Chin. Sci. Bull. (2014) 59(4):349–355
DOI 10.1007/s11434-013-0007-6

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Review

Environmental Chemistry

Environmental chemical stressors as epigenome modifiers: a new horizon in assessment of toxicological effects

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Received: 7 February 2013 / Accepted: 9 April 2013 / Published online: 31 December 2013

Abstract In eukaryotic cells, chromatin transformation from euchromatin into heterochromatin as a means of controlling gene expression and replication has been known as the "accessibility hypothesis". The interplay of epigenetic changes including histone modifications, DNA methylation, RNA interference (RNAi) and other functional epigenetic components are intricate. It is believed that these changes are well-programmed, inherited and can be modified by environmental contaminant stressors. Environmentally-driven epigenetic alterations during development, e.g. embryonic, foetal or neonatal stage, may influence disease susceptibility in adulthood. Therefore, understanding how epigenome modifications develop in response to environmental chemicals and, how epigenetic-xenobiotic interactions influence human health will shed new insights into gene-environment interactions in the epidemiology of several diseases including cancer. In this review, we consider studies of chemical modifiers including nutritional and xenobiotic effects on epigenetic components in vitro or in vivo. By examining the most-studied epigenome modifications and how their respective roles are interlinked, we highlight the central role of xenbiotic-modified epigenetic mechanisms. A major requirement will be to study and understand effects following environmentally-relevant exposures. We suggest that the study of epigenetic toxicology will open up new opportunities to devise strategies for the prevention or treatment of at-risk populations.

Keywords DNA methylation · Epigenetics · Environmental stressor · Epigenetic toxicology · Histone modifications · Noncoding RNA (ncRNA)

In eukaryotic cells, chromatin transformation from euchromatin into heterochromatin as a means of controlling gene expression and replication has been known as the "accessibility hypothesis". Various epigenome modifications can remodel chromatin accessibility [1, 2]. Within the cell nucleus, the most actively transcribed chromatin is lightly-packed euchromatin, which is characteristically hyperacetylated at N-terminal lysine residues in core Histones H3 (H3Kac; i.e. H3 lysine-9/14 acetylation) and H4 (H4Kac; i.e. Histone H4 acetylated lysine) along with hypomethylated CpG islands in related gene promoter regions. Some constitutive euchromatin may be "always turned on", including regions encoding housekeeping genes. Rendering it inaccessible, tightly-packed heterochromatin usually expresses different variations of hypoacetylated histones ranging between the two extreme levels representing constitutive and facultative. Constitutive heterochromatin is poorly expressed and consists mainly of repetitive structures such as (peri) centromeric satellites and telomeric repeats with typically tri-methylated lysine residues H3K9 (H3K9me3; i.e. Histone H3 trimethyl

Electronic supplementary material The online version of this article (doi:10.1007/s11434-013-0007-6) contains supplementary material, which is available to authorized users.

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Lysine 9), in which the histone methyltransferases (HMTs) and heterochromatin protein 1 (HP1) are specifically bound to H3K9me3 [3–5].

For some genes subject to developmental regulation, sequences may be either tightly packaged in facultative heterochromatin containing hypermethylated CpG islands in one cell whilst in another, they may occur in euchromatin with hypomethylated CpG islands; this could include the X chromosome genes that are inactive in female mammals but active in males and the inactive alleles of methylated genes with monoallelic expression subject to imprinting [6]. In facultative heterochromatin, H3K9 (i.e. Histone H3 Lysine 9) and H4K20 (i.e. Histone H4 Lysine 20) are in general di- or mono-methylated; the silenced gene is maintained by H3K27me3 (i.e. Histone H3 trimethyl Lysine 27) and mono-ubiquitylated H2AK119 [5]. Histone modifications also include phosphorylation, ubiquitinylation, sumoylation, ADP-ribosylation, carbonylation, deimination and proline isomerization [7].

In addition, chromatin architecture is regulated by ncRNAs; microRNAs (miRNAs) often act in concert with various components of the cell's chromatin and DNA methylation machinery to achieve stable silencing via the RNAi pathway, with associated alterations to chromatin structure [8]; these are believed to regulate up to one-third of all human genes by interfering with mRNA functions [9]. Heterochromatin formation appears to be broadly regulated by small RNAs, i.e. RNAi-related processes [8]. Several additional classes of ncRNAs, such as repeat-associated small-interfering (si) RNAs (RasiRNAs) in Drosophila and their mammalian counterparts Piwi protein-interacting RNAs (piRNAs), are found to be involved in the regulation of genomic architecture, the maintenance of germline genomic integrity and the ageing process [7, 8]. Moreover, as parental imprinting is intimately linked to ncRNAs [8], this reflects the fact that RNA-directed regulatory processes may also transfer epigenetic information not only within cells but also between cells and organ systems, as well as being trans-generational [10]. Recent research suggests *LINE-1* retrotransposon RNA is an essential structural and functional epigenetic component for centromeric activity [11] and non-coding genes *Xist* (X-inactive specific transcript), an RNA gene on the X chromosome of placental mammals that acts as an effector of the X-inactivation process, can regulate the expansion of heterochromatin [12].

