINE-1 was negatively related to long-term exposure to PM_{10}.[173] In contrast, an animal experiment on mice exposed to air particles collected from a steel plant showed global DNA hypermethylation in sperm genomic DNA, a change that persisted after removal of environmental exposure.[174] Inhaled diesel exhaust particles' exposure and intranasal *Aspergillus fumigatus* induced hypermethylation of several sites of the *interferon gamma* (*IFNγ*) promoter and hypomethylation at a CpG site of the *IL-4* promoter in mice. Altered methylation of promoters of both genes was correlated with changes in IgE levels.[175,176]

We recently also associated PM exposure with histone modifications in the above-mentioned steel workers with high exposure level to PM.[177] In this study, exposure duration (years of work in the foundry) was associated with increased H3K4me2 and H3K4ac in blood leucocytes.[177] In the same study, we showed that exposure to metal-rich PM induced rapid changes in the expression of two inflammation-related miRNAs, i.e. miR-21 and miR-222, measured in peripheral blood leucocytes.[178] Using microarray profiling, Jardim *et al.*[172] have shown extensive alterations of miRNA expression profiles in human bronchial epithelial cells treated with diesel exhaust particles. Out of 313 detected miRNAs, 197 were either up- or down-regulated by at least 1.5-fold.[172]

Benzene

Benzene is an environmental chemical that has been associated with increased risk of haematological malignancies, particularly with acute myeloid leukaemia and acute nonlymphocytic leukaemia.[179–184] Benzene ranks among the top 20 chemicals for production volume in USA.[185] Our results from a study of police officers and gas-station attendants have shown that low-dose exposure to airborne benzene is associated with alterations in DNA methylation in blood DNA of healthy subjects that resemble those found in haematological malignancies,[165–168,186] including hypomethylation of LINE-1 and Alu repetitive elements, hypermethylation of *p15* tumour suppressor gene and hypomethylation of *MAGEA1* (melanoma-associated antigen 1 gene). Consistently, reductions of global DNA methylation has been recently shown in human

lymphoblastoid cells treated with benzene metabolites.[187] *In vitro* experiments have also shown that benzene exposure induces hypermethylation of poly (ADP-ribose) polymerases-1 (*PARP-1*), a gene involved in DNA repair.[188]

Bisphenol A

Bisphenol A (BPA) is an endocrine disruptor with potential reproductive effects, as well as a weak carcinogen associated with increased cancer risk in adult life through fetal exposures.[189,190] BPA is widely used as an industrial plasticizer in epoxy resins for food and beverage containers, baby bottles and dental composites.[191] Dolinoy *et al.*[192] reported that periconceptional exposure to BPA shifted the coat colour distribution of the viable yellow agouti (A^{vy}) mouse offspring toward yellow by decreasing CpG methylation in an intracisternal A particle (IAP) retrotransposon upstream of the Agouti gene.[193] In this animal model, the yellow-coat phenotype is associated with increased cancer rates, as well as with obesity and insulin resistance. In the same set of experiments, maternal dietary supplementation, with either methyl donors like folic acid or the phytoestrogen genistein, blunted the effect of BPA on IAP methylation and prevented the coat colour change caused by BPA exposure.[192] In pregnant CD-1 mice treated with BPA, Bromer *et al.*[194] found decreased methylation and increased expression of the homeobox gene *Hoxa10*, which controls uterine organogenesis. In breast epithelial cells treated with low-dose BPA, gene expression profiling identified 170 genes with expression changes in response to BPA, of which expression of lysosomal-associated membrane protein 3 (*LAMP3*) was shown to be silenced due to DNA hypermethylation in its promoter.[195]

In a recent study by Avissar-Whiting *et al.*,[196] an elevated expression of miR-146a was observed in BPA-treated placental cell lines and miR-146a expression was associated with slower cell proliferation and higher sensitivity to the bleomycin-induced DNA damage.

