Environmental Epigenetics and Its Implication on Disease Risk and Health Outcomes

Shuk-Mei Ho, Abby Johnson, Pheruza Tarapore, Vinothini Janakiram, Xiang Zhang, and Yuet-Kin Leung

Abstract

This review focuses on how environmental factors through epigenetics modify disease risk and health outcomes. Major epigenetic events, such as histone modifications, DNA methylation, and microRNA expression, are described. The function of dose, duration, composition, and window of exposure in remodeling the individual's epigenetic terrain and disease susceptibility are addressed. The ideas of lifelong editing of early-life epigenetic memories, transgenerational effects through germline transmission, and the potential role of hydroxylmethylation of cytosine in developmental reprogramming are discussed. Finally, the epigenetic effects of several major classes of environmental factors are reviewed in the context of pathogenesis of disease. These include endocrine disruptors, tobacco smoke, polycyclic aromatic hydrocarbons, infectious pathogens, particulate matter, diesel exhaust particles, dust mites, fungi, heavy metals, and other indoor and outdoor pollutants. We conclude that the summation of epigenetic modifications induced by multiple environmental exposures, accumulated over time, represented as broad or narrow, acute or chronic, developmental or lifelong, may provide a more precise assessment of risk and consequences. Future investigations may focus on their use as readouts or biomarkers of the totality of past exposure for the prediction of future disease risk and the prescription of effective countermeasures.

Key Words: developmental basis of disease; environmental epigenetics; epigenetic memories; exposome; histone modification; low-dose effects; susceptible windows; ten-eleven translocations; 5'-hydroxylmethylcytosine

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Shuk-Mei Ho, PhD, is a professor and chair; Abby Johnson is a PhD student; Pheruza Tarapore, PhD, is a research assistant professor; Vinothini Janakiram, PhD, is a postdoctoral fellow; Xiang Zhang, PhD, is a senior research associate; and Yuet-Kin Leung, PhD, is a research assistant professor, all at Division of Environmental Genetics and Molecular Toxicology, Department of Environmental Health, College of Medicine, University of Cincinnati, Ohio.

Address correspondence and reprint requests to Dr. Shuk-Mei Ho, Division of Environmental Genetics and Molecular Toxicology, Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, OH 45267 or email shuk-mei.ho@uc.edu.

Environmental Epigenetics and Disease Risk

In this review, we have examined the current literature and expert opinions on environmental epigenetics, a term that is narrowly defined as how epigenetics explains the variability in the risk and severity of environmental disease. There is no good definition of environmental diseases; in this review, we have focused on those diseases that are caused by factors that exist in our external environment, omitting those caused by lifestyle factors linked to stress, abuse, addiction, alcoholism, and metabolic changes because the scope of these topics is too large to be included. We strive to find examples that illustrate the concept of a complex, multidimensional interaction involving genetics, epigenetics, exposures, and developmental stages of life at work over time and space to influence disease risk and health outcomes.

Epigenetics—A Mechanism Underpinning Susceptibility to and Development of Environmental Disease

Inheritable information carried in the primary sequence of DNA plays a major role in determining variations in the susceptibility and severity of disease. Genome-wide association studies have greatly expanded our understanding of how germline genetic variations influence disease predisposition and outcome (Gibson 2011; Hartman et al. 2010; Sivakumaran et al. 2011). In addition, somatic changes in DNA sequence drastically disrupt gene expression programs, leading to the genesis and progression of disease (Hartman et al. 2010). In recent years, however, research has firmly established that genome-wide association study findings (common genetic variants) alone tend not to identify causal loci of complex diseases and predict individual disease risk (Gibson 2012). This opens up opportunities to assess the importance of epigenetics as a functional modifier of the genome and a key determinant of disease risk and etiology (Feil and Fraga 2011; Petronis 2010).

During early development (e.g., embryonic and fetal), epigenetics serves as a key mechanism controlling cell and tissue differentiation by partitioning the genome into transcriptionally active and quiescent domains. Furthermore, during subsequent life stages or critical windows of differentiation, epigenetics serves to bring about the orderly expression or inactivation of sets of transcribable genes that

ultimately define the mature phenotype of a cell or tissue at the specific developmental stages (e.g., puberty, pregnancy, aging). Disruptions of either the sequence or composition of the epigenetically regulated genes that result in their aberrant expression are the basis of aberrant differentiation and disease development. Epigenetics allows a cell or tissue or an individual to sample and respond to environment cues and to modify how the genome is read (Crews et al. 2011; Feil and Fraga 2011; Ho 2010; Zhang et al. 2011a). A great variety of external environmental factors can alter epigenetic programs in multiple cells and tissues and thereby heighten or lessen the risk of disease development (Crews and Gore 2011; Feil et al. 2011; Ho 2010; Zhang and Ho 2011). In some cases, the impacts of an epigenetic disruption only surface upon a defined stage later in life (Tang et al. 2008; Tang, Morey, et al. 2012), which explains the Barker hypothesis of the early origin of adult disease (Godfrey and Barker 2001; Hales and Barker 2001).

It is worth mentioning a few unique features of epigenetic changes that are different from genetic changes because they may explain the differences between diseases that have a strong epigenetic influence and those driven primarily by genetics. First, epigenetic events do not involve alterations of the primary DNA sequence and thus, in principle, are reversible (Goldberg et al. 2007). Second, they are mitotically inheritable and therefore can be long lasting (Hitchins and Ward 2007; Rakyan et al. 2002), and the prospect that they can be passed on to the next generation is becoming increasingly well established (Skinner 2011). Third, epigenetic events are uniquely susceptible to being "reset" by endogenous or exogenous factors during critical developmental life stages and hence are also sensitive barometers of the environment by lifespan interaction (Tang, Morey, et al. 2012). These features allow epigenetics to explain certain phenomena related to disease variability that could not be fully accounted for by genetic variations and changes.

Susceptible Windows of Epigenetic Programming

Sperms and eggs are highly differentiated cells. After fertilization, epigenetic marks (DNA methylation marks) on sperm DNA are erased within hours; those on the egg remain intact and only begin to be removed during early development (Migicovsky and Kovalchuk 2011). Each cell type and organ in the body starts placing epigenetic marks as differentiation begins. The purpose of this process is to establish a mature and unique phenotype for each mammalian cell or tissue for optimal function. Duration of differentiation may last for weeks, months, and even years, depending on the cell or tissue type. During this period, the cell or tissue has the flexibility to undergo transdifferentiation, as defined by Waddington (1957), or epigenetic reprogramming, as used in the modern literature (Ho and Tang 2007). Because of developmental plasticity (Bateson et al. 2004), each cell or tissue, based on clues in early life, is able to establish an adaptive long-term phenotype that meets the probable demands in later life. Under the influence of morphogens, different sets of

genes are packaged into heterochromatin or euchromatin (Emerson 2002), having the status of "poised" (transcribable) or quiescent, respectively. However, exposure to adverse environment factors, such as xeno-chemicals, environmental pollutants, specific drugs, or pathogens that have morphogenic activities, during differentiation, may lead to the aberrant distribution of genes between heterochromatin and euchromatin. Cells or tissues with such aberrations might develop abnormally or not in synchrony with future needs. If early differentiation meets the needs of future demands, health is expected; if there is a high degree of mismatch, increased disease risk in later life is expected. These scenarios may explain the observations made by Barker and Martyn (1992), who reported higher prevalence of chronic diseases, such as type 2 diabetes, stroke, hypertension, and cardiovascular disease, in individuals exposed to severe maternal hyponutrition. In this regard, the topic of development origins of later-life disease has been covered extensively in many reviews (Crews and Gore 2011; Gluckman et al. 2008; Lucas et al. 1999; Szyf 2009, 2011; Tang and Ho 2007; Waterland and Michels 2007) and will only be mentioned where appropriate in this review.

Developmental stages other than early life are also susceptible to epigenetic programming. These other periods are likely dependent on cell or tissue type because each has a unique time line of differentiation. For example, in addition to pre- and perinatal development, the breast is likely susceptible during peripuberty development and pregnancy, when drastic tissue remodeling and changes in hormonal milieu occur (De Assis and Hilakivi-Clarke 2006). Similarly, for the brain, the peripuberty–juvenile transition period was found to be equally as susceptible to environmental reprogramming as the pre- and perinatal periods (Crews 2010; Isgor et al. 2004). A reciprocal question that remains unanswered is whether each class of environmental factors has a specific window of opportunity to exert its epigenetic effects.

Implications of Lifelong Editing of Early-Life Epigenetic Memories

The concept of continued editing of early-life epigenetic markings or memories during adult life has been proposed on the basis of evidence from limited experimental studies (Tang et al. 2008; Tang, Morey, et al. 2012). Exposure of mice to diethylstilbestrol (DES[1], a xenoestrogen) or genistein (a phytoestrogen) during the perinatal period induced specific epigenetic markings in their uteri. However, some of these epigenetic markings (hypomethylation of *Nsbp1*) remained "hidden" during prepuberty life and appeared in adulthood only in the exposed intact females but not in their ovariectomized

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[1]Abbreviations that appear ≥3x throughout this article: BPA, bisphenol A; CpGs, cytosine-guanine dinucleotides; DES, diethylstilbestrol; DNMT, DNA methyltransferases; EDC, endocrine-disrupting chemicals; HAT, histone acetyltransferase; HDAC, deacetylase; hmC, 5-hydroxymethyl cytosine; mC, 5-methyl cytosine; miRNA, microRNA; mRNA, messenger RNA; PAH, polycyclic aromatic hydrocarbon; PM, particulate matter; TET, ten-eleven translocation; TLR, Toll-like receptor.

counterparts (Tang et al. 2008), suggesting that adult exposure to ovarian steroids may cause these markings to "surface." Coincidentally, the prevalence of uterine cancer was higher in neonatally exposed intact mice, but not in mice ovariectormized before puberty.

A similar scenario was observed in promoter hypomethylation of *Pde4d* in rat prostates induced by neonatal exposure to estradiol-17β or bisphenol A (BPA[1]). This epigenetic mark was not apparent until the males reached sexual maturation (Tang, Morey, et al. 2012). In the male model, there were other marks (e.g., hypermethylation of the *Hpcal1* promoter) that appeared only after neonatally exposed animals were given a cancer-inducing regimen of hormones (Tang, Morey, et al. 2012).

Collectively, these findings support the hypothesis that early epigenetic markings are subject to incessant editing by life stage–specific experiences, which may modify disease susceptibility and health outcome continuously in a progressive but potentially interruptible manner. The concept of continuous editing (addition or erasure) of epigenetic marks over the life course is in agreement with findings from monozygotic twin studies showing the phenotypes and epigenomes of twin pairs become more different over time (Bell and Spector 2011; Foley et al. 2009; Fraga et al. 2005). It also fits in well with many observations on the epigenetic reprogramming of the brain, where life-stage experiences such as childhood abuse can reprogram the epigenetic regulation of glucocorticoid receptor expression (McGowan et al. 2009) and other neurobehavioral disorders (Szyf and Bick 2012).

Mechanisms That Shape the Epigenome(s)

The best studied of the epigenetic events that shape the epigenome of a cell are DNA methylation, histone modifications, and the feedback and feed-forward circuitry of microRNAs (miRNA[1]). Together, these processes affect patterns of gene expression and transcript stability, influence DNA accessibility and chromatin compaction, regulate the integrity and function of the genome, and maintain higher-order nuclear organization in a manner that determines the normalcy and disease risk of the cell or tissue (Alabert and Groth 2012; Calvanese et al. 2012).

Methylation of cytosines or the 5th base refers to the process of adding a methyl group to the 5′ position of the cytosine pyrimidine ring and primarily targets the cytosine-guanine dinucleotides (CpGs[1]) (Ooi et al. 2009). Hypermethylation of CpG island(s) in a gene promoter is commonly associated with the suppression of gene expression (Dean et al. 2005). The methylated promoter region has diminished affinity for transcription factors and increased affinity for methylated DNA-binding proteins (Bogdanovic and Veenstra 2009), histone deacetyltransferases and methyltransferases, and/or corepressors (Tiwari et al. 2008). The methylation state is actively maintained by the activities of DNA methyltransferases (DNMTs[1]), including DNMT1, which facilitates replication of the DNA methylation pattern between

cell generations, and DNMT3a and DNMT3b, which mediate de novo methylation (Hermann et al. 2004; Siedlecki and Zielenkiewicz 2006). The mechanism underlying cytosine demethylation remains unclear and may, in part, be a result of reduced binding of methylated DNA-binding proteins to the susceptible CpGs or CpG islands (a dense cluster of CpGs). It has been proposed that cytosine demethylation involves the association of MBD2 or MBD4 with 5-methyl cytosine (mC[1]) (Lal and Bromberg 2009; Patra and Bettuzzi 2009). More recently, attention has turned to a family of enzymes known as ten-eleven translocations (TETs[1]), which may participate in the removal of methylation from cytosine by the process of hydroxylmethylation.

A second modified cytosine base, 5-hydroxymethyl cytosine (hmC[1]), was recently identified and found to be highly expressed in embryonic cells, the brain, and bone marrow (Branco et al. 2012; Ficz et al. 2011; Ito et al. 2010; Koh et al. 2011; Kriaucionisand Heintz 2009; Li and Liu 2011) and has since been referred to as the 6th base (Willer et al. 1990). The TETs have been identified as the family of enzymes responsible for the conversion of mC to hmC, providing a potential mechanism for DNA demethylation and transcriptional activation (Williams et al. 2012). The TETs are believed to play an essential role in embryonic stem cell maintenance and inner cell mass specification because of their high expression in these cells (Ito et al. 2010). In addition, hmC may exert its action through interfering with the binding of methyl-binding proteins (e.g., DNMT1, MBD proteins) to DNA (Hashimoto et al. 2012; Valinluck and Sowers 2007). The influence of environmental factors in the regulation of hmC and TET expression is poorly understood. Oxidative stress caused by environmental factors has been proposed to regulate the degree of DNA hydroxylmethylation at the promoters of specific genes because the TETs, like many other chromatin-modeling enzymes, are highly sensitive to the intracellular redox environment (Chia et al. 2011; Willer et al. 1990). Future studies on how environmental factors influence the distribution of hmC versus mC in gene promoters or regulatory elements or the localization of TETs and their activities in various cell types are clearly warranted because these parameters may have significant effects on epigenetic reprogramming.

Histones are the major proteins that facilitate the assembly of DNA into nucleosomes, the basic units of chromatin. Specific amino acids in the *N*-terminal ends of the histones undergo unique posttranslational modifications, such as acetylation, methylation, phosphorylation, sumoylation, and ubiquitination (Cosgrove et al. 2004), by the activities of specific enzymes, including histone acetyltransferases (HATs[1]), deacetylases (HDAC), methyltransferases, and demethylases (Miremadi et al. 2007). These modifications determine whether the DNA wrapped around histones is available for transcription and how fast transcription occurs. In addition to regulating gene transcription, histone modification influences other chromatin remodeling events that control replication, recombination, and higher-order organization of the chromosomes (Clapier and Cairns 2009).

At the cellular level, histone modifications serve to transduce extracellular signals to genomic events through alterations of chromatin structure (Barth and Imhof 2010; Cheung et al. 2000). Overall, histone modification works in concert with DNA methylation to regulate acute and persistent changes in transcriptional programs through reorganization of the chromatin architecture (Kondo 2009).

MicroRNAs are a class of small, noncoding RNAs transcribed from their cognate genes or derived from introns or exons of other genes (Pritchard et al. 2012; Rodriguez et al. 2004). Through either complete or incomplete complementarities, they bind to the 3' end of gene transcripts and initiate messenger RNA (mRNA[1]) degradation or suppression of protein translation (Cannell et al. 2008). One miRNA can target hundreds of gene transcripts, and the transcription of a specific gene can be regulated by multiple miRNAs. These complex recriprocal influences between miRNAs and mRNAs establish intricate feedback and feed-forward gene regulatory circuitaries in a cell (Sato et al. 2011). The overall functional outcomes of miRNA activities are to fine-tune the level of transcription and translation, create checks and balances within and across gene networks, and serve as regulatory "hubs" for phenotype expression (Tsang et al. 2010). In addition to regulating transcriptional circuitries, miRNAs have profound influences on the expression of other epigenetic regulators, including various DNMTs and histone-modification enzymes (Sato et al. 2011).

Environmental Epigenetic Changes Are Dependent on Dose and Duration of Exposures

Epigenetic changes are sensitive readouts of the effects of acute and chronic exposures to environmental factors. However, the responses are often nonlinear and dependent on life stages. An acute, low-dose exposure to an environmental factor, if it occurs during the susceptibility window of development of the fetus, could have far greater effects than high-dose exposure in the adult. For example, global DNA hypermethylation was observed in cord blood DNA as levels of polycyclic aromatic hydrocarbon (PAH[1]) DNA adducts increased in cord blood (Perera et al. 2011), indicating that the fetal epigenome can be altered by PAH exposure. More important, the estimated dose of PAH exposure to the fetus was at least 10 times lower than that to the mother, suggesting a higher sensitivity in the fetus than in adults. At the same time, low-dose, chronic exposures may in some cases give results equivalent or even opposite that observed for acute high-dose exposures. Recent studies exploring the effects of cadmium (Cd) exposure on DNA methylation patterns indicate that Cd induces DNA hypermethylation or hypomethylation depending on the duration of exposure. Acute low- or high-dose Cd treatment noncompetitively inhibits DNMT activity, resulting in a decrease in DNA methylation in rat liver cells. However, chronic, prolonged, low-dose exposure to Cd has the opposite effect, leading to

enhanced DNMT activity, DNA hypermethylation, increased cell proliferation, and cellular transformation (Benbrahim-Tallaa et al. 2007; Jiang et al. 2008; Takiguchi et al. 2003). Another factor to consider in the whole animal is the difference in sensitivity among various organs. Whereas some tissues, such as the rat uterus, may respond to endocrine-disrupting chemicals (EDCs[1]) in a monotonic manner and at higher dose (20 mg per kg of body weight) with regard to epigenetic changes (Varayoud et al. 2008), other tissues, such as the fetal prostate, have been shown to exhibit low-dose effects (Ho et al. 2006; Prins et al 2011; Taylor et al. 2011). In this case, exposure of newborn rats to 10 µg per kg body weight of BPA produced an internal exposure similar to levels commonly observed in humans and led to aberrant methylation of gene promoters and the evolution of prostatic preneoplastic lesions in adulthood (Ho et al. 2006; Tang, Morey, et al. 2012). These findings are consistent with the widely observed phenomenon of low-dose effects and nonmonotonic responses of EDCs (Kamrin 2007; Sekizawa 2008; Vandenberg et al. 2012; vom Saal and Hughes 2005; Witorsch 2002).

Epigenetic Factors Shown to Trigger Epigenetic Events and Affect Disease States

Environmental factors such as endocrine disruptors, PAHs, infectious pathogens, outdoor pollutants, indoor allergens, and heavy metals have been shown to trigger epigenetic changes in an exposure- and/or a disease-related manner. These relationships are observed in many complex diseases, including cancer, cardiovascular disease, pulmonary diseases, asthma, obesity, stroke, and neurodegenerative disorders (Irigaray et al. 2007; Lorenzen et al. 2012; Mathers et al. 2010; Nise et al. 2010). In addition, there is strong evidence that the severity and course of progression of these diseases are dependent on early-life epigenetic reprogramming as well as additional epigenetic changes during adult life before or after the onset of the disease or disorder. In this regard, some of the epigenetic marks may serve as biomarkers of exposure or prognostic markers of disease risk and progression, whereas others may provide new insight into the mode of action of the environmental factor. A better understanding of the mechanisms underlying these epigenetic changes may shed light on the etiology of environmental disease and facilitate future development of primary or secondary disease prevention strategies. Below we address several major classes of environmental factors with epigenetic effects. Our discussions are organized around the diseases in relationship to the types of epigenetic modifications induced by the environmental factors.

Endocrine Disruptors

Endocrine disruptors can be defined as exogenous chemicals that mimic the functions of the endocrine system by acting as agonists or antagonists of hormones and disrupting hormone signaling or production (Schug et al. 2011). Endocrine

disruptors may have an animal, human, or plant source. However, the focus of this review is on xeno- or phyto-chemicals with endocrine-disrupting functions, referred to as EDCs. Several recent reviews have covered EDCs and their actions in great details (Anway and Skinner 2008; Diamanti-Kandarakis et al. 2010; Vandenberg et al. 2012; Zhang and Ho 2011). Our emphasis is on the less-reviewed relationship between the epigenetic actions of EDCs and the risk and etiology of environmental disease.

Exposure to EDCs during early developmental periods is a major health concern because it can cause persistent changes in gene expression through epigenetic reprogramming in somatic cells, as well as germ-line cells, and subsequently promote transgenerational inheritance (McLachlan 2001). The xenoestrogen DES was widely used in cattle and other livestock industries and is still an EDC in many populations (McLachlan 2001). Early-life exposure of mice to DES increases risk of uterine cancer that is accompanied by demethylation of an estrogen-responsive gene, lactoferrin, in the mouse uterus (Li et al. 1997). In utero exposure of mice to DES triggered hypermethylation of the homeobox A10 with attended uterine hyperplasia and neoplasia in later life (Bromer et al. 2010). A more recent report documented hypermethylation of nucleosome binding protein 1 (*Nsbp1* or *Hmgn5*) as a hidden uterine epigenetic mark after neonatal DES exposure that only appeared upon sexual maturation of the exposed mice but failed to manifest if the animals were ovarietomized before puberty (Tang et al. 2008). Of significant interest is the transgenerational effect of developmental exposure of mice to DES that promoted c-fos expression, hypomethylation of specific exon CpGs, and increased susceptibility to tumorigenesis in the F2 generation (Li et al. 2003). These experimental data support the hypothesis that epigenetic reprogramming is responsible for the devastating consequences observed in the offspring of women who took DES during pregnancy. The DES effects include female genital abnormalities, vaginal cancer, and male urogenital disorders (Ruden et al. 2005). The adverse effects may be reverberating in the grandchildren of these women (Newbold 2004).

BPA is another epigenetically active xenoestrogen. In utero exposure of Agouti mice to BPA was found to induce hypomethylation in an intracisternal A particle retrotransposon upstream of the Agouti gene in offspring (Anderson et al. 2012; Dolinoy et al. 2007). Cotreatment with a methyl donor of a phytoestrogen was able to reverse its epigenetic effects (Dolinoy et al. 2007). Moreover, neonatal exposure to BPA has the ability to alter patterns of DNA methylation of key genes (*Pde4d4, Nsbp1, and Hpcal1*) that produce related transcriptional changes associated with carcinogenic processes in the rat prostate (Ho et al. 2006; Tang, Morey, et al. 2012). The EDC also induced persistent aberrant expression of DNMT3b and MBD2 throughout life in this model (Tang, Morey, et al. 2012). In addition to tumorigenesis, in utero exposure of mice to BPA has been found to alter gene transcription by methylation of specific gene promoters in the forebrain and induce abnormal behavior in the offspring (Palanza et al. 2008; Yaoi et al. 2008). These findings support the hypothesis

that exposure to EDCs affects neuroendocrine systems and behavior (Crews 2008; Crews et al. 2007; Gore 2008; Skinner et al. 2008). Last, evidence is growing in support of EDCs, such as BPA, p,p'-dichlorodiphenyldichloroethylene, and phthalates, as obesogens or developmental obesogens (Lee et al. 2011; Lind, Roos, et al 2012; Shankar et al. 2012; Tang-Péronard et al. 2011; vom Saal et al. 2012). They have also been shown to associate with prevalent diabetes in humans (James-Todd et al. 2012; Lind, Zethelius, et al. 2012) and metabolic disruptors in model systems (Batista et al. 2012; Soriano et al. 2012). Future investigation is needed to determine whether these EDCