Current Epidemiology Reports (2018) 5:450–460
https://doi.org/10.1007/s40471-018-0175-7

GENETIC EPIDEMIOLOGY (C AMOS, SECTION EDITOR)

Environmentally Induced Epigenetic Plasticity in Development: Epigenetic Toxicity and Epigenetic Adaptation

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Published online: 2 October 2018

Abstract

Purpose of Review Epigenetic processes represent important mechanisms underlying developmental plasticity in response to environmental exposures. The current review discusses three classes of environmentally induced epigenetic changes reflecting two aspects of that plasticity, toxicity effects as well as adaptation in the process of development.

Recent Findings Due to innate resilience, epigenetic changes caused by environmental exposures may not always lead to impairments but may allow the organisms to achieve positive developmental outcomes through appropriate adaptation and a buffering response. Thus, some epigenetic adaptive responses to an immediate stimulus or exposure early in life would be expected to have a survival advantage but these same responses may also result in adverse developmental outcomes as they persist into later life stages. Although accumulating literature has identified environmentally induced epigenetic changes and linked them to health outcomes, we currently face challenges in the interpretation of the functional impact of their epigenetic plasticity.

Summary Current environmental epigenetic research suggests that epigenetic processes may serve as a mechanism for resilience, and that they can be considered in terms of their impact on toxicity as a negative outcome, but also on adaptation for improved survival or health. This review encourages epigenetic environmental studies to move deeper into the functional meaning of epigenetic plasticity in development.

Keywords Epigenetics · DNA methylation · Environmental exposures · Toxicity · Plasticity · Adaptation

Introduction

Adaptation is a critical mechanism to allow for survival in the changing environment. On a large timescale and population level, adaptation relies on changes in gene frequencies based on natural selection; yet, in response to more immediate fluctuations and individual levels, homeostasis represents the critical process allowing for buffering of the effects of temporary and quick environmental changes [1]. However, neither of the modes can efficiently assist an organism to adapt to and survive in an emerging baseline environmental state, such as prenatal undernutrition/overnutrition, exposure to maltreatment or stress in early life, and environmental pollution or toxicants [1]. Instead, developmental plasticity allows for response to such environmental changes, representing an intermediate between the slow process of natural selection and the transient processes represented as homeostasis [1]. Developmental plasticity summarizes the capacity to modify developmental biology in response to and to fit the environmental experiences [2, 3]. On the positive side of developmental plasticity, resilience serves as the process through which organisms achieve positive adaptation to environmental changes and prepares for future adverse experiences [4, 5]; meanwhile, on the negative side, once the impacts of environmental experiences exceed the capacity of resilience, impaired or disrupted development outcomes will be the results of incomplete buffering [6]. Researchers highlight the value of epigenetic mechanisms in studies of environmental health and developmental plasticity because of its function in regulating gene expression without altering the DNA sequence [7] as well as its persistence and relative dynamic plasticity in response to environmental factors [8]. Thus, these mechanisms are critical to developmental outcomes (Fig. 1). Epigenetic events include the widely studied DNA methylation as well as histone modifications and non-coding RNA,

This article is part of the Topical Collection on *Genetic Epidemiology*

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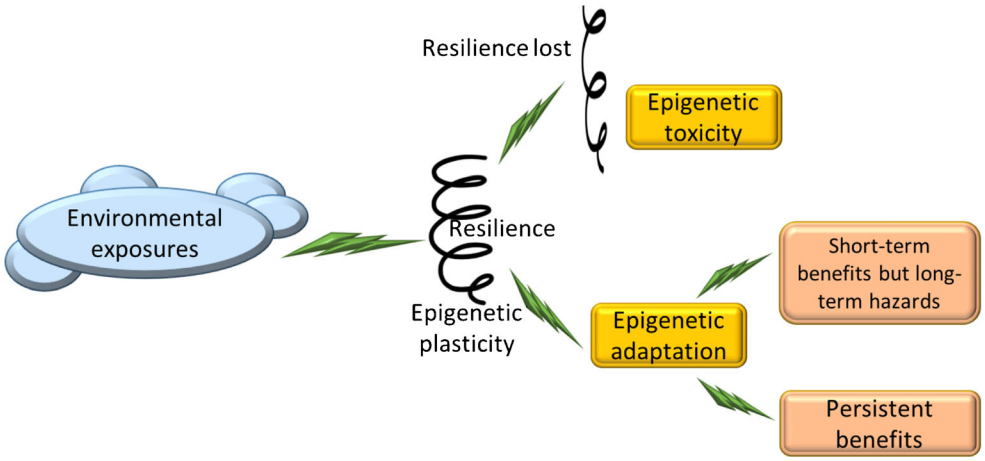

Fig. 1 Epigenetic plasticity summarizes the capacity to modify developmental biology in response to and to fit environmental experiences. Once the impacts of environmental experiences exceed the capacity of resilience, epigenetic toxicity effects will be the result of incomplete buffering; on the contrary, the resilience serves as the processes through which the organism achieves epigenetic adaptation to environmental changes and to prepare the organisms for adverse experiences. However, the epigenetic adaptations can lead to both positive and negative long-term developmental outcomes

mechanisms that are less widely explored [9]. In this review, we mainly consider the role of DNA methylation as a mechanism of plasticity in response to environmental exposures.

DNA methylation is a process by which a methyl group is added to individual cytosines in the context of CpG dinucleotides. When this addition occurs in gene promoters, it is most often associated with transcriptional gene silencing or the reduction of gene activity [7]; however, the correlation between promoter DNA methylation and gene expression is not always in the expected direction and the exact impact of each unique instance of DNA methylation has not yet been fully characterized [10]. DNA methylation is implicated in aiding the persistent memory of environmental cues; but, it has been shown that DNA methylation is dynamic and changeable [11]. DNA cytosine methylation modifications are embodied in two major ways, through processes of methylation and demethylation. The processes involved in DNA methylation include de novo and maintenance activities while demethylation includes active and passive processes. These processes are critical in embryonic and fetal development, where a wave of demethylation after fertilization allows for pluripotency of the initial embryonic stem cells. This is followed by cell type-specific de novo methylation allowing for differentiation and maturation [12]. This process of de novo methylation is catalyzed by the DNA methyltransferases (DNMT) 3 family and is regulated by many other factors, such as DNMT3L (a non-catalytic paralog), unmethylated histone H3 lysine 4 tails, and piwi RNAs (piRNAs) [13, 14]. The process of de-programming and re-programming provides the fetus developmental plasticity and also introduces a critical period during which the organisms are sensitive to environmental exposures [12]. The established DNA methylation pattern is maintained by DNMT1 during DNA replication [14]. DNMT1 functions to copy the methylated strand of the hemi-methylated DNA to the nascent strand. Studies have demonstrated that environmental exposures, such as tobacco smoke [15], ethanol [16], and methyl-group donor intake [17], can interfere the activities of DNMT1. The absence of maintenance of DNA methylation leads to a passive loss of methylation; although, demethylation can also occur in active ways [13]. For example, ten-eleven translocation (TET) enzymes and thymine-DNA glycosylase (TDG) catalyze the subsequent products of the oxidized 5-methylcytosine to form abasic sites which are changed to be unmethylated sites through the base excision repair pathway [18]. These dynamic processes of DNA methylation provide environmental exposures various opportunities to influence the growth and development of organisms.

Recent data also suggests that through epigenetic variation, the organism not only reacts to the environmental experience of the current environment during the pre-/post-natal period [19] but also, potentially, to the environmental events experienced by its parental ancestors (reviewed by [20–22]). A great body of literature has made efforts to understand what epigenetic variations can be induced by specific environmental factors throughout the lifetime [12, 23–26]. In particular, with the growth of high-throughput technology, epigenome-wide studies allow us a holistic insight into the epigenetic programming in response to specific environmental factors [27–31].

Evidence is accumulating that there is complexity to epigenetic plasticity in response to environmental exposures. On the one hand, a certain environmental factor may induce epigenetic variation involved in multiple functional pathways in one type of tissue. On the other hand, epigenetic changes in the same region of the same gene in the same tissue may vary in response to different types of environmental factors. For example, studies of tobacco smoking-associated DNA methylation in infant cord blood have compellingly identified DNA methylation changes in

genes such as *AHRR*, *CYP1A1*, *GFI1* (reviewed by Green et al. [32]), and hypomethylation of CpGs at the *ESR1* (estrogen receptor 1) transcription start sites (TSS) in response to prenatal smoking exposure through epigenome-wide association study (EWAS) meta-analysis [33••]. ESR1 is a transcription factor mediating estrogen's involvement in the regulation of growth and development [34] as well as an important tumor suppressor gene [35]. Interestingly, White and colleagues [36••] found that ever active smoking as well as residential environmental tobacco smoking were also associated with lower promoter methylation of *ESR1* in breast tumor tissue. However, for most exposures, such as prenatal benzophenone-3 (BP-3) [37], hepatitis virus infection [38], inflammatory cytokine IL-1β [39], a western diet with bisphenol A (BPA) [40], and high-stress level [41], hypermethylation of *ESR1* was widely reported. Moreover, hypermethylation of *ESR1* and inactivation of this tumor suppressor were well documented as one of the main mechanisms underlying the presence and prognosis of malignancies like breast cancer [42], colorectal cancer [43], hepatocellular carcinoma [44], and ovarian cancer [45]. Therefore, comparing these studies, the unexpected inverse association between smoking and *ESR1* methylation in cord blood and even breast tumor tissue cannot simply be interpreted as the carcinogenic effect of smoking. This kind of complexity of DNA methylation changes was also observed in placenta tissue. The demethylation of the *P2RX4* (Purinergic Receptor P2X, Ligand-Gated Ion Channel 4) promoter and elevated expression were observed in the placental tissues of preeclampsia cases compared to the normal mother-child pairs [46], suggesting an overexpression of P2RX4 induced by preeclampsia. On the contrary, another study found that prenatal nitrogen dioxide (NO_2) exposure was associated with placental hypermethylation of the CpG site in the same *P2RX4* region detected in the preeclampsia study, potentially suggesting a suppressed P2RX4 expression [47••]. These observations suggest a need for careful interpretation of these exposure-related epigenetic changes. We need to consider if the alterations in DNA methylation are a reflection of environmentally induced toxicity, a way to adapt to environmental cues to benefit survival, or merely neutral reliable biomarkers of exposures.

In this review, first, we discuss epigenetic toxicity of environmental exposures. We then discuss the role of epigenetic plasticity in human adaptation to environmental cues focusing on developmental adaption studies. Last, we raise several challenges in the interpretation of epigenetic changes induced by environmental exposures. While this review is not meant to exhaust all the studies of exposure-induced epigenetic modifications in each class, it encourages epigenetic environmental studies to consider more fully the functional meaning of epigenetic plasticity in development.

Epigenetic Toxicity

Epigenetic toxicity is exposure-induced epigenetic modifications leading to undesirable health effects on organisms, potentially underpinning the predisposition to diseases due to environmental exposures [48]. Exposure-induced epigenetic toxic modifications appear to result from insufficient buffering of perturbations; in other words, the toxicity of the environmental factors exceed the capacity of resilience. The adverse effects of epigenetic toxicity are relatively direct, compared to the effects of the inappropriate epigenetic adaptation (discussed later). While epigenetic toxicity can lead to immediate developmental problems, it does not have to cause a problem initially, suggesting a time lag between epigenetic changes and health effects appearance. In the context of epigenetic toxicity, it is necessary to study the relative stability of the observed epigenetic markers in order to fully understand their impact on lagged health effects. However, currently, very few studies have measured the epigenetic markers at multiple time points to prove the persistence of modifications. We will discuss in greater depth below using examples.

