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Toxicoepigenetics and Environmental Health: Challenges and Opportunities

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Abstract

The rapidly growing field of toxicoepigenetics seeks to understand how toxicant exposures interact with the epigenome to influence disease risk. Toxicoepigenetics is a promising field of environmental health research, as integrating epigenetics into the field of toxicology will enable a more thorough evaluation of toxicant-induced disease mechanisms as well as the elucidation of the role of the epigenome as a biomarker of exposure and disease and possible mediator of exposure effects. Likewise, toxicoepigenetics will enhance our knowledge of how environmental exposures, lifestyle factors, and diet interact to influence health. Ultimately, an understanding of how the environment impacts the epigenome to cause disease may inform risk assessment, permit noninvasive biomonitoring, and provide potential opportunities for therapeutic intervention.

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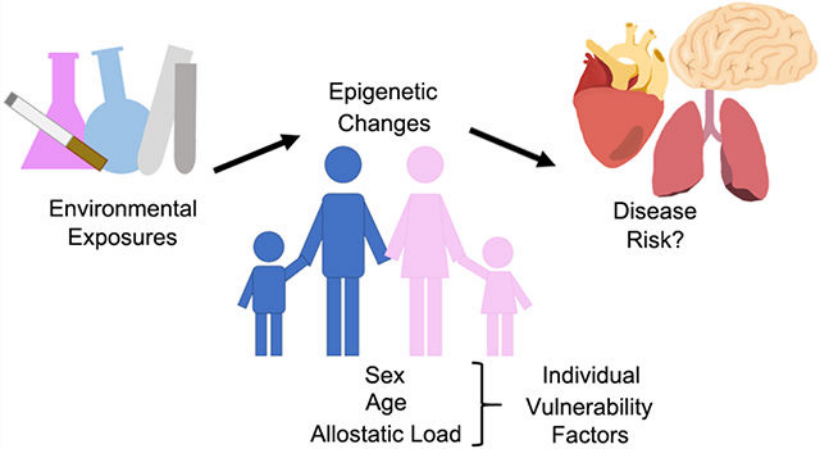
However, the translation of research from this exciting field into benefits for human and animal health presents several challenges and opportunities. Here, we describe four significant areas in which we see opportunity to transform the field and improve human health by reducing the disease burden caused by environmental exposures. These include (1) research into the mechanistic role for epigenetic change in environment-induced disease, (2) understanding key factors influencing vulnerability to the adverse effects of environmental exposures, (3) identifying appropriate biomarkers of environmental exposures and their associated diseases, and (4) determining whether the adverse effects of environment on the epigenome and human health are reversible through pharmacologic, dietary, or behavioral interventions. We then highlight several initiatives currently underway to address these challenges.

Graphical Abstract



BACKGROUND: TYPES OF EPIGENETIC INFORMATION

The term epigenetics broadly refers to heritable and potentially modifiable information stored in the nucleus of cells that controls cellular processes through mechanisms that are independent of the DNA sequence itself. The human genome comprises approximately 25,000 protein coding genes,[1] and epigenetic processes cooperate with transcription factors and regulatory elements to control the timing, location, and level of gene expression. This spatiotemporal control of gene expression governs normal development and tissue identity. Epigenetic information includes an assortment of covalent modifications to the histone proteins which form the molecular scaffold for the genome, as well as methylation/hydroxymethylation of cytosine bases on DNA.[2] In addition, noncoding RNAs also play critical roles in the regulation of the epigenome.[2,3] The epigenome can be modified by intrinsic cellular factors, such as metabolic pathways, as well as extrinsic factors such as diet, chemical exposures, and behaviors.[4–8] Whether the epigenome directly regulates gene expression, or vice versa, is often unclear, and newly developed genome and epigenome editing tools may yield more insight into this important question.[9–12] Nevertheless, it is clear that the epigenome plays a pivotal role in the pathogenesis of diseases. Extensive research on the epigenome has broadened our insight into the molecular basis of diseases such as cancer, cardiovascular diseases, diabetes, and neurodegenerative diseases.[13] Likewise, our

understanding of the effects of environmental exposures on the epigenome has expanded in recent years, and the field of toxicoepigenetics is rapidly gaining momentum.

While it is common to refer to this field as “epigenetic toxicology”, the term “toxicoepigenetics” has been used because the former connotes a narrow focus on epigenetic mechanisms underlying toxicity. Toxicoepigenetics is a more inclusive term to refer to the particular type(s) of epigenetic alterations at specific loci in the genome that might arise following environmental exposures, including chemical and nonchemical stressors and their possible interactions, and the role of the epigenome as a possible mediator of exposure effects (Figure 1).

DNA Methylation.

DNA methylation, or 5-methylcytosine, is the most extensively studied and well-characterized epigenetic modification. DNA methylation has multiple functions in the regulation of gene and transposable element (TE) expression.[14] DNA methylation in promoters is generally associated with repression of gene expression, while methylation in gene bodies is often associated with active gene transcription and may regulate tissue-specific gene expression.[14,15] More recent work has shown that, as in promoters, DNA methylation of the first intron is negatively associated with gene expression.[16] DNA methylation regulates gene expression through multiple mechanisms, such as blocking the binding of some transcription factors to DNA.[17] Likewise, methylated DNA can recruit methyl CpG binding proteins and, in turn, other factors involved in chromatin remodeling and gene silencing.[18,19] In addition, DNA methylation at insulator regions can regulate the interactions between enhancers and promoters by blocking binding of the transcription factor CTCF.[20]

DNA methylation is catalyzed by DNA methyltransferase enzymes (DNMTs), using *S*-adenosylmethionine (SAM) as the methyl donor.[21] Three catalytically active DNMTs have been identified, including the maintenance methyltransferase DNMT1 as well as two *de novo* methyltransferases, DNMT3A and DNMT3B.[22,23] DNMT3A/B function in large part to establish DNA methylation patterns during early development, while DNMT1 maintains the methylation of these sites across subsequent cellular divisions.[22,24] Although the canonical function of DNMT1 is maintenance DNA methylation, recent work highlights a role for DNMT1 in *de novo* DNA methylation in specific contexts, such as TEs.[25] Likewise, roles for DNMT3A/B in the maintenance of DNA methylation in somatic cells have also been identified.[26,27] DNA methylation functions in regulation of several important cellular processes, including X-chromosome inactivation, genomic imprinting, and silencing of TEs.[28–30]

DNA Hydroxymethylation.

Numerous recent studies have highlighted the critical role for DNA hydroxymethylation in the context of environmental exposures and disease.[31–34] DNA hydroxymethylation entails the oxidative conversion of 5-methylcytosine to 5-hydroxymethylcytosine by TET dioxygenases.[35,36] While 5-hydroxymethylcytosine is an intermediate in the process of active DNA demethylation, it is also now considered to be a stable epigenetic modification

and is associated with regulation of gene expression and alternative splicing.[37–39] TET dioxygenases convert 5-methylcytosine to 5-hydroxymethylcytosine using iron (Fe II), α-ketoglutarate, and vitamin C as cofactors,[36] and can also catalyze the further oxidation of 5-hydroxymethylcytosine to 5-formylcytosine and 5-carboxylcytosine.[40,41] Like 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxylcytosine are intermediates in the process of demethylation of DNA through both replication-dependent dilution as well as pathways involving DNA repair enzymes such as thymine DNA glycosylase.[41,42] Three TET dioxygenases, TET1, TET2, and TET3 have been identified and each show distinct expression patterns during normal development and in differentiated tissues.[35,43] TETs are most highly expressed in embryonic stem cells and during early development, where they function in active DNA demethylation during both waves of reprogramming. 5-Hydroxymethylcytosine is present to a notable degree in embryonic stem cells and the brain.[44–46] The specific role of 5-hydroxymethylcytosine in the brain is only beginning to be characterized, but there is evidence to suggest it plays a role in neurodevelopment[47] and aging,[46] and its aberrant expression is implicated in several neurological disorders.[48,49] Furthermore, 5-hydroxymethylcytosine is influenced by the environment, with exposures such as arsenic, lead, and pesticides associated with alterations in 5-hydroxymethylcytosine in the brain and blood.[8,34,50] Future studies will undoubtedly continue to clarify the role for 5-hydroxymethylcytosine in normal neurodevelopment, environmental health, and disease.

Programming of DNA Methylation and Hydroxymethylation During Development.

During early development, DNA methylation undergoes two distinct waves of reprogramming.[51,52] The first wave of reprogramming occurs immediately after fertilization, in which the parental DNA methylation marks are erased. In this wave, the paternal genome undergoes a rapid demethylation, while the maternal genome undergoes a more gradual demethylation during the first few cellular divisions.[53,54] Although TET3-mediated formation of 5-hydroxymethylcytosine was thought to be necessary for the rapid DNA demethylation of the paternal genome, recent work suggests that these processes are mechanistically uncoupled, challenging widely held assumptions about timing and mechanisms of post-fertilization 5-methylcytosine programming.[55] Parental genomic imprints are retained during this initial stage of programming.[56] Remethylation in the somatic cells then gradually occurs between implantation and birth.[52] The second wave of reprogramming occurs in the primordial germ cells of the developing embryo, as they migrate toward the genital ridge. At this stage, somatic DNA methylation marks are erased, along with parental genomic imprints.[57] Contrary to previous assumptions, however, global demethylation in the primordial germ cells does not require formation of 5-hydroxymethylcytosine.[58] Remethylation then occurs to establish the appropriate sex-specific patterns of methylation, with remethylation completed at birth in males and after birth in females.[59–61] Because of these extensive reprogramming events, and the relative stability of DNA methylation, early development is exquisitely sensitive to disruption by environmental perturbations, with potential long-term health implications.

Histone Modifications.

In the somatic cells of eukaryotic organisms, genomic DNA is wrapped around nucleosomes, which are composed of histone proteins. Covalent modifications to histone

protein tails represent another important form of epigenetic information. A wide array of histone modifications have been identified, including methylation, acetylation, phosphorylation, sumoylation, ubiquitination, and ADP ribosylation, among others.[62] The effects of these modifications on gene expression are often highly context-dependent, and there is significant cross-talk between the various modifications and with other epigenetic mechanisms such as DNA methylation.[63,64] Histone methylation, acetylation, and phosphorylation are among the most widely studied modifications. Histone methylation occurs on both lysines and arginines, and is associated with either gene activation or repression, depending on the location of the lysine or arginine.[62] For example, trimethylation of lysine 4 on histone H3 (H3K4me3) is associated with gene activation, while trimethylation of lysine 27 on histone H3 (H3K27me3) is linked to repression of gene expression.[62] Similarly, both activating (H3R17me2) and repressive (H4R3me2) arginine methylation marks have been identified.[65,66] Histone acetylation is generally linked to gene activation, as the addition of the acidic, negatively charged acetyl group repels the negatively charged phosphate backbone of DNA, resulting in a more open chromatin conformation.[62,67] Histone phosphorylation can occur on serine, threonine, or tyrosine residues and is associated with gene activation, DNA repair, and chromatin condensation during mitosis and meiosis.[68]

Like DNA methylation, histone modifications exhibit dynamic reprogramming during early prenatal and postnatal development,[69–71] and vulnerability to environment-induced disease has been linked to changes in histone modifications.[72–77] Several recent studies have demonstrated that histone modifications may be heritable and involved in the processes of genomic imprinting and transgenerational epigenetic inheritance.[70,78,79] Although most toxicoepigenetics studies have focused on DNA methylation, recent work has identified global changes in histone modifications as biomarkers of environmental exposures in human populations.[76,80–82]

Noncoding RNA.