Dioxin

Dioxin is a compound that has been classified as a human carcinogen by the International Agency for Research on Cancer. As dioxin is only a weak mutagen, extensive research has been conducted to identify potential mechanisms contributing to carcinogenesis. One proposed pathway to carcinogenesis is related to the powerful dioxin-induced activation of microsomal enzymes, such as CYP1B1, that might activate other procarcinogen compounds to active carcinogen. The capability of dioxin to induce *CYP1B1* has been recently shown *in vitro* to depend on the methylation state of the *CYP1B1* promoter.[197] Also, dioxin was shown to reduce the DNA methylation level of *Igf2* in rat liver.[198] Recently, alterations in DNA methylation at multiple genomic regions were identified in splenocytes of mice treated with dioxin, a finding potentially related to dioxin immunotoxicity.[199] In a xenograft mouse model of hepatocellular carcinoma, Elyakim *et al.*[200] have also found that dioxin up-regulated miR-191. In the same study, inhibition of miR-191 inhibited apoptosis and decreased cell proliferation, suggesting that increased miR-191 expression may contribute to determine dioxin-induced carcinogenicity.

Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX, also known as hexogen or cyclonite)

Hexahydro-1,3,5-trinitro-1,3,5-triazine (commonly known as RDX, the British code name for Royal Demolition Explosive) is an explosive polynitramine and common ammunition constituent used in military and civil activities. Although most of this environmental pollutant is found in soils, RDX and its metabolites are also found in water sources.[201] Exposure to RDX and its metabolites could cause neurotoxicity, immunotoxicity and cancers.[202] Zhang *et al.*[202] have recently evaluated the effects of RDX on miRNA expression in mouse brain and liver. In this study, out of 113 miRNAs, 10 were up-regulated and 3 were down-regulated. Most of the miRNAs that showed altered expression, including let-7, miR-17-92, miR-10b, miR-15, miR-16, miR-26 and miR-181, were found to regulate toxicant-metabolizing enzymes, as well as genes related to carcinogenesis and neurotoxicity.[202]

Diethylstilbestrol

Diethylstilbestrol (DES) is a synthetic oestrogen that was used to prevent miscarriages in pregnant women between the 1940s and the 1960s.[203] A moderate increase in breast cancer risk has been shown both in daughters of women who were treated with DES during pregnancy, as well as in their daughters.[204] Hsu *et al.*[205] have demonstrated that the expression of 82 miRNAs (9.1% of the 898 miRNAs evaluated) were altered in breast epithelial cells when exposed to DES. In particular, the suppression of miR-9-3 expression was accompanied by promoter hypermethylation of the miR-9-3 coding gene in DES-treated epithelial cells.[205]

Chemicals in drinking water

Chlorination by-products are formed as a result of the water chlorination for anti-fouling purposes. Various chlorination by-products in drinking water, such as triethyltin,[206] chloroform[207] and trihalomethanes,[208] have been questioned for potential adverse health effects.[209] These chemicals have been shown to induce certain epigenetic changes. Rats that were chronically intoxicated with triethyltin in drinking water showed development of cerebral oedema as well as an increase of phosphatidylethanolamine-*N*-methyltransferase activities. This increased methylation might be a compensatory mechanism for counteracting the membrane damages induced by triethyltin.[206] Chloroform, dichloroacetic acid (DCA) and trichloroacetic acid (TCA), three liver and kidney carcinogens, are by-products of chlorine disinfection found in drinking water.[210,211] Mice treated with DCA, TCA and chloroform show global hypomethylation and increased expression of c-*myc*, a proto-oncogene involved in liver and kidney tumours.[207] Trihalomethanes (chloroform, bromodichloromethane, chlorodibromomethane and bromoform) are regulated organic contaminants in chlorinated drinking water. In female B6C3F1 mouse liver, trihalomethanes demonstrated carcinogenic activity. Chloroform and bromodichloromethane decreased the level of 5-methylcytosine in hepatic DNA. Methylation in the promoter region of the *c-myc* gene was reduced by the trihalomethanes, consistent with their carcinogenic activity.[208]

Environmental epigenomics: challenges and opportunities for epidemiologic studies

The studies reviewed in this article have demonstrated the potential effects of environmental pollutants on the epigenome. Several of the epigenomic changes observed in response to environmental exposures might be mechanistically associated with susceptibility to diseases (Table 1). Further studies of epigenetic mechanisms in disease pathogenesis, including the role of epigenetics in the developmental origins of health and disease, their relationships with environmental exposures and the pathways associated with the disease phenotype may help develop preventive and therapeutic strategies.

Epigenetics and developmental origins of health and disease

During embryogenesis, epigenetic patterns change dynamically to adapt embryos to be fit for further differentiation.[7] Two waves of epigenetic reprogramming, which take place at the zygote stage and during primordial germ cells formation, accompany mammalian development.[212]

Experiments on mice carrying the A^{vy} have demonstrated that embryo life is a window of exquisite sensitivity to the environment. In viable yellow (A^{vy}/a) mice, transcription originating in a IAP retrotransposon inserted upstream of the agouti gene (A) causes ectopic expression of agouti protein, resulting in yellow fur, obesity, diabetes and increased susceptibility to tumours.[213] BPA is a high-production-volume chemical used in the manufacture of polycarbonate plastic. In utero or neonatal exposure to BPA is associated with higher body weight, increased breast and prostate cancer and altered reproductive function.

Additional experimental studies have suggested epigenetic mechanisms as potential intermediates for the effects of prenatal exposures to pesticides such as vinclozolin and methoxyclor,[154] as well as of other conditions such as nutritional supplies of methyl donors.[192] Evidence has also been

accumulating in humans. Investigations of candidate loci among individuals prenatally exposed to poor nutrition during the Dutch famine in 1944–45 indicate that epigenetic changes induced by prenatal exposures may be common in humans, although they appear to be relatively small and greatly dependent on the timing of the exposure during gestation.[214,215] Based on findings of changes in DNA methylation in subjects exposed to the Dutch famine, Heijmans *et al.*[216] have suggested that the epigenome may represent a molecular archive of the prenatal environment, via which the in-utero environment may produce serious ramifications on health and disease later in life. Terry *et al.*[217] found that prenatal exposure to cigarette smoke was associated with increased overall blood DNA methylation level in adulthood. Other examples include decreased LINE-1 and Sat 2 methylation level in adults and children prenatally exposed to smoking,[218] and global DNA hypomethylation in newborns with utero exposures of maternal smoking.[219] In addition to these DNA methylation changes, Maccani *et al.*[220] have recently observed that miR-16, miR-21 and miR-146a were down-regulated in cigarette smoke-exposed placentas compared to controls.

Additional well-conducted epigenetic studies are now warranted to generate a catalogue of regions that are sensitive to the prenatal environment and may reflect developmental influences on human disease.

Can we develop epigenomic biosensors of past exposures?

An important property of epigenomic signatures is that, because they can be propagated through cell division even in cells with high turnover, they can persist even after the exposure is removed. In addition, as discussed above, an individual's epigenome may also reflect his/her prenatal environmental exposure experience. Thus, epigenomic profiling of individuals exposed to environmental pollutants might provide biosensors or molecular archives of one's past or even prenatal environmental exposures. Using epigenomics, exposure assessment might be brought to research investigations and preventive settings where repeated collections of exposure data might be unfeasible or exceedingly expensive. Further research is needed to establish how rapid are the changes induced by environmental pollutants, as well as whether they accumulate in response to repeated or continuous exposure and how long they persist after the exposure is removed.

What are suitable study designs and approaches for environmental epigenomics?

The field of environmental epigenetics has evolved rapidly in the past several years. As research applications grow, investigators will be facing several difficulties and challenges. Some studies have produced inconsistent results on same pollutants. Several factors may contribute to the inconsistencies. Epigenetic alterations are tissue specific.[221] It is conceivable that the same environmental pollutant may produce different epigenetic changes in different tissues, and even within the same tissue on different cell types. Larger studies with well-defined exposure information that allows examining epigenetic changes across different tissues are needed. Different study design, small sample size and different laboratory methods may also be major causes for the inconsistency. Replicating results and identifying the sources of variability across studies is a major challenge for epigenetic investigations. Because epigenetic markers change over time, disease outcomes are prone to reverse causation, i.e. an association between a disease and an epigenetic marker may be determined by an influence of the disease on the epigenetic patterns, rather than vice versa.[222] Although epigenetic alterations that were found to be induced by or associated with environmental pollutants were also found in various diseases, almost no study has examined the sequence of exposures, epigenetic alterations and diseases.

Longitudinal studies with prospective collection of objective measures of exposure, biospecimens for epigenetic analyses and preclinical and clinical disease outcomes are needed to appropriately establish causality. Existing prospective epidemiology investigations might provide resources for mapping epigenomic changes in response to specific chemicals. However,

cohort studies in which biospecimens have been previously collected for genetic or biochemical studies might pose several challenges. Most studies have collected biospecimens, such as blood, urine or buccal cells, which might not necessarily participate in the aetiology of the disease of interest. Methods of collection and processing (e.g. whole blood vs buffy coat) might modify the cell types stored, thus potentially impacting on epigenetic marks. In addition, high-coverage methods providing high-dimensional data on DNA methylation, histone modifications and miRNA expression are increasingly used in human investigations.

Albeit epigenetic mechanisms have properties that make them ideal molecular intermediates of environmental effects, the proportion of the effects of any individual environmental exposure that might be mediated through epigenetic mechanisms is still undetermined. Epidemiology and statistical approaches, including well-designed prospective studies and advanced statistical methods for causal inference are urgently needed. Similarly to genomic studies,[223] epidemiological causal reasoning in epigenomics should include careful consideration of knowledge, data, methods and techniques from multiple disciplines.

The potential interactions between different forms of epigenetic modification

Most studies in environmental epigenetics have separately evaluated only one of the types of the epigenetic marks, i.e. DNA methylation, histone modifications or miRNA expression. However, epigenetic marks are related by an intricate series of interactions that may generate a self-reinforcing cycle of epigenetic events directed to control gene expression.[224] For instance, histone deacetylation and methylation at specific amino acid residues contribute to the establishment of DNA methylation patterns. miRNA expression is controlled by DNA methylation in miRNA encoding genes, and, in turn, miRNAs have been shown to modify DNA methylation.[225] Future studies that include comprehensive investigations of multiple epigenetic mechanisms might help elucidate the timing and participation of DNA methylation, histone modifications and miRNAs to determine environmental effects on disease development.

Can epigenomics be used for prevention?

One major objective of epidemiology investigations is to provide the groundwork for future preventive interventions. Numerous clinical and preclinical studies showed that most of the epigenetic changes are reversible, which offers novel insights to develop new preventive and therapeutic strategies that might take advantage of molecules that modify the activities of epigenetic enzymes, such as DNMTs and HDACs, as well as of the growing field of RNAi therapeutics. Drugs have been designed and developed that produce functional effects, such as histone acetylation and DNA hypomethylation that might be used to restore the normal transcription level of genes. Future epidemiology studies have a unique opportunity to evaluate whether the effects of environmental exposures on the epigenome are mitigated by positive changes in lifestyles, or worsened by the interaction with other risk factors. Future epigenomic research may provide information for developing preventive strategies, including exposure reduction, as well as pharmacological, dietary or lifestyle interventions.

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KEY MESSAGES

- Rapidly growing evidence has linked environmental pollutants with epigenetic variations, including changes in DNA methylation, histone modifications and microRNAs.
- Some of such epigenetic changes have been associated with various diseases.

- Further studies of epigenetic mechanisms in disease pathogenesis, their relationships with environmental exposures and related pathways are needed for the development of preventive and therapeutic strategies.
- Future epidemiology studies on environmental pollutants and epigenome face several challenges.

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