Although cross-talk with constitutive processes is a major epigenomic regulator [13–16], one also needs to consider the role that chemical modifiers, including nutritional and xenobiotic, play in modifying epigenetic components in vitro or in vivo. The core focus of this review will be on how xenobiotics-induced adverse epigenetic alterations or epigenetic toxicity beyond the DNA sequence impacts on heritable gene expression or phenotype.

1 Chemical-induced epigenetic component alterations

Whilst one inherits their genetic sequence code, the expression or silencing of individual genes can be modified by environmental factors [10, 17]. Recent research suggests that exposure to environmental stressors, including nutritional factors and chemical or physical pollutants can alter gene expression via altered epigenetic components [18–22]. Such epigenetic processes play a significant role in acclimation to environmental stresses. A wide range of environmental factors, including xenobiotic chemicals, diet, stress, behaviour, geographic location and even weather patterns have been shown to alter gene expression via epigenetic alterations [20, 21, 23]. Certain environmental stressor-stimulated epigenetic alterations can be passed from one generation to the future generations [24, 25]; however, these findings need to be robustly tested in future studies.

1.1 Inorganic chemicals

Acetylation has been linked with transcriptional stimulation [3]. Recent studies have associated nickel with histone modifications and altered chromatin organization. At non-toxic levels, it induces decreases of Histone H4 acetylation in yeast [26]. Post-nickel exposure, decreased gene expression coincided with three major histone modifications, including loss of acetylation (of H2A, H2B, H3 and H4), increased H3K9me2 (i.e. Histone H3 dimethyl Lysine 9), and increased ubiquitinylation of H2A and H2B [27–29]. Chromium exposure was linked to epigenetic-controlled gene expression alterations via interactions with histone acetyltransferases (HATs) and histone deacetylases (HDACs) [30], the enzymes that catalyze histone deacetylation and acetylation, respectively. Chromium reduces phosphorylation and trimethylation in H3, modifies a variety of acetylation marks in H3 and H4, and influences *P16* hypermethylation in lung cancer tissues [30–32]. Developmental mouse exposure to low levels of methylmercury may induce epigenetic suppression via DNA hypermethylation of gene expression particularly of the brain-derived neurotrophic factor (BDNF) promoter region in the hippocampus, an increase in histone H3K27me3 (i.e. Histone H3 trimethyl Lysine 27) and a decrease in H3ac (i.e. acetylated Histone H3) at the promoter IV [33].

Occupational or environmental exposure to cadmium, arsenic, nickel, chromium, methylmercury or lead can result in altered DNA methylation [21]; following heavy metal (cadmium, arsenic or nickel) exposures, the resulting

pathologies in rodents exhibit an epigenetic profile that resembles that of animals fed a methyl-deficient diet. Short-term cadmium exposure inhibits DNA methyltransferases (DNMT) activity, but prolonged exposure increases DNA methylation and DNMT activity, resulting in neoplastic transformation in rat hepatocytes [34, 35]. Cadmium alterations of DNA methylation may be responsible for its carcinogenic properties. By promoter hypermethylation in human lung adenocarcinoma, plutonium can target *P16* for inactivation [36]. Arsenic is also associated with gene-specific hypermethylation as well as global DNA hypomethylation, which depletes SAM (*S*-adenosyl methionine) and represses DNMT1 and DNMT3A activity [37]. Adult mice exposed to sodium arsenite exhibit reduced DNA methylation whilst co-exposure of sodium arsenite with a methyl-deficient diet results in gene-specific hypomethylation in the promoter region of the oncogene *Ha-ras* [38]. An India-based human study showed a dose–response relationship between hypermethylation and arsenic exposure from drinking water [39]. Similarly, a dose-dependent hypermethylation in blood DNA was associated with chronic arsenic exposure in Bangladeshi adults [40].