Historically regarded as “junk”, non-coding RNA (ncRNA), RNA molecules that are not translated into protein, possess substantial regulatory capacity and are a significant contributor to transcriptional and post-transcriptional regulation of gene expression. While roughly three-quarters of our genome is estimated to be transcribed, less than 2% of that accounts for protein-coding genes.[83,84] ncRNA is commonly classified by size, with long and short ncRNA being longer or shorter than 200 nucleotides in length, respectively.[85] Depending on the type of RNA and often in concert with protein complexes, ncRNA regulates gene expression at the transcriptional as well as translational level, modulates splicing, and controls TE expression.[86–91] These functions are commonly involved in processes such as cellular growth and proliferation, differentiation, and heterochromatin formation.[92–96] The aberrant expression of some ncRNA has been associated with adverse health outcomes such as cardiovascular disease, neurological disorders, and many types of cancer.[97–104]

The various classes of ncRNA differ substantially in terms of their size, function, and the protein complexes they commonly interact with. Micro-RNA (miRNA), the most thoroughly

studied class of ncRNA, is 21–25 nucleotides in length and regulates gene expression post-transcriptionally. In concert with the RNA-induced silencing complex (RISC), a ribonucleoprotein (RNP) commonly including Argonaute proteins, miRNA acts as a guide to targeted mRNA.[105] The RISC can degrade the mRNA or act as a translational block.[106,107] Small interfering RNA (siRNA) is similar in size to miRNA and also interacts with proteins of the Argonaute clade, assembling into a RISC to carry out their function.[108,109] Post-transcriptionally, siRNA acts as a guide, similarly to miRNA, to seek out mRNA transcripts for degradation. At the transcriptional level, short ncRNA has also been shown to regulate the formation of heterochromatin[110] via the RNA-induced initiation of transcriptional silencing (RITS) pathway.

PIWI-interacting RNA (piRNA) is the largest subclass of small ncRNA that interacts primarily with the PIWI clade of Argonaute proteins. piRNA has been most extensively characterized within the germline, where its expression is most abundant, and with regard to its functions in regulation of TE expression.[111] piRNA transcripts (24–32 nucleotides in length) direct PIWI protein complexes to targets in the cytoplasm, and, much like their miRNA and siRNA counterparts, the piRNA-PIWI complex post-transcriptionally regulates gene expression via the degradation of TE RNA.[91] The piRNA-PIWI complex has also been shown to relocate to the nucleus, where it has been linked to *de novo* methylation and acts upstream of DNA methylation machinery such as DNMT3A/B.[112,113] Suppression of piRNA expression results in increased rates of transposition mutagenesis, whereas increased piRNA expression results in greater DNMT3A expression and inhibition of TE activity in mice.[114] Finally, piRNA has been shown to guide heterochromatin formation, providing a second form of transcriptional gene regulation.[115,116]

There are several additional classes of ncRNA that function in regulation of gene expression. Circular RNA (circRNA) is single-stranded RNA in which the 3′ and 5′ ends have been covalently linked. Some circRNA contains an miRNA response element, or MRE, allowing it to bind to specific miRNA and suppress activity.[117] Several circRNAs have also been shown to bind to various proteins and transcription factors, thereby acting as transcriptional regulators.[92,118] Small nuclear RNA (snRNA) is most well-known for its pre-mRNA splicing activity. snRNAs U1, U2, U4, U5, and U6 associate with proteins in a small nuclear RNP (snRNP) to carry out this form of post-transcriptional regulation.[119,120] Larger than the classes of short ncRNA discussed here, long ncRNA (lncRNA) is >200 nucleotides long and has a wide array of regulatory functions, including X chromosome inactivation during mammalian female development,[121,122] as well as regulating the parent of origin monoalleleic expression of imprinted genes.[123]

CHALLENGES AND OPPORTUNITIES IN TOXICOEPIGENETICS

Challenge 1: Determining Whether Epigenetic Changes Are Mechanistic Mediators of Environment-Induced Disease.

Numerous studies in humans and animals demonstrate that environmental exposures are associated with epigenetic changes and that these epigenetic changes, in turn, are associated with disease. However, in many circumstances it remains unclear whether epigenetic changes fall within the causal pathway linking environmental exposures to adverse health

outcomes or if they represent biomarkers of exposure and/or disease (Figure 1). Randomized controlled trials are the gold standard for assessing cause and effect in human studies; however, because it is not ethical to assign humans to receive injurious exposures, this approach is not feasible. In addition, cross-sectional studies demonstrate that environmental exposures are associated with conditions such as cardiovascular disease,[124] obesity,[125,126] reproductive health issues,[127] diabetes,[128] and neurodegenerative diseases, concomitant with altered DNA methylation. However, it is unclear whether the observed epigenetic changes precede and potentially cause the disease or whether they may be an effect of the disease process itself.

