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Review

Epigenetics and the exposome: DNA methylation as a proxy for health impacts of prenatal environmental exposures

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Abstract

The accumulation of everyday exposures can impact health across the life course, but our understanding of such exposures is impeded by our ability to delineate the relationship between an individual's early-life exposome and later life health effects. Measuring the exposome is challenging. Exposure assessed at a given time point captures a snapshot of the exposome but does not represent the full spectrum of exposures across the life course. In addition, the assessment of early-life exposures and their effects is often further challenged by lack of relevant samples and the time gap between exposures and related health outcomes later in life. Epigenetics, specifically DNA methylation, has the potential to overcome these barriers as environmental epigenetic perturbances can be retained through time. In this review, we describe how DNA methylation can be framed in the world of the exposome. We offer three compelling examples of common environmental exposures, including cigarette smoke, the endocrine active compound bisphenol A, and the metal lead, to illustrate the application of DNA methylation as a proxy to measure the exposome. We discuss areas for future explorations and the current limitations of this approach. Epigenetic profiling is a promising and rapidly developing tool and field of study offering us a unique and powerful way to assess the early-life exposome and its effects across different life stages.

Keywords: developmental origins of disease (DOHaD); DNA methylation; environmental epigenetics; exposome; toxicoepigenetics

The epigenome as a proxy for the exposome

Environmental factors, including chemical exposures, diet, social stressors, the built environment, and lifestyle choices, contribute to risk of disease across the life course; these factors collectively make up the exposome [1]. The exposome interacts at multiple biological levels, including on the genome and epigenome, to impact health outcomes. Clinical and population approaches to health and disease research traditionally evaluate genetic contributions while, historically, the environment and epigenetics have received less attention. The epigenome controls cellular processes, such as mitotically heritable gene expression, independent of the DNA sequence itself [2]. Most importantly, the epigenome is modified by environmental factors. Unlike other substrates that undergo rapid and transient perturbations, the epigenome can both maintain and retain environment-induced changes. Thus, the epigenome can reflect an individual's lifetime exposures, providing value to understanding and interpreting the exposome.

The field of exposomics is a part of the emerging discipline of Precision Environmental Health, which seeks to (1) increase our understanding of exposures over the life course and their impact on individual health, (2) determine factors for individualized response, and (3) provide individualized interventions to improve health and prevent disease (Baccarelli, Dolinoy, Walker in revision *Nature Communications*). But achieving these precision environmental health goals requires new approaches to evaluate the effects of the exposome on health. One focus has honed in on epigenomics in the prenatal period, as environmental exposures during this time can alter epigenetic programming and the trajectory of offspring health [3]. Our ability to measure or approximate environmental exposures during gestation and early life is often hindered by the collection and availability of appropriate biospecimens. Thus, when assessing the early-life exposome is not feasible, the evaluation of the epigenome (e.g. DNA methylation) as a proxy for the exposome may provide useful information for achieving precision environmental health.

The intersection of the epigenome and exposome

The Developmental Origins of Health and Disease paradigm states that environmental exposures during critical periods of life (e.g. preconception, gestation, infancy, adolescence) impact the onset of disease later in life [3]. Research over the last three decades has provided epidemiological and animal model evidence supporting the link between prenatal environmental exposures and increased

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risk of disease into adulthood. In humans, undernutrition during gestation has been associated with adverse birth outcomes and increased rates of cardiovascular disease and non-insulin-dependent diabetes later in life [4]. The effects of undernutrition and metabolic dysfunction are echoed in rodent models [5].

Developmental toxicant exposures also have an impact on offspring health. Human populations exposed to high levels of arsenic-contaminated water during fetal development have increased rates of adult-onset lung cancer and bronchiectasis [6]. Similarly, prenatally arsenic-exposed mice had several soft tissue cancers as adults, including lung, kidney, and liver cancer [7]. The epigenome is one mechanism underlying the relationship between developmental exposures and the onset of late-life diseases.

The epigenome can regulate gene expression via several encompassing mechanisms, including modifications to amino acids on histones [8], the methylation of DNA [9], and the interaction of non-coding RNA with DNA [10]. Here, we focus on DNA methylation and its interactions with early-life exposure as it is the most extensively studied and stable epigenetic mechanism.