The immediate effects of epigenetic toxicity have been studied in response to a wide range of environmental exposures. Liu et al. utilized the human lymphoblastoid TK6 cell to identify that lead exposure resulted in DNA damage via inducing hypermethylation and suppression of DNA repair genes, suggesting immediate epigenetic toxicity induced by lead exposure [49••]. Similarly, in a human study, Paul et al. found that higher levels of arsenic exposure led to hypomethylation of the promoter and enhanced expression of *ERCC2* (Excision Repair Cross-Complementing rodent repair, complementation group 2) that further inhibited DNA repair process in dermatological lesion patients [50]. Another study of adults occupationally exposed to volatile organic compounds (VOCs) has suggested that the synergistic, hematotoxic/leukemogenic effect of VOCs is represented by the toxic effects on the aberrant promoter methylation in genes involved in oxidative stress, DNA repair, and inflammation [51]. Additionally, the immediate epigenetic toxicity may appear in the placenta which is a fetal organ serving as the vehicle for communication of environmental signals between mother and fetus as well as a metabolic, endocrine, and immune organ regulating intrauterine fetus development. Disruption of the placental epigenome induced by environmental exposures has been associated with dysfunction of the placenta as well as fetal development (reviewed by Marsit [52]). A recent study reported that smoking mothers had lower placental DNA methylation of *CYP1A1* (cytochrome P450, family 1, subfamily A, polypeptide 1) and enhanced oxidative stress, in turn associated with lower mitochondrial DNA content that reflects mitochondrial dysfunction and impairment of placenta [53••]. Everson's cadmium-associated epigenome-wide study observed differential DNA methylation of the genes involved

in inflammatory signaling and their corresponding effect on gene expression in the placenta. These alterations of gene expression were also associated with birth weight, suggesting the reproductive toxicity of cadmium on growth may be partially through epigenetic toxicity and its downstream impacts [31]. The cadmium-associated epigenetic toxicity was also detected in a mouse model which suggested DNA methylation modifications and the expression patterns of *Cdkn1c* and *Peg10* involved in the etiology of cadmium-induced fetal growth restriction [54].

The Developmental Origins of Health and Disease (DOHaD) hypothesis emphasized the long-term impact of early life exposures on the susceptibility of diseases later in life. To explore the underlying mechanisms, a growing body of studies have investigated the link between environmentally induced epigenetic modifications and the lagged health events in both animals and humans (reviewed by Marczylo et al. [55]). Most of the studies have only single time point epigenetic measurement taken either early in life with a particular exposure or later in life with the outcomes. For example, Kaushal et al. reported that prenatal arsenic exposure leads to the changes in methylation of five CpGs in cord blood which were in the pathways related to cardiovascular diseases; also, the changed DNA methylation was associated with low-density lipoprotein of the children at the age of 2 to 14 years [30]. Additionally, prenatal particulate matter $(PM)_{2.5}$ exposure was associated with hypermethylation of children's nasal epithelia glutathione S-transferase P1 (*GSTP1*) gene that is also inversely associated with reduced children's lung function in early childhood [56]. Although this evidence may suggest potential epigenetic toxicity of environmental exposures on health later in life, they are powerless to illustrate if the environmentally induced epigenetic changes early in life are stable and functional until the occurrence of health events later in life, and vice versa. Therefore, we need to explore epigenetic toxicity at multiple time points in response to environmental exposures as well as outcomes. One recent example, from a prospective pregnancy cohort study in which the researchers evaluated the association of prenatal mercury exposure with the children's DNA methylation changes and cognitive performance, found that children exposed to prenatal mercury had lower regional DNA methylation at the paraoxonase 1 gene (*PON1*) in cord blood that predicted lower cognitive test scores measured in childhood; moreover, the mercury-related demethylation of *PON1* was also identifiable in childhood, building evidence that the neurodevelopmental toxicity of mercury may be partially through fetal epigenetic toxicity [57••].

In addition to gene-specific studies, DNA methylation age has gained significant interest in studies of environmentally induced epigenetic toxicity. DNA methylation age is a novel epigenome-wide DNA methylation-based measure of individual biological aging predicting chronological age [58] as well as capturing the interpersonal differences in the risk of many functional alterations, diseases, and mortality [59]. In adults, increased $PM_{2.5}$ exposure has been linked to accelerated DNA methylation age [60–62], which provides an improved understanding of the role of $PM_{2.5}$ as a contributor to accelerated aging and aging-related diseases [63–67], such as cardiopulmonary disease, and cognitive decline. Other perturbation-related DNA methylation age modifications are also documented. For example, one study detected cigarette pack-years were negatively correlated with DNA methylation age [61], but another study found a null association [68]. Obesity has also been reported to be associated with accelerating epigenetic aging in human liver [69].

Epigenetic Adaptation: Positive Effects

Environmental exposures do not always lead to epigenetic toxicity and impairments but can benefit organisms to achieve positive developmental outcomes through appropriate epigenetic adaptation. A growing body of studies has discussed the positive effect of environmental exposures through epigenetic mechanisms. Lactation represents an important early life period during which the DNA methylation in the still developing infant can be susceptible to environmental changes. Before birth, the fetus mainly takes the energy from glucose [70]. With the onset of breastfeeding, the infant starts to take advantage of more energy from fat [71], and breast milk assists infants to adapt to the change of energy source. Breast milk lipids may bind to PPARα (Peroxisome proliferator-activated receptor alpha) which in turn decreases the DNA methylation of genes related to lipid metabolism and increases their expression in neonatal livers; thus, breastfeeding assists hepatic lipid metabolism and liver maturation [71]. The DNA methylation changes of these genes can be regarded as a positive adaptive response to the increased lipid nutritional environment. These adaptive DNA methylation changes may benefit the lipid metabolism of the infants in later life, as indicated by human studies on breastfeeding and children's metabolic diseases [72]. In line with human studies, animal models have shown that the adaptive demethylation of *FGF21* (fibroblast growth factor 21, involved in lipid metabolism) and enhanced expression are persistent into adulthood, resulting in attenuation of diet-induced obesity of adults [73••]. Another well-known study in an animal model is that of the viable yellow agouti mouse, which examined the effects of maternal dietary genistein on the decreasing *Agouti* gene expression through increasing the methylation levels of a retrotransposable element in the promoter of the *Agouti* gene. The genistein-induced hypermethylation and decreased *Agouti* expression persisted into adulthood and protected offspring from obesity. This animal study provided the evidence that parental environmental exposures can benefit the offspring to achieve

positive metabolic set points by permanent epigenome adaptation [74].

Studies on asthma provide additional evidence to the benefits of early environmentally induced epigenetic adaptation for health condition later in life. Early life microbial exposure instructs the body to mount a well-adapted immune response to allergens via inducing epigenetic adaptation [75]. Munthe-Kaas and colleagues found that children with pets at home had lower DNA methylation of *CD14* at age 2 and this association persisted until age 10 [76], suggesting an enhanced *CD14* expression induced by the animal living environment (more microbial exposure) [77]. As the co-receptor of Toll-like receptors (TLRs), CD14 activates TLRs-mediated innate immune responses [78] which serves as a greatly important first defensive line against invading pathogens [79]. The children raised in such early life environments are at decreased risk of developing allergies [80–82], under which the mechanism may be the higher expression of CD14 deviating immune responses away from the allergen-reactive type 2 helper T cells [83], resulting in an attenuated sensitivity to allergens later in life [77]. Therefore, in the early stage, the changed methylation of CD14 in response to microbial exposure is a stable epigenetic adaptation of the immune system, which in turn exerts beneficial effects of reducing the vulnerability of children to asthma later in life.

Epigenetic Adaptation: Negative Effects

Epigenetic adaptations are not always to the benefit of the organisms' development. Especially during pregnancy, the fetus must adapt to its environment in order to optimize growth and to minimize the potential adverse effects of perturbations. Although such adaptation to fluctuations could attenuate immediate impacts of environmental perturbations on the fetus and benefit in utero and early life survival, these adaptive alterations can also be potentially deleterious to the long-term health of an individual depending on the particular environment experienced later in life.

A convincing example is social environment-induced neurobehavioral disorders governed by epigenetic mechanisms via hypothalamic pituitary adrenal (HPA) axis programming. The epigenetic programming of the HPA axis reflects the need to coordinate fetal development in preparation for responsiveness to stressors as determined by the upregulated regulatory set point of negative feedback of the HPA axis. However, this inhibition of negative feedback of the HPA axis impairs the offspring's interaction with stimuli later. The HPA axis is one of the most well-studied hormonal signaling pathway in responding to stress, through its regulation of the production of the stress hormone cortisol [84]. Various genes are involved in the regulation pathway, such as *NR3C1* (Nuclear Receptor Subfamily 3 Group C Member 1, encoding a glucocorticoid receptor protein) and *FKBP5* (FK506 binding protein 51, encoding a protein binding to glucocorticoid receptor) [84]. Nagarajan has systematically reviewed and shown that adverse maternal mental health (i.e., prenatal depression, anxiety, stress) is consistently associated with increased neonatal promoter methylation of *NR3C1* [85], suggesting a decreased glucocorticoid receptor expression and an inhibition of negative feedback of the HPA axis followed by enhanced cortisol reactivity [86]. FKBP5 is a glucocorticoid receptor (GR) regulator inhibiting GR-mediated negative feedback of the HPA axis by competing with cortisol to bind to GR [87]. Studies observed the demethylation of a key regulatory locus in *FKBP5* in saliva DNA of children exposed to maltreatment within 6 months [88]; moreover, the interaction of maltreatment and contextual stress could lead to persistent demethylation of *FKBP5* even 1 year after the stimuli [89]. Demethylation of *FKBP5* results in increased gene expression and decreased GR signaling as reported in children exposed to maltreatment [90], suggesting increased cortisol reactivity but reduced GR sensitivity and negative feedback of HPA axis. Cortisol is essential for fetal development and prepares infants for stress response, which is typically portrayed as the "fight-or-flight" process, mobilizing energy rapidly in order to cope with threatening stimuli to survival [91]. Cortisol increases the availability of energy from endogenous stores by mobilization of glucose [92], fat [93], protein [94], and inhibiting insulin secretion [95]; this hormone also regulates the supply of energy to critical systems, such as the central nervous system [84]. In light of this, increased promoter methylation of *NR3C1* that occurs in response to prenatal or early life stress could increase the HPA axis responsivity and cortisol level, providing, at least initially, an offspring survival advantage to cope with a stressful living environment. However, this overactivation, which does not allow the HPA axis to fully return to normal, can lead to a state of an exhausted HPA axis [96, 97]. Such exhausting may manifest itself in terms of persistent hypermethylation of *NR3C1* but decreased cortisol concentration in the long term, which results in a restriction of stress adaptation responses and increases the vulnerability to chronic complex disorders, in both the mental and physical realms, later in life [98]. This interpretation is supported by a cross-sectional study which showed that hypermethylation of *NR3C1* was associated with a flattened cortisol recovery slope (a delayed recovery time) in adolescents [99]. A recent study demonstrated that the increased methylation of *NR3C1* and cortisol concentration in the depressed adult patients was related to childhood emotional abuse severity, further suggesting early stress-induced higher basal HPA axis activity and limited stress-response capacity results in emotion dysregulation [100]. Similar associations were observed by Peng [101].

Animal models examining various aspects of stress and trauma and epigenetic effects on the HPA axis are abundant and provide compelling mechanistic evidence for an impact of psychosocial factors on health through epigenetic alterations.

For example, a rat model study demonstrated that chronic stress led to increased DNA methylation at the *Nr3c1* promoter which in turn induced increases in visceral pain [102]. Another rat study also revealed that the increased hippocampal *Nr3c1* methylation levels causally mediated the effect of preconception paternal stress on the anxiety-related behaviors in offspring [103]. In a highly cited study, Weaver and colleagues demonstrated, also, that positive environments, modeled as rat maternal licking and grooming behaviors, can also impact long-term HPA axis programming and stress responses through alteration of hippocampal *Nr3c1* promoter methylation [104]. These models open up opportunities for translation of these research findings into human clinical and epidemiologic analyses.

Fortunately, due to the epigenetic plasticity, the programmed epigenetic patterns in response to perturbation early in life, to some extent, can be modified to adapt to the emergence of new environmental stimuli later. This allows for strategies that switch the undesirable epigenetic changes towards the optimal condition. As mentioned above, maltreatment exposure within 6 months led to demethylation of *FKBP5* and hypermethylation of *NR3C1* of children [88]. A further study found that social service utilization may improve the methylation levels of *FKBP5* over time, even after adjusting for maltreatment and contextual stress, which implied a positive effect of service utilization on HPA axis epigenetic programming [89]. However, the epigenetic effect of service utilization was not measured in the children with maltreatment; thus, more studies are needed to conclude that service utilization or other interventions can induce reversal of maltreatment-related epigenetic effects. Child maltreatment is associated with higher initial levels of *NR3C1* promoter methylation within 6 months of documented maltreatment but lower methylation of *NR3C1* 1 year after the maltreatment exposure [105]. This dynamic stress-related DNA methylation changes of *NR3C1* reflect the organisms' early acute response resulting in neurobehavioral dysregulation and later adaptive changes for maintaining high levels of readiness for chronically repeated stressful or unstable conditions [105, 106]. Overall, these studies demonstrate the potential reversibility of epigenetic processes, although further work is needed to better characterize and demonstrate such phenomenon.

Challenges and Outlook

The DNA methylation changes induced by environmental factors and discussed above are just a small part of the accumulating evidence of the exposure-related epigenetic changes reflecting developmental epigenetic plasticity. For most of the identified epigenetic markers in response to exposures, we currently face a number of challenges to interpret their functional meaning in the context of epigenetic plasticity.

First, an important concern is that in human epidemiologic studies, most epigenetic markers were measured in accessible tissues, such as blood or saliva, and these are not always the disease- or function-relevant target tissues. Since the epigenetic markers are highly tissue specific, we must use caution when we interpret the association between environmental exposures and epigenetic modifications in one accessible tissue to the other more disease-relevant target tissues, especially in the interpretation of epigenetic toxicity, even though the studies suggest some accessible tissues have the potential ability to capture the pathological process in the targeted tissue [107, 108], or in the case of blood, may represent immune system perturbation.

Second, for many of the identified epigenetic changes induced by a particular environmental exposure, we have very limited knowledge about their role in developmental adaptation, mostly because of a dearth of prospective studies linking environmental exposures, epigenetic changes, and health events. For example, Green et al. identified demethylation of *LYRM2* in the placenta and increased expression induced by increasing prenatal arsenic exposure. However, the *LYRM2* currently lacks a known function in the placenta and there was no demonstrated link between *LYRM2* methylation variation and developmental outcomes of the placenta or fetus [29]. Hence, it is hard to postulate if the *LYRM2* methylation change is epigenetic toxicity, adaptation, or just a neutral biomarker of arsenic. This is the case with another arsenic-related study [109], and with a large body of research on the effect of the environment on epigenetic variation.

Sometimes, we may understand that the epigenetic change is an adaptive process, but we may not know if it is positive or negative in long term. A recent crossover randomized study detected, in healthy subjects, an acute particulate matter (PM)-induced reduction of vagal modulation coupled with a down-regulation of the pro-inflammatory pathway characterized by hypermethylation at the promoter region of *IFN-γ* gene [110]. The research implied that the unexpected decreased inflammatory response is a phenomenon under a homeostatic control counteracting the changes in neural reflexes (vagal deregulation) [110, 111]; in other words, the finding reflects an epigenetic resilience in adapting to the unstable homeostasis resulting from PM exposure. However, we know little about the persistence of the PM-induced methylation change and its long-term effects.