1.2 Organic chemicals

Exposure to some endocrine disruptors has been linked with epigenetic alterations that are inherited trans-generationally [24, 25] via germ line transmission of imprinted genes exhibiting an altered methylation pattern. Transient exposure to the oestrogenic insecticide methoxychlor and the antiandrogenic fungicide vinclozolin at the time of sex determination appeared to alter methylation of two imprinted genes of LPLase and cytokine-inducible SH2 protein in the male germ line of pregnant rats [24]. Adverse effects were reported to last for four subsequent generations in approximately 90 % of males and, suggested vinclozolin-induced DNA methylation changes are inherited [41]. Vinclozolin may also target Sertoli cells in mice, and exploit miRNAs to elicit its anti-androgenic effects [42]. The oestrogenic diethylstilbestrol (DES) caused the aberrant DNA methylation of oestrogen-regulated genes such as lactoferrin (*LF*) in mice exposed in utero or perinatally and transgenerational effects were observed in DES-exposed individuals [43–45]. Neonatal exposure to oestradiol and environmental levels of bisphenol A (BPA) resulted in multiple changes in cell signalling gene-specific DNA methylation patterns in rat prostate [46]. Exposure to BPA during early development was found to decrease *agouti* gene methylation. When pregnant yellow *agouti* mothers were fed BPA, yellower and unhealthier offspring compared to those on control diets were born. However, pregnant yellow mice administered BPA but kept on a methyl-rich diet had offspring that were predominantly brown [47]. Nonylphenol-treated cell lines (MCF-7 and HepG2 cells) exhibited altered miRNA profiles of let-7c, miR-16, -195, -200b, 200c, 205, -589, which are related to metabolism, immune responses, apoptosis, and cell differentiation [48]. Pre-implantation exposure of mice embryos to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) resulted in altered methylation status of imprinted genes *H19* and *IGF2* (insulin-like growth factor 2) [49]. Other endocrine disruptors including phthalates, polychlorinated biphenyls (PCBs) and organochlorine pesticides may also affect the reproductive system or induce tumour development by altering DNA methylation [50–53].

Many other chemical stressors can alter epigenetic markers. Exposure to oxidative stressor-like H_2O_2 increased HAT activity, which promoted acetylation and induced chromatin remodelling in alveolar epithelial cells [54]. Nucleoside analogues such as azacitidine that are incorporated into replicating DNA, inhibit methylation and reactivate previously-silenced genes [55]. The antisense oligonucleotide drug MG98 that down-regulates DNMT1 showed promise in phase I clinical trials [56]. Similarly, small molecules such as valproic acid that down-regulate HDACs are being used to induce growth arrest and tumour cell death [57]. Pogribny et al. [58] found Fisher 344 rat exposure to tamoxifen, a potent hepatocarcinogen in rats, leads to a significant up-regulation of known oncogenic miRNAs, such as the 17-92 cluster, miR-106a, and miR-34.

1.3 Lifestyle-related and nutritional chemicals

Polyphenols such as genistein, catechins and bioflavonoids in green tea can inhibit DNMTs and further inhibit methylation of candidate genes [59–63]; the pathways by which these chemicals affect DNA methylation remain obscure [60, 62, 64]. When a woman is exposed during pregnancy to polycyclic aromatic hydrocarbons (PAHs) from tobacco smoke, methylation of specific genes in the developing foetus is affected, and this is associated with a fourfold increase in asthma symptoms in children <5 years [65]. Exposure to airborne PAHs during pregnancy resulted in methylation of *ACSL3* (expressed in lung and thymus tissue) with associated parental reporting of increased prevalence of child's asthma <5 years age; 73 % of children with asthma exhibited *ACSL3* methylation compared to 41 % who were asymptomatic [66]. Cigarette smoking can also stimulate the demethylation of metastatic genes [67] and aberrant promoter hypermethylation of death-related protein kinase genes [67] in lung cancer, and downregulate miRNA expression in the lungs of rats [68]. A detrimental effect on the physical and mental development of offspring due to paternal chronic alcohol consumption, even in the absence of in utero

alcohol exposure, was suggested to be the result of incorrect *H19* methylation and intergenic differentially-methylated region (IG-DMR) [69]. Cocaine abuse may lead to histone acetylation and activation of genes, altering locomotor and rewarding responses to the drug [70]. Long-term PM_{10} exposure was inversely associated with methylation in both *Alu* and *LINE-1* (long interspersed nuclear element 1) [71]. Jardim et al. [72] found disruption of miRNA expression in human airway cells by diesel exhaust particles is linked to tumorigenesis-associated pathways. A human study showed that miRNA expression (miR-222, miR-21, and miR-146a related with oxidative stress and inflammatory processes) could be a novel mechanism mediating responses to PM (i.e. particulate matter) and its metal components [73].