Several lines of evidence suggest that epigenetic changes may have a mechanistic role in environment-induced disease. It is clear that epigenetic changes can play a critical role in disease pathogenesis, as demonstrated in several cancers, overgrowth syndromes, dwarfism, and neurological diseases that are driven by mutations or epimutations in epigenetic modifiers or histone proteins.[129–131] Longitudinal studies show that epigenetic alterations can often precede the onset of disease brought on by early environmental exposures,[72,73,132–134] suggesting that such reprogramming may have a causal role in disease. Indeed, early environmental exposures may reprogram the epigenome in a manner that does not affect basal gene expression, but primes genes to be hyper-responsive to stimuli later in life, leading to disease.[72,73] For example, developmental bisphenol a (BPA) exposure in rats reprograms histone methylation at hormone-responsive genes, making them hyper-responsive to hormonal challenges later in life and more susceptible to prostate tumor development.[73] In numerous studies, statistical approaches have demonstrated that DNA methylation is a mediator of environment-induced diseases including diabetes, asthma, cancer, and schizophrenia, among others.[134–137] It is likely that environmental exposures cause disease through multiple interrelated mechanisms including epigenetic, genetic, and metabolic alterations.[138]

Challenge 2: Understanding the Factors That Influence Vulnerability to Environmental Exposures.

Toxicoepigenetics studies are further complicated by several biological and socioeconomic factors that influence vulnerability to environmental exposures and susceptibility to environment-induced disease. Three key factors include sex, age, and membership in a marginalized group (Figure 1). Importantly, these factors do not function independently to modulate environmental susceptibility and disease, but likely interact via complex mechanisms.[139,140]

Sex and Environmental Exposures.—There is arguably no other attribute that has a greater impact on mammalian phenotype, physiology, and disease than sex, yet sex effects in research studies ranging from human to cellular models have been systematically understudied until recently.[141] Diseases with a well-established environmental etiology, such as cardiovascular diseases, liver diseases, neurodegenerative diseases, diabetes, and cancer also exhibit sexual dimorphism,[142–146] suggesting that sex-dependent effects of environmental exposures may underlie some of the observed differences in disease pathogenesis between males and females. Recent studies have identified sexually dimorphic

patterns of gene expression and epigenetic regulation during the development of almost every organ, including the liver, heart, kidney, and brain,[147–150] which are present during the earliest stages of development and persist into adulthood. Specifically, sex differences have been identified across multiple tissues in DNA methylation, histone marks, and ncRNA expression across the lifespan.[143,151–154] Although this sexual dimorphism has largely been attributed to sex hormones, sex differences in gene expression and the epigenome have been observed in embryonic stem cells and in the earliest stages of development, prior to gonadal hormone release.[147,148,155] Thus, non-hormonal factors such as sex chromosomes and sex-specific expression and localization of transcription factors,[148] likely govern sex-specific gene expression patterns. Consideration of sex will be imperative in toxicoepigenetics studies aimed at identifying epigenetic mechanisms and biomarkers linking environmental exposures and disease. Indeed, work from our lab and others has identified sex-specific effects of environmental exposures on DNA methylation and histone marks.[156–161] We recently demonstrated that a comparison of DNA methylation changes between liver and blood in mice perinatally exposed to lead showed few overlaps between blood and liver, and the overlaps identified were sex-specific.[156] Similar sex differences in blood DNA methylation have also been identified in human populations.[162,163] These findings have important implications for environmental epidemiology studies that seek to find epigenomic markers of exposures and disease in surrogate samples such as blood, hair, and saliva.

Age–Environment Interactions.—Age plays a critical role in the effects of environmental exposures on the epigenome. At a molecular level, there are several hallmarks of epigenomic aging, including a general shift from heterochromatin toward euchromatin, with formation of distinct heterochromatic foci (senescence-associated heterochromatin foci), a loss of nucleosomes, an increase in age-related histone variants, an increase in activating histone marks, and global hypomethylation of DNA concomitant with hypermethylation at CpG-rich regions of the genome.[164–169] Age-related epigenetic changes include predictable changes that occur with normal aging, as well as stochastic epigenetic drift that differs from person to person and likely occurs as a result of inefficiencies in epigenetic modifying proteins over the course of time.[170–173] Age-related changes in DNA methylation at distinct CpG sites, referred to as “epigenetic clocks”, have been demonstrated to predict longevity as well as risk of cancer, Alzheimer’s disease, physical decline, and mortality.[174,175] Further, age–environment epigenetic interactions can be explained through the framework behind environmental deflection of the aging epigenome, which is defined as environment- or toxicant-induced shifts in baseline age-related methylation or epigenetic drift.[170,176] Several twin studies have demonstrated that DNA methylation in twins diverges with age, suggesting that the aging epigenome is shaped by environmental factors, not just genetics.[172,177] Likewise, human studies demonstrate that exposure to stress, chemical exposure, and diet can influence the trajectory of epigenetic aging.[7,178–181] Although the majority of studies in this area have focused on DNA methylation, recent work has demonstrated that early environmental exposures and stress can also modify age-related changes in histone marks, ncRNA, and gene transcription.[72,182,183]

Given the interaction between the environment and aging, future environmental epigenetics studies should not be limited to cross-sectional analyses and should consider longitudinal

changes in the epigenome. Indeed, as chemical exposures may cause precocious aging of the epigenome, a single cross-sectional study of adult tissues may miss important exposure-related changes.[72] Moreover, biomarkers of environmental exposures and disease may differ based on age.[184]

Marginalized Status and Environment.—In addition to the intrinsic characteristics of sex and age, external factors also differentially affect epigenomic programming and disease risk in response to environmental exposures and are important considerations in toxicoepigenetics studies. One key example of this is membership in marginalized groups. It is clear that members of minority groups frequently experience substantially greater social stress, economic hardship, neighborhood violence, poor diet, discrimination, and environmental injustice.[185,186] Stress from these factors may accumulate over time to adversely affect overall health. Multiple mechanisms have been identified by which chronic stress promotes negative health effects and increased disease susceptibility.[187–190] The term allostatic load has been coined to describe these cumulative stressors, and various metrics for measuring allostatic load have been developed.[190–192] Although allostatic load has been associated with accelerated epigenetic aging, the two metrics appear to measure distinct processes.[193] On a molecular level, several studies link increased allostatic load to altered programming of DNA methylation, histone marks, and ncRNA,[194–196] suggesting that epigenetic mechanisms may play a mechanistic role in the adverse health effects of chronic stress.