Third, the dynamic nature of the epigenome will require an emphasis on future longitudinal studies in which the epigenome is profiled over time. However, due to lack of time-series bio-samples and efficient computational approaches for epigenome-wide studies, only a few studies model the trajectory of the dynamic epigenetic changes in response to exposures in human epidemiology studies. Birth and children's cohorts provide the opportunity to obtain the bio-samples [112, 113], and longitudinal analysis strategies for modeling epigenetic trajectory have been developed recently [114].

Fourth, most recent epidemiologic studies of DNA methylation lack the power to conclude causal effects, but some cohort studies have explored and proved the causal role of DNA methylation in the relationship between environmental exposures and developmental outcomes using epidemiologic methods. A study from the Avon Longitudinal Study of Parents and Children (ALSPAC) supports cord blood DNA methylation as a consequence of maternal vitamin B12 levels having a causal effect on children's cognition development [115]. Kupers and colleagues identify that the cord blood DNA methylation of *GFI1* causally mediates the effect of maternal smoking on birthweight [116]. Animal studies can also provide additional and complimentary lines of evidence to epidemiologic studies for the causal effects of DNA methylation, and there is a growing literature examining epigenetic mechanism as causal pathways in various animal model systems.

Finally, one of the limitations of current epigenetic epidemiology has been the focus on single exposures, denoting a need to begin to consider an exposomic approach. As the analytical tools emerge to characterize the full exposome, studies on the combined burden of multiple exposures on the epigenome can be undertaken. An early example has been a study of the independent effect of maternal lead on *LINE-1* DNA methylation changes of children, wherein, Goodrich and colleagues considered and controlled for the influence of maternal bisphenol A and nine phthalate metabolites that were represented by four components created by principal component analysis [19], although the potential synergistic effects were not examined. Another recent study has demonstrated that among 16 measured chemicals, CB-105 was identified as the most "epigenetically active" pollutant for female newborns [117]. One of our prior studies has investigated a positive association of co-action between prenatal metal exposure assessed by a cumulative risk score (higher scores represent greater cumulative metal exposure risk) with placental *NR3C1* methylation [24], which suggested multiple metal exposures jointly exert accumulated epigenetic impacts. Demethylation of *AHRR* in the cord blood of children with prenatal smoking exposure is broadly reported. One recent study further discovered the interactive effect of maternal smoking and high folate level, suggesting that adequate maternal folate levels attenuate the impact of smoking on the hypomethylation of *AHRR* [118••]. As these studies mature and elaborate on these co-exposure effects, we may be able to better classify and understand the epigenetic plasticity to the complexity and mixture of exposures.

Conclusion

In this review, we discuss three classes of environmentally induced epigenetic changes reflecting two aspects of epigenetic plasticity, including those resulting in toxic as compared to adaptive processes. There remain challenges to fully defining and interpreting the reported environmentally associated epigenetic variants, but keeping in mind that these processes may represent both pathology and resiliency will be critical as data grows and future work considers these effects more broadly.

Acknowledgments This work was supported by the National Institutes of Health (NIH-NIEHS R01ES022223, P01 ES022832, R21 ES028226, R24 ES028507) and by the U.S. Environmental Protection Agency (EPA) (U.S. EPA grant RD83544201). Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the U.S. EPA. Further, the U.S. EPA does not endorse the purchase of any commercial products or services mentioned in the presentation.

Compliance with Ethical Standards

Conflict of Interest Fu-Ying Tian reports grants from the National Institutes of Health, grants from U.S. Environmental Protection Agency, during the conduct of the study. Carmen Marsit reports grants from the National Institutes of Health, grants from US. Environmental Protection Agency, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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