DNA methylation typically involves the addition of a methyl group to the fifth carbon of cytosine within a cytosine–guanine dinucleotide, referred to as a CpG site. DNA methylation can be modified with oxidizing enzymes to hydroxymethylation, a stable intermediate [11]. Regulation of gene expression by DNA methylation and hydroxymethylation is dependent on the location within the genome. In general, the presence of DNA methylation at promoters is associated with gene repression, whereas the lack of DNA methylation in intragenic regions is correlated with transcription [12, 13]. The oxidization of methylation to hydroxymethylation primarily has a reverse effect; hydroxymethylation is associated with increased transcription when compared to methylation [14]. However, there is evidence that this canonical relationship is dependent on where in the genome these DNA modifications exist [15].

DNA methylation is an attractive proxy for the exposome due to its ease of interpretation, the ability to efficiently detect and profile DNA methylation patterns, and its responsiveness to exposures. DNA methylation is detectable in readily available tissues such as blood and saliva; responds to environmental exposures that accumulate over the lifetime starting during embryonic development; and provides insight into dysregulated genic regions associated with the disease. The extent of DNA modifications at a given gene can be influenced by environmental exposures. Previous work has identified epigenetic reprogramming, waves of demethylation, and *de novo* methylation within the developing embryo and primordial germ cells during gestation, as sensitive to environmental exposures [16]. Thus, the epigenome accumulates damage beginning in the gamete's preconception, continuing through fertilization, prenatal development, and longitudinally throughout the lifetime of an individual (Figure 1). In mammals, epigenome-wide reprogramming occurs shortly after fertilization—within the first 3 weeks of human gestation and the first 4 days of rodent gestation. While multiple periods of life (e.g. infancy, adolescence) are sensitive to environmentally induced epigenetic perturbation, the epigenome is particularly sensitive during developmental reprogramming [17].

The exposome represents the totality of exposures received by an individual throughout a life course and can alter the trajectory of health and disease [1]. The assessment of exposures, especially perinatal exposures, however, is challenging due to the lack of comprehensive longitudinal studies assessing long-term health [18]. Historically, only a few studies have had the resources to collect samples preserved for exposure assessment (i.e. urine, plasma, whole blood stored in contaminant-free containers) during pregnancy. Similarly, especially in human populations, it is costly and time dependent to follow the health trajectories of individuals for decades into adulthood when diseases may manifest.

The epigenome can provide a historical footprint of exposures starting as soon as early gestation, when epigenetic reprogramming occurs, long before a detectable disease phenotype. In addition, unlike the transient collection of RNA (e.g. transcriptome) or metabolites (e.g. metabolome), DNA methylation is stable over time and assayable in biobank specimens (e.g. neonatal blood spots, cord blood, tissues). For example, the Healthy Families Project used state government-archived neonatal blood spot samples to demonstrate associations between lead (Pb) exposure and increased variability in DNA methylation at multiple loci [19]. In the same study, neonatal DNA methylation of long interspersed nuclear elements (LINEs) and *IGF2* were associated with the likelihood to develop obesity during childhood [20]. Even when neonatal samples are not available, there is evidence that the epigenome in childhood or adulthood can reflect past exposures. Perhaps, the most striking example comes from a study focused on the impact of the Dutch Hunger Winter Famine. Individuals whose early gestation occurred during this period had altered DNA methylation at *IGF2* detectable in blood samples collected at >60 years of age. These and other studies described later in this review demonstrate the potential for the epigenome to serve as a marker of both past exposures and future health effects [21].

Methods for DNA methylation detection

We briefly discuss common methods used for DNA methylation assessment in epidemiological studies and their potential to be used in exposome biomarker development. The gold standard for all methods begins with bisulfite-converted DNA. This process allows the end user to differentiate unmodified cytosines from modified cytosines via the deamination of unmodified cytosine to uracil. Importantly, bisulfite conversion is used in the vast majority of human studies, but this method does not differentiate between DNA methylation and DNA hydroxymethylation. Some environmental epidemiology studies have used additional methods to differentiate these marks [22-24], but the literature on this topic is still limited.

Common methods to assay DNA methylation can be categorized into three major approaches: (a) global methylation levels; (b) targeted or candidate gene sequencing; and (c) genome-wide DNA methylation screening. First, global approximations of total genomic DNA methylation are utilized as a biosensor of broad changes from environmental exposures. Quantifying CpG DNA methylation of repetitive elements as a proxy for global methylation is common in human studies, especially of LINEs (which comprise >20% of the human genome) and *Alu* repeats (11%–14% of the human genome) [25-27]. Mass spectrometry-based methods [28, 29] and enzyme-linked immunosorbent assays can also be used to quantify total methylcytosine or other DNA methylation modifications such as hydroxymethylcytosine. While associations between numerous environmental exposures and altered global methylation have been reported in human studies using these methods, the utility of global methylation to serve as a reliable biomarker of past exposure is limited. Global methylation status likely reflects the impact of multiple exposures and would not be specific enough to represent a single exposure. However, the use of global methylation status to represent cumulative harm from multiple exposures could be considered.

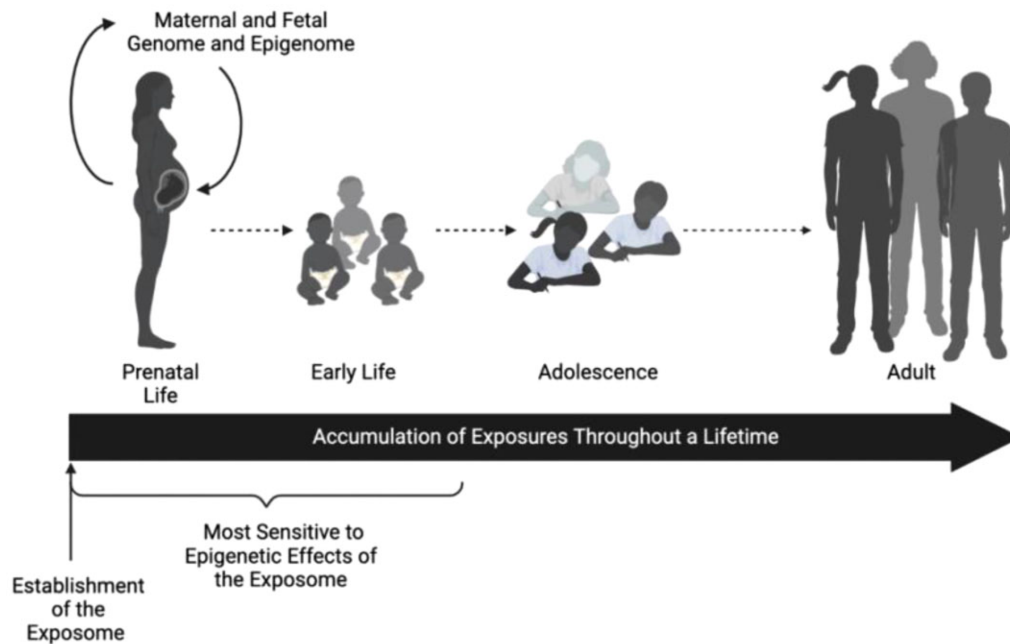

Figure 1. Continuing throughout gestation and early postnatal life, the epigenome remains sensitive to environmental insults as epigenetic patterns are established and maintained in rapidly developing tissues. These environmental perturbations to epigenetic programming and maintenance can be stable and serve as biomarkers of past exposures or predictors of future disease later in the life course. Exposures in childhood, adolescence, and beyond may impart additional epigenetic alterations. *Created using Biorender.com*.

Second, targeted/candidate gene approaches are advantageous when certain genes/loci are known to be responsive to exposures or important for health outcomes of interest. Accurate quantitative methods include pyrosequencing [30] and the mass spectrometry-based EpiTYPER assay [31], which can interrogate short (∼100 or ∼600 bp, respectively) regions of DNA. Recent advancements in the field include targeted bisulfite sequencing, which utilize next-generation sequencing (NGS) after the amplification of genes of interest to provide coverage of longer segments of genes simultaneously [32-34]. When specific genes/loci have been identified that are strongly associated with a given exposure, targeted approaches can be utilized to cost-effectively screen DNA methylation status at those loci and assess whether this association replicates in other populations. DNA methylation at the loci can also be screened in a high-throughput manner and used to predict past exposure status in individuals without exposure history [35, 36].

Finally, discovery-based genome-wide approaches using DNA methylome-wide screening are commonly used in epidemiological studies. The most widespread tools are probe-based arrays from the Illumina Infinium series. The most recent version, the EPIC array, quantifies DNA methylation at more than 850 000 CpG sites throughout the genome [37]. Meta-analyses across birth cohorts with Infinium array data are accelerating our understanding of the gestational exposures that modify the newborn and child methylome [38, 39]. Whole-genome bisulfite sequencing [40], reduced representation bisulfite sequencing [41], and enhanced reduced representation [42] bisulfite sequencing are NGS methods that provide broader to complete coverage of all possible CpG sites compared to the arrays. The cost of these NGS methods and the complexity of the data, however, have hindered their widespread use in large epidemiological studies to date. Widely used arrays such as the Infinium series have great potential to identify epigenetic biomarkers of exposure by screening a large number of loci in one experiment. Importantly, since the array always captures the same loci, it is possible to validate and replicate potential biomarkers of exposure across other cohorts collecting data with the same platform, an essential step to develop a robust epigenetic biomarker of past exposure.

Examples of early assessment of perinatal exposure and DNA methylation

Early-life epigenetic signatures, which can persist across the life course, hold promise for acting as a recorder of an individual's exposures, even when those exposures occurred far in the past or across extended periods of time. In this section, we provide examples of three illustrative individual exposures—cigarette smoke, the endocrine active compound bisphenol A (BPA), and the metal lead (Pb)—as an approach that could be extended to the exposome as a whole and as evidence for biomarkers of past exposure.

Nicotine/smoking

Maternal tobacco use has been linked to several health risks including low birth weight, preterm birth, increased risk of stillbirth, sudden infant death syndrome, maternal cardiovascular disease, maternal chronic obstructive pulmonary disease, and maternal lung cancer [43]. Recent studies reveal that 7.2% of the birthing people in the USA smoke cigarettes, with the highest prevalence among individuals aged 20–24 years (10.7%) [44]. Additionally, prenatal nicotine exposure has been associated with effects later in life, including poor lung function, persistent wheezing, and asthma in childhood, as well as metabolic syndrome later in life [45, 46].

Studies investigating the role of prenatal nicotine/smoking exposure on epigenetics, pregnancy outcomes, and fetal origins of health and disease are becoming more common and have successfully identified genes, loci, and pathways of interest. One study assessing fetal lung and concordant placental tissue in

nicotine-exposed mother–infant pairs found differences in DNA methylation in genes linked to asthma and immune disorders [46]. Additionally, Suter *et al.* [47] observed that maternal tobacco use was associated with aberrant placental epigenome-wide DNA methylation and gene expression.

Other studies have focused on hematologic samples for analysis. A meta-analysis from the Pregnancy and Childhood Environmental (PACE) Consortium provided the most promising evidence for an epigenetic biomarker of exposure. This analysis focused on maternal smoking, with 25% of the newborns experiencing exposure during at least part of the gestational period. Using data from 13 cohorts and 6685 newborns, associations between smoking exposure and cord blood DNA methylation were strongest in infants exposed persistently to prenatal smoking [38]. From this study, several loci exhibited associations between smoking and DNA methylation that persisted into later childhood. CpG sites within the *AHRR gene* were the most statistically significant sites associated with prenatal smoking in newborns. Importantly, several studies have found CpG methylation within *AHRR* in blood as a valid biomarker of smoking [48-50], and methylation at these same CpG sites in *AHRR* has been replicated in other studies of prenatal smoking exposure. A dose-dependent relationship between maternal smoking and offspring methylation was also observed using pathway interrogation that revealed differentially methylated genes were enriched in gene sets involved in cancer development, obesity, developmental processes, detoxification, cell signaling, and nicotine dependence [48]. Collectively, these studies support a role of prenatal cigarette smoke exposure by altering epigenome programming in a global and site-specific way. The altered methylation status of these genes could be developed as a biomarker of exposure in the absence of available smoking status information. In adults, a machine-learning algorithm called 'EpiSmokEr' has been developed that uses Infinium array data at more than 100 CpG sites to predict whether an individual never smoked, formerly smoked, or currently smokes regularly [35]. Attempts to develop methylation scores (also based on DNA methylation status at multiple loci) that predict exposure to smoking during gestation have also been successful, with some models predicting prenatal exposure decades later [49, 51].

Bisphenol A

BPA is a widespread chemical and endocrine disruptor that is ubiquitous in the environment. Given the high degree of BPA exposure in the general population and evidence of penetrance into human tissues [52], it is important to understand how prenatal BPA exposure impacts childhood outcomes. A 2020 meta-analysis that included over 3500 pregnancies revealed an increased risk of preterm birth associated with prenatal BPA exposure, especially at higher urinary concentrations (>2.16 ng/mL) [53]. Studies reporting the influence of early-life BPA exposure on metabolic outcomes are increasing [54]. A recent longitudinal study investigating prenatal BPA exposure and the development of obesity found increased prenatal urinary BPA concentrations associated with increased fat mass index, percent body fat, and waist circumference in children at the age of 7 years [55].

Compelling evidence using the viable yellow agouti mouse model demonstrated prenatal BPA exposure changes offspring phenotype by altering the epigenome [56]. Recent human studies also show maternal exposure to BPA affects childhood phenotypic measurements via altered epigenomic programming. A study evaluating third trimester maternal urinary BPA levels and DNA methylation in blood leukocytes of children aged 8–14 years ($n = 278$) evaluated LINEs and environmentally responsive genes (*IGF2*, *H19*, and *HSD11B2*) [57]. Children belonging to the second and highest tertiles of maternal urinary BPA had 1.26% and 1.81% higher methylation of the imprinted gene *IGF2* when compared to children of the lowest tertile. *IGF2* methylation, known to be important in early development, may also impact child and adolescent metabolic health. For example, differential methylation of the imprinted control region of *IGF2* is associated with increased adiposity and greater skin fold thickness in young adults [58]. Interestingly, other studies have associated prenatal BPA exposure with *IGF2* methylation. In a longitudinal study examining urinary BPA during the second trimester of pregnancy (1.34 ± 0.60 to 7.92 ± 4.97 μg/g), body mass index (BMI) was measured at 2, 4, 6, and 8 years of age, and DNA methylation was assessed within whole blood of children ($n = 59$) using the EPIC array [59]. Out of the 594 CpG sites known to be associated with BMI or obesity, *IGF2R*, the maternally expressed allele compared to the paternally expressed allele *IGF2* was hypomethylated in children at 2 years of age but not at 6 years of age. The association between increased BMI and *IGF2R* methylation was only identified in females at ages 2–8 years, not in males. Another study identified *IGF2* and *PPARA* hypomethylation by pyrosequencing in cord blood leukocytes ($n = 116$) [60]. Urinary maternal BPA (0.04–4.76 ng/mL) in the first trimester was associated with a 1.35% decrease in *IGF2* methylation and a 1.22% decrease in *PPARA* methylation in offspring ($n = 56$) compared to unexposed individuals. Interestingly, *PPARA* expression is related to the adipogenesis pathway and is associated with fatty liver disease and lipid metabolism disorder [61]. Collectively, data from these studies provide a foundation to explore if imprinted gene methylation may serve as a potential biomarker of exposure. However, as discussed below, imprinted genes may be modified by multiple exposures, and they may not serve as a marker of specific exposures in humans exposed to various chemicals early in life. Thus, more research is needed to determine how imprinted genes can best serve the field of exposomics and to understand phenotypic outcomes that are impacted by modifications to these genes.

Lead

Lead (Pb) exposure remains a global public health concern even though it is one of the most intensely monitored chemicals [62]. Pb is a legacy chemical, but environmental exposures persist regardless of the diminishing use of Pb-based gasoline, pipes, paint, and Pb–acid battery production and recycling [63]. Of concern, pregnant women and children are considered the most vulnerable to the toxic effects of Pb exposure due to the rapid periods of fetal growth [64]. Neurotoxicity from Pb is well characterized and can be detected in early infancy. For example, infants exposed to Pb during gestation had significant delays in auditory and visual maturity compared to children of low or no exposure [65]. A recent study found that blood lead level (BLL) of >10 μg/dL caused significant decreases in IQ, where an increase in BLL concentration is parallel to a decrease in IQ [66]. In a longitudinal study focusing on brain integrity in adults, high BLLs measured during childhood were associated with differences in MRI measurements of brain structure in adults at 45 years of age [67]. Findings from this study found lower cognitive performance and changes in structural brain integrity, suggesting an increased risk of neurodegenerative diseases later in life. Outside of neurocognitive outcomes, early-life Pb exposure is also associated with altered growth and adiposity [68-70], cardiometabolic risks [71, 72], among other outcomes.

Several human [73-75] and rodent [76-79] studies show evidence for the impact of Pb on the epigenome as a biomarker of exposure. Mirroring phenotypic evidence of prenatal Pb exposure, most differentially methylated CpG sites by Pb have been identified in genes associated with neuronal development, cognitive delays, and dysregulated metabolism later in life. A recent study identified 18 CpG sites using the EPIC array with cord blood of children associated with Pb concentrations during pregnancy ($n = 364$, cord blood 3.00–26.12 μg/dL) [80]. Detected CpG sites included loci within *PHACTR2* and *GPR155*, genes associated with brain development and autism spectrum disorder, respectively. Another study identified correlations between trimester-specific maternal BLL and cord blood DNA methylation using the EPIC array [81]. While the main findings from this study included the identification of several hypomethylated genes associated with neuronal function (*RAB5A* [82], *EXT1* [83], *TRHR* [84]), this study provides evidence that trimester-specific exposure has an effect on DNA methylation in infant cord blood. Interestingly, other studies have detected associations between BLL in infants and DNA methylation by assessment of dried neonatal bloodspots using Infinium arrays [85, 86]. A key longitudinal study using neonatal dried bloodspots for DNA methylation and Pb concentration identified 33 differentially methylated CpG sites by the EPIC array ($n = 96$, average exposure 0.78 μg/dL) [19]. This study identified loci that were enriched within developmental and neurological function biological pathways, using only an estimated 3.1 μL of blood for both DNA methylation and Pb assessment. This study is foundational due to the breadth of coverage from the EPIC array analysis, the cunning application of a time-stamped resource, and the minimal amount of blood used for detection. If associations between prenatal Pb and DNA methylation observed here can be replicated across studies, there is potential to develop a reliable biomarker of past exposure. As with smoking, a multi-loci biomarker would likely have better predictive power. Using Infinium array data, a methylation score based on 59 and 138 CpG sites has been developed which discriminates between high and low Pb exposure according to the patella or tibia bone Pb levels (biomarker of long-term exposure), respectively, among adults with fairly high sensitivity and specificity (>70%) [36].

Challenges and opportunities for use of the epigenome as a proxy for the exposome

While DNA methylation is more stable compared to other molecular markers of exposure, it is important to address caveats of the application of DNA methylation as a proxy for the exposome. First, despite their establishment during development and maintenance through cellular replication, DNA methylation levels demonstrate clear changes with age. Predictable, unidirectional changes in DNA methylation that occur with age are referred to as "age-related methylation." [87]. Separate from these predictable changes, there are also stochastic, bidirectional alterations in epigenetic variability that occur with age; these are referred to as "epigenetic drift." [88, 89]. Combined, these two processes represent "epigenetic aging," a phenotype of age-associated changes in the epigenome. Epigenetic age can be accelerated by environmental exposures or molecular cues associated with cell senescence [90, 91], a process we defined as "environmental deflection" [92]. Thus, delineating between DNA methylation shifts caused by exposure or epigenetic aging raises a cause of concern as a proxy for the exposome. In addition, some differentially methylated loci recover over time where age influences the recovery rate. In particular, *AHRR* methylation in younger individuals (<55 years) who quit smoking had a faster methylation recovery rate compared to older previous smoking individuals (>65 years) [93].

Second, literature has reported that some genic regions are consistently responsive to multiple environmental exposures, which makes identifying a single responsible exposure for altered epigenetic change very difficult. For example, several human epidemiological studies have identified DNA methylation changes in the imprinted gene *IGF2* associated with air pollution, Pb, or BPA exposure [59, 94, 95]. Incidentally, epigenetic profiles at metastable epialleles and imprinted genes are set very early in development, are responsive to maternal environmental cues, and remain stable across tissues over time [96, 97], mitigating some of the stability and age-related concerns identified above; but, DNA methylation within these genomic regions is responsive to multiple stressors. For example, the metastable epiallele within the mouse viable yellow agouti locus is responsive to developmental nutritional status, alcohol, Pb, BPA, and radiation exposures [98-103]; thus, the locus lacks the characteristic of an exposure-specific biomarker. It is important to identify that certain regions of the genome are responsive to multiple developmental exposures, these regions may still serve as a proxy for developmental markers of exposure early in life [101, 104]. However, since the goal of exposomics is to evaluate the totality of exposures received by an individual throughout a life course, epigenetic age-independent epigenetic proxies are an opportunity for identifying cumulative exposures.

Conclusion: DNA methylation as an exposome biomarker

Here, we presented evidence that the early environment can influence epigenetic programming and the risk of later-in-life diseases, but the causal relationship of these associations and the effects of multiple exposures (e.g. the exposome) has yet to be fully elucidated. Despite these shortcomings, the epigenome still holds tremendous potential for advancing exposomics and precision environmental health. Epigenetics plays an essential role in metabolism and growth, brain development, plasticity, and health throughout life, and the exposome can positively and negatively elicit impact. As the exposome field progresses, there is now optimism for capitalizing on epigenetics as biomarkers of past exposure or even for disease prevention or treatment. The highly replicated and persistent DNA methylation biomarker of prenatal smoking exposure introduced above demonstrates the potential for these biomarkers to be developed [38].

To identify such biomarkers for other exposures or multiple exposures, pooling biospecimen resources and data across cohorts is needed to develop proxy epigenomic maps that are predictive of past exposures. Big consortia of birth cohorts and children's studies, such as the PACE Consortium [105] and the Environmental influences on Child Health Outcomes Program [106], are starting to combine data sets across cohorts to identify epigenetic associations with exposures. First, rigorous assessment of exposure-induced epigenetic regulation can serve as the link between exposome analysis and disease progression. One example, the National Institute of Environmental Health Sciences (NIEHS) TaRGET II Consortium, uses a multi-omics approach with human-relevant mouse models to explore whether epigenetic signatures induced by multiple developmental environmental factors occur in both surrogate (e.g. blood) and target tissues (e.g. brain or liver) [107]. Second, epigenome therapy and/or epigenetic editing technologies can be adapted for environmental

health applications as methods to test molecular mechanisms of toxicology and act as potential interventions. For example, histone methylation has been used to reduce schizophrenic-like symptoms in mice [108]. MicroRNAs may be good biomarkers for post-traumatic stress disorder [109], or contribute to resiliency and treatment response in models of depression [110]. In addition, piRNA is being developed as a locus-specific epigenome editor of DNA methylation [111]. As we advance our understanding of epigenetics as a link between the environment as a whole—the exposome—and disease development, we can use novel research to inform treatment as well as broader health policies [112]. While this field of exposomic epigenetics is in its infancy today, tomorrow it holds extreme promise and excitement, directing future science, practice, and policy.

Human and animal rights and informed consent

This article reviews previous literature and did not directly involve human or animal subjects.

Data availability

No new data were generated or analyzed in support of this research.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Author's contributions

Mathia L. Colwell (Conceptualization [equal], Writing—original draft [equal], Writing—review and editing [equal]), Courtney Townsel (Writing—original draft, Writing—review and editing), Rebekah Petroff (Writing—original draft, Writing—review and editing), Jaclyn Goodrich (Conceptualization [equal], Writing—original draft [equal], Writing—review and editing [equal]), and Dana Dolinoy (Conceptualization [equal], Writing—original draft [equal], Writing—review and editing [equal]). M.L.C., J.M.G., and D.C.D. provided direction and guidance through the preparation of the manuscript. All authors reviewed the literature, drafted, and revised the manuscript. All authors have read and approved the manuscript prior to submission.

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