Chemicals sourced from nutritional sources are also involved in DNA methylation pathways. Folic acid, vitamin B_{12} and SAM are key elements in some one-carbon metabolism pathways, which can couple the DNA methylation pathway. DNMTs catalyze the transfer of a methyl group from the methyl donor SAM onto the 5′-position of the cytosine ring residing, in most cases, at the dinucleotide CG sequence. DNMTs use the molecule SAM as their primary source of methyl groups. SAM is manufactured via the folate and methionine pathways, using methionine, choline, folic acid and vitamin B_{12} ingested in the diet. Studies have shown that DNA methylation correlates positively with folate status in the human body [74]. Diets with high methyl-donating nutrients quickly modify the epigenome, especially in early development. It has been reported [75–78] that feeding female mice with methyl donor diets before and after pregnancy permanently increased DNA methylation in their offspring at the viable yellow *agouti* (A^{vy}) metastable epiallele; the feeding resulted in brown, healthy offspring. The deficiency of methyl-donating folate or choline during the late foetal or early postnatal developmental stages led to hypomethylation [77]. In adults, a methyl-deficient diet can also result in a decrease of DNA methylation, but this is reversible with a normal diet [79]. However, high maternal dietary intake of methyl donors during gestation was associated with a higher incidence of asthma in mice offspring; decreased transcriptional activity of *Runx3*, a gene associated with suppression of allergic airway disease, was caused by increased DNA methylation and this was reversible through the administration of a demethylating agent [80]. Aberrant methylation mediated by folate levels has been a suggested risk factor in Alzheimer's disease [81]. Dietary selenium may also influence DNA methylation status and further influence disease predisposition, e.g. cancer [57, 82, 83], by affecting one-carbon metabolism in a different way compared to folate.

2 Chemical-epigenetic interactions

Chemical-modified gene activation may involve the ordered cascade of epigenetic events that begin with histone modifications and finalize with alterations in DNA methylation in promoter CpG islands [3, 84]. A general hypothesis of environmental chemicals as lifelong modulators of DNA hypomethylation is that such xenobiotics, including metals, influences one-carbon metabolism directly or indirectly [85, 86]. This may explain the population cohort studies that exhibit significant inverse linear relationships between POPs or metals exposures and blood global DNA methylation [87–89]. Patients with atherosclerotic vascular disease often exhibit higher homocysteine and *S*-adenosyl homocysteine (SAHC) and lower genomic DNA methylation status [90, 91], which is directly connected with one-carbon pathways. Indirectly, oxidative stress mechanisms generated by xenobiotics may also involve aberrant epigenetic modification of DNA [85] and histones [92] via the depletion of glutathione (GSH) and changing the ratio of reduced GSH and its oxidized form, GSSG (i.e. GSH disulphide). Oxidative stress may also alter epigenetic modification via mitochondrial dysfunction [93–95]. To be inhibitors, isoflavones, polyphenol, zinc and cadmium may inhibit DNMTs directly and indirectly, and further inhibit methylation of candidate genes [34, 59, 60, 62, 64].

Coinciding with gene-specific aberrant methylation following exposure to endocrine disrupting chemicals, DNMTs were abnormally expressed in some cases [45, 49]. Endocrine disrupting chemicals induced aberrant methylation of oestrogen-regulated genes [43–45]; steroid hormone interacts with chromatin-modifying enzymes by binding the receptors [16] may suggest other pathways by which chemicals alter epigenetic markers, i.e. they may involve the expression of target genes by modifying their epigenetic regulators directly.

3 Concluding remarks

In the broadest sense, environmental chemicals appear to alter epigenomic marking and, subsequently gene expression. Particular gene expression profiles can pre-dispose both parental and subsequent generations to an elevated susceptibility to disease [10]. Therefore, these stressors very probably modulate disease susceptibility. The field of environmental epigenomics is still in its infancy; however, a growing body of information is improving our understanding of the interplay between epigenetic alterations, gene expression and environmental stressors. There's an urgent need to study the consequences of exposures at environmentally-relevant levels; this will allow the

determination of real-world effects and the true relevance of epigenetic mechanisms. It is probable that such epigenetic markers will be used for early molecular diagnosis in those with a predisposition to developing adult diseases due to environmental exposure. For instance, the abnormal methylation of *Igf2* and *H19* gene expression in sperm of adults may indicate a susceptibility to diabetes in subsequent generations [96]. Furthermore, as the epigenome is modifiable or reversible, this allows for the implementation of strategies to allow disease prevention and targeted treatment. In summary, pollutant-induced epigenetic toxicities turn on or determine latent alterations in gene regulation (Tables S1, S2 and S3 online), such epimutagenic events open up a new horizon in assessment of environmental health.

Acknowledgments This work was supported by Hundred Talent Program of Chinese Academy of Sciences for 2010 on Human Exposure to Environmental Pollutant and Health Effect, National Natural Science Foundation of China (21177123) and Xiamen Science and Technology Fund (3502Z20122003).

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