Unanswered questions exist with regard to the effects of allostatic load on vulnerability to environmental exposure. One important question is whether a higher allostatic load may program the epigenome in a manner that increases vulnerability to toxicant exposures. Recent studies support the hypothesis that higher allostatic load interacts with environmental exposures to increase the risk of disease.[197–201] However, the molecular basis for this cooperative effect, including epigenomic programming, is unclear. A second consideration is whether epigenetic biomarkers of exposure and disease will differ depending on the allostatic load experienced by an individual. A higher allostatic load is closely correlated with race and ethnicity, with communities of color experiencing a higher load compared to those with European ancestry.[186] Careful examination of population-specific factors is necessary in the design of environmental epigenetics studies and in the extrapolation of epigenomic data on mechanisms and biomarkers from one group to another.

Challenge 3: Identifying Biomarkers of Exposure.

One important aim of toxicoepigenetics studies is to identify epigenetic biomarkers linking past, present, and cumulative environmental exposures to disease, in order to identify vulnerable populations who may benefit from intervention. The ideal epigenetic biomarker should be stable, such that exposures during early life, which are difficult to measure at the time, can be identified later in life. It should also reflect the timing, duration, and dose of the exposure. Here, we highlight several widely used and emerging epigenetic biomarkers of environmental exposures, followed by challenges associated with their use (Figure 1).

DNA Methylation as a Biomarker.—DNA methylation is the most widely utilized epigenetic biomarker, due in large part to its stability, persistence, and heritability across cellular divisions. Exposure-induced changes in DNA methylation may persist after the insult is no longer present, providing a signature of exposure and a potential mechanism by which cells "remember" prior insults.[11] The relative ease of tissue collection methods necessary to preserve the modification as well as readily available, standardized assays also make DNA methylation an ideal candidate for toxicoepigenetics studies. One example of a toxicant with robust DNA methylation biomarker data is smoking. A recent meta-analysis demonstrated that changes in infant cord blood DNA methylation at thousands of CpG sites were linked to maternal smoking.[202] Many smoking-related DNA methylation changes persist into later life, are sensitive to the level of maternal or adult smoking, and are reflective of the time since quitting.[202–206] DNA methylation biomarkers have also been identified for other exposures, such as alcohol and the metal lead,[207–210] although few are as robust and extensively studied as smoking. Such comprehensive exposure and methylation data in the same human samples are lacking for many toxicants, necessitating further research.

Transposons as Biomarkers.—Due to their genomic plasticity, abundance, and distribution in the genome; copy number variations; and respective roles in epigenetic regulation,[211,212] TEs can serve as biomarkers of both environmental exposure and human health and disease status. *Alu* and LINE1, the two most studied TEs in humans, remain hypermethylated under normal conditions and serve as an indicator for global DNA methylation across the genome. Environmental, chemical, or disease factors can lead to altered DNA methylation levels at these TEs, making them reliable biomarkers. In mice, the intracisternal A particle (IAP) is a TE that includes long terminal repeats (LTRs) at its ends that are CpG dense. The agouti viable yellow (A^{vy}) mouse model displays a coat color indicative of the DNA methylation state of the IAP insertion LTRs.[211] This mouse model has been widely used to identify potential molecular mechanisms and modes of intervention related to toxicant exposures such as BPA,[213] phytoestrogens such as genistein,[214] or folic acid supplementation.[215] Perinatal exposure to environmental toxicants including lead[216] and phthalates[217] demonstrate that DNA methylation changes at the IAPs are sex- and tissue-dependent.

TEs have shown variable levels of DNA methylation by tissue and environmental exposure in human epidemiological studies. Multiple human studies have discovered TE biomarkers in response to arsenic,[218,219] lead,[220,221] mercury,[222] industrial environment particulate matter,[223] other chemicals,[224,225] and disease states.[226,227] Recent studies implicate maternal and fetal LINE1 DNA methylation as a potential molecular mechanism associated with preterm birth[228,229] and that early maternal care may contribute to restoring DNA methylation at LINE1 to improve neurodevelopmental outcomes.[230] *Alu* DNA methylation changes have been associated with nutritional factors and age in population studies,[231] with its methylation tightly regulated by epigenetic mechanisms acting on a single CpG site.

ncRNA-Based Biomarkers.—Some ncRNA types are preferred over others for use as biomarkers due to their prevalence in common human samples including urine, blood, saliva,

and cell-free RNA sources.[232,233] Their prevalence can be attributed in part to their stability, which is conferred by localization or unique structural features. miRNA and circRNA can be excreted to extracellular fluid and harbored by exosomes, extracellular vesicles, or proteins, which protect the miRNA from degradation.[233,234] On the other hand, piRNA biomarkers typically contain a 2′-*O*-methylation at their 3′ end, which increases stability and resists degradation by ribonucleases,[235,236] while circRNAs are resistant to exonuclease RNase R.[237]

miRNA is the most extensively studied class of ncRNA biomarkers in toxicological research. Numerous studies have highlighted miRNA biomarkers in response to cadmium,[238] mercury,[233] and other metals,[239] as well as radiation,[234] environmental stress,[240] particulate matter,[241] and diseases. Due to miRNA versatility and the growing body of toxicological research, routine evaluation of miRNA biomarker detection methods and regulatory mechanisms is required to advance future miRNA research. To date, piRNA biomarkers have been discovered from cell lines and multiple species in response to ethinylestradiol,[242] fluoride,[243] tetrabromodiphenyl ether (DBE-47),[182] cigarette smoke,[244] dichlorodiphenyltri-chloroethane,[245] and diseases.[246,247]

circRNA biomarkers are emerging players in toxicological research. Due to their novelty, very few investigations have reported circRNA associations to environmental exposures. Exposures to lead,[248] particulate matter,[249] cigarette smoke,[250] and diseases[251,252] have identified potential circRNA biomarkers in toxicology.[237]

In a small number of studies, lncRNAs have been linked to environmental exposures including phthalates,[253] cadmium,[233] BPA,[254] benzene,[255] ethanol,[240] and certain human diseases.[256,257] A typical imprinted gene cluster contains at least one lncRNA that regulates the DNA methylation imprint at a given imprinted locus.[123] Toxicological studies may also include lncRNA biomarkers associated with imprinting. For instance, *Meg3* lncRNA is impacted by low dose cadmium exposure[258] and inorganic arsenic.[259] These studies warrant further exploration of additional lncRNA regulation mechanisms, including genomic imprinting.

Challenges in Development of Exposure-Based Biomarkers.—Several challenges exist regarding the use of epigenetic biomarkers in toxicoepigenetics studies. In addition to the aforementioned issues associated with sex, age, ethnicity, and socioeconomic status, additional important challenges include tissue specificity of epigenetic changes, tissue and cellular heterogeneity, and availability of tissues targeted by the exposure.[260] First, because human disease-relevant tissues are often not accessible, human toxicoepigenetics studies rely on easily obtainable surrogate samples (blood, buccal swab, skin, saliva, hair) as proxies for exposures to inaccessible target tissues (brain, liver, heart, kidney).[260] However, the extent to which epigenetic changes in these surrogate tissues reflect the changes occurring in target tissues is unclear.

Additionally, many chemical exposures may only exhibit their effects on a specific cell type in a tissue,[261] making isolation of an adequate quantity of cells for DNA and RNA analysis very difficult. Moreover, there is significant epigenetic heterogeneity within a given

tissue and even within individual cell types.[262–266] Recent work demonstrated that estimates of epigenetic age or correlations between DNA methylation and environmental exposures vary widely within the same individual, depending upon the sample type investigated.[263] Likewise, environmental exposures may alter the relative proportions of cell types in a given tissue,[267,268] making it difficult to distinguish between epigenetic programming at the cellular level from shifts in cell type. TE biomarker research poses some unique challenges due to the need for refined TE detection and DNA methylation analysis, especially since nonconserved CpGs in multiple copies of TEs may confound the true DNA methylation status.[211] The use of ncRNA biomarkers poses additional challenges, as investigators often use large and unrefined public databases to assess their case-specific small RNA sequencing data derived from an environmental exposure of interest.[211]

Challenge 4: Identification of Potential Interventions to Mitigate Environment-Induced Effects on the Epigenome and Health.

Dietary Factors.—Given the potential reversibility of epigenetic changes, a great deal of research is focused on targeting the epigenome for treatment of diseases. The most rigorous efforts thus far have focused on cancer, where epigenetic therapies are either approved for use or in clinical and preclinical trials.[269] Several studies have demonstrated that dietary and behavioral interventions mitigate the effects of environmental factors on the epigenome as well as the adverse health effects. The role for diet in modulating environment–epigenome interactions has garnered significant interest in recent years. Regulation of the epigenome is closely coupled to cellular metabolic pathways, which are, in turn, influenced by dietary factors.[270,271] Epigenetic modifying enzymes are critically dependent upon cofactors for their function, which are derived from the diet. For example, DNMTs and histone methyltransferases methylate their substrates using the cofactor *S*-adenosylmethionine (SAM) as a methyl donor, generating *S*-adenosylhomocysteine (SAH) in the process.[270] Importantly, dietary methionine and folate levels can influence the level of SAM as well as 5-methylcytosine, 5-hydroxymethylcytosine, and histone methylation.[4,5] Moreover, TET dioxygenases and Jumonji histone demethylases utilize iron (Fe^{2+}), α-ketoglutarate, and vitamin C as cofactors to demethylate their substrates.[272] Fluctuations in vitamin C have been shown to regulate DNA methylation, hydroxymethylation, and histone methylation, underscoring the intimate link between diet and the epigenome.[272] Histone acetyltransferases require the cofactor acetyl coenzyme A (acetyl-CoA), which is generated by both glucose and fatty acid oxidation. Thus, fluctuations in this critical cofactor influence histone acetylation.[273] Several other dietary factors have been shown to alter the epigenome, including sulforaphane and phytoestrogens.[133,274,275] Numerous dietary supplements, including B vitamins, folic acid, choline, genistein, and polyphenols, can mitigate the adverse effects of environment on the epigenome and health. For example, BPA-induced hypomethylation of the IAP TE in the A^{vy} mouse was abolished by maternal dietary supplementation with nutrients that bolster one carbon metabolism (folic acid, betaine, vitamin B_{12}, and choline) or the phytoestrogen genistein.[133,214] Thus, dietary interventions may prove useful in mitigation of environment-induced epigenetic deregulation and disease.

Lifestyle Factors.—In addition to dietary factors, lifestyle modifications may mitigate the deleterious effects of the environment on the epigenome and health. Supportive

family environments may attenuate the increase in epigenetic aging conferred by racial discrimination or harsh parenting,[276,277] and environmental enrichment has been shown to attenuate the effects of parental or ancestral stress on cognitive and psychiatric function via regulation of DNA methylation or miRNA expression.[278,279] Likewise, exercise may be an effective intervention against radiation-induced brain injury or cognitive impairment from anesthetic exposure via modulation of 5-hydroxymethylcytosine or histone acetylation, respectively.[6,280] Collectively, these studies suggest that exposure-mediated effects on the epigenome may, in some cases, be reversible. However, the precise timing, doses, and combinations of interventions necessary to obtain the optimal benefit are important unanswered questions. In addition, it is necessary to identify whether interventions should differ based on sex, other genetic factors, preexisting diseases, or age.

ONGOING INITIATIVES TO ADDRESS CHALLENGES TO THE FIELD OF TOXICOEPIGENETICS

The NIEHS TaRGET II Consortium.

The TaRGET (Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription) Consortium is engaged in understanding how early environmental exposures program the epigenome across the life course in multiple tissues.[260] Launched by NIEHS, TaRGET I explored how adverse environmental exposures impact the epigenome. TaRGET II established a multi-institution consortium to validate the robustness and feasibility of using surrogate tissues (e.g., blood) to detect epigenetic reprogramming by early life exposures in mouse models.[260] The third phase, TaRGET III, will support the translation of epigenomic data from mouse- and cell-based studies to population-based studies in which epigenomic data are available. The fourth phase, TaRGET IV, will support integrated analyses in population-based studies, using several genomic and epigenomic databases to develop more comprehensive epigenomic/genomic analyses.

Our recent work in TaRGET II demonstrates that changes in DNA methylation after perinatal exposure to lead or the plasticizer di-2-ethylhexyl phthalate are highly tissue- and sex-dependent, with little concordance between liver and blood.[156,184,281] Our findings are in keeping with recent work in human subjects, which found correlation in DNA methylation between blood and the liver at only a minority of CpG sites within 35 hemostatic genes.[282] Additional studies have demonstrated limited correlation in DNA methylation between human blood and other tissues.[283–286] These findings have important implications for environmental epidemiology studies and suggest that the most meaningful biomarkers may be restricted to a subset of genes that are correlated across tissue, sex, and age. Further investigations into epigenetic signatures across surrogate and target tissues are necessary to identify meaningful disease and exposure-specific biomarkers.

Cellular and Tissue Heterogeneity.

Cellular heterogeneity within and across tissues in a single individual, as well as across individuals, may confound toxicoepigenetics studies. Several approaches have been developed to address this issue including separation and quantification of the individual cell types, single cell profiling, and cell type deconvolution *in silico*, each with specific

strengths and limitations.[287] Separation and quantification of cell types can be achieved via several methods, including sedimentation, fluorescence-activated cell sorting, magnetic separation, microfluidics, affinity chromatography, and electrophoresis.[288] Selection of the appropriate method is based on considerations of time, cost, antibody availability, knowledge of the distinguishing characteristics of the different cell types, and desired purity. Single cell profiling provides a second approach to address heterogeneity. Commercialized and increasingly affordable approaches are now available to profile gene expression, DNA sequence, DNA methylation, and chromatin accessibility at single cell resolution.[289] Additional methods are currently being developed to allow retention of spatial information about the cell in the context of its native tissue.[289] Cellular deconvolution methods *in silico* offer a third mechanism to deal with heterogeneity. Bioinformatics algorithms have been designed which utilize cell specific gene expression or DNA methylation profiles as references.[289] Reference-free methods are also available that rely on mathematical models to account for biological and nonbiological variability in the data.[287]

Genome and Epigenome Editing as Tools for Mechanistic Studies and Precision Environmental Health.

Genome and epigenome editing tools have the potential to improve our understanding of how epigenetic factors function in regulation of gene expression and disease pathogenesis, as well as provide potential opportunities for therapeutic intervention.[290] These technologies allow the precise modulation of epigenetic modifications at predetermined locations of interest to regulate expression of target genes. For example, approaches using CRISPR/dCas9 to target DNA methylation and other epigenetic marks at specific loci are beginning to address important questions of cause and effect regarding the role of the epigenome in modulating gene expression and disease risk.[9,10,291] The piRNA system may provide another opportunity for targeted epigenome editing. The PIWI/piRNA system uses a piRNA-induced silencing complex to recruit DNA methylation to silence TEs.[211] This ncRNA-based silencing mechanism may be adapted to target-specifically silence potential genes of interest by inducing DNA methylation at a specific locus. In addition to its potential in therapy, this approach may be utilized in mechanistic research studies to identify the causal role for DNA methylation in environment-induced disease. Insight about endogenous PIWI/piRNA expression profiles, synthetic piRNA manipulation and DNA methylation response, the role of piRNA biomarkers of environmental exposures, as well as *in vitro* and *in vivo* manipulation are necessary to successfully determine the efficacy and specificity of piRNA delivery as a possible therapeutic approach in toxicology.

EXAMPLES AT THE FOREFRONT OF EPIGENETICS AND HUMAN HEALTH

In spite of the aforementioned challenges, there are numerous examples of the successful use of epigenetic biomarkers and therapies in non-toxicology fields, particularly in cancer. Reprogramming of the epigenome is recognized as an important hallmark of cancer. Epigenetic instability is caused by both mutational and nonmutational mechanisms, leading to tumor-cell heterogeneity and promotion of the malignant phenotype.[292,293] Epigenetic changes at several genes are currently being used as clinical cancer biomarkers, and many more are in preclinical studies. For colon cancer screening, the ColoGuard test detects

BMP3 and *NDRG4* DNA methylation, in addition to *KRAS* mutations and hemoglobin in stool samples, while the Epi proColon test detects *SEPT9* DNA methylation in plasma.[294,295] DNA methylation of the *BRCA1* gene is currently in phase II clinical trials for use as a biomarker of treatment response in tumor biopsy samples.[296] Additionally, *in vitro* tools are being developed for lung cancer diagnosis that measure *SHOX2* and *PTGER4* DNA methylation in pleural effusion samples.[297,298] Other epigenetic biomarkers of cancer are under evaluation for clinical applications such as subtype classification, prognosis, and diagnosis.[299–301] Outside of cancer, epigenetic biomarkers show promise in clinical trials for detection of diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and autism.[302] Several therapies targeting the epigenome have also been developed, and many are approved or in clinical trials for numerous human cancers. For example, inhibitors of DNA methylation and histone deacetylation are currently approved by the FDA or European agencies for the treatment of several hematological malignancies and lymphomas.[303] Moreover, inhibitors of specific epigenetic modifying enzymes such as EZH2, LSD1, and DOT1L are in clinical trials for the treatment of various solid and liquid malignancies.[303] These examples collectively demonstrate that epigenetic biomarkers and therapies have the potential to improve human health and provide a beacon for the field of toxicoepigenetics.

CONCLUSIONS

Toxicoepigenetics has the potential to identify epigenetic biomarkers of environmental exposure, as well as increase our understanding of the molecular mechanisms underlying environment-induced disease (Figure 1). Epigenetic marks may confer memory of, and serve as proxies for, a previous environmental exposure. Consideration of factors such as age, sex, ethnicity, socioeconomic status, and preexisting disease state in toxicoepigenetics studies will be paramount, as each of these factors may affect utility of specific biomarkers and susceptibility to environment-induced disease. Likewise, data from surrogate tissues, particularly bulk tissue consisting of multiple cell types, must be interpreted with caution. In spite of significant challenges, research in the field of toxicoepigenetics has adapted with novel approaches to address these limitations. Furthermore, the field has made significant strides in expanding the repertoire of epigenetic biomarkers to include DNA hydroxymethylation, histone marks, ncRNA, and TEs. Toxicoepigenetics studies have shed light on the dietary and lifestyle factors that may mitigate the effects of toxic exposures on disease risk, highlighting opportunities for intervention. Moreover, the continued development of epigenome editing tools, such as the CRISPR/dCas9 and piRNA systems, hold the promise of precision environmental health interventions to reverse environment-mediated epigenetic changes and disease.

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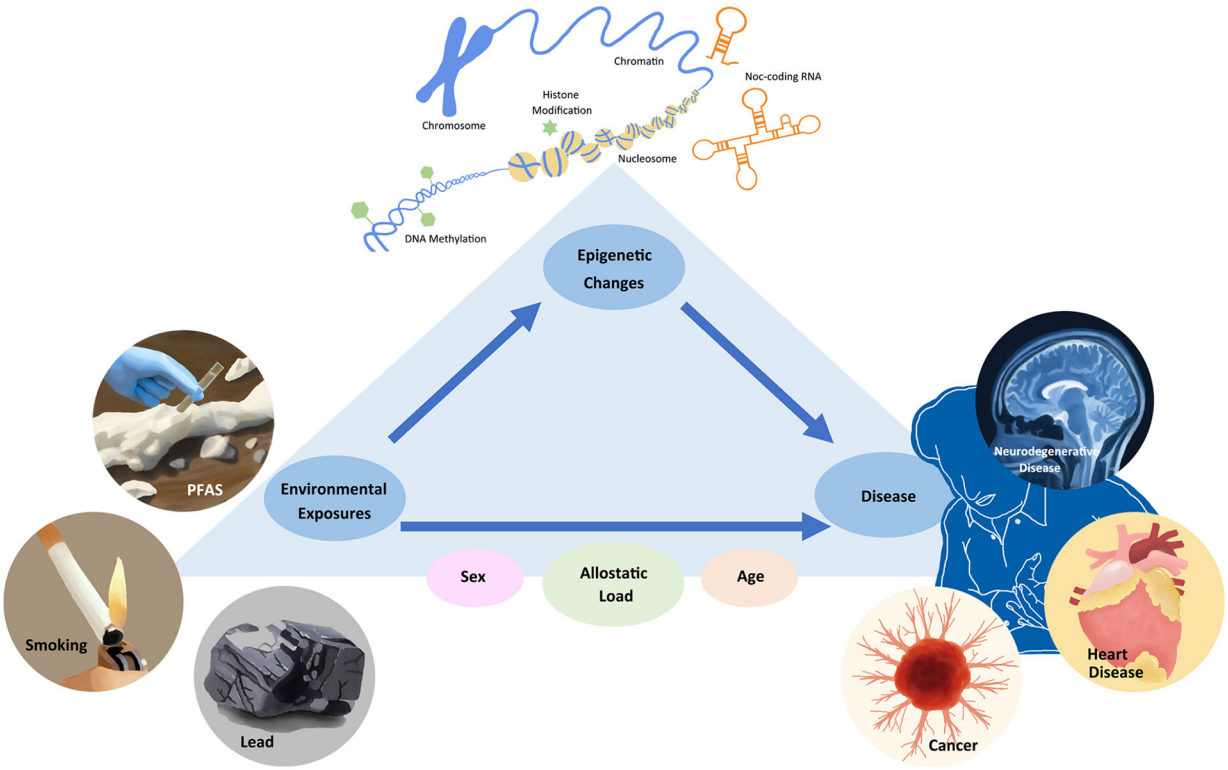

Figure 1.

Schematic illustrating the interplay between the environment, the epigenome, and human health. Numerous environmental toxicants play a role in the etiology of human diseases. A few examples of toxicants linked to disease include perfluoroalkyl substances (PFAS), which are ubiquitous in the environment and bioaccumulate in the human body, tobacco products, and the heavy metal lead. Epigenetic changes may be biomarkers of exposure and/or disease, mechanistic mediators of environment-induced disease, or both. Factors such as sex, age, and allostatic load alter susceptibility to environment-induced disease, but the role of the epigenome in these interactions is currently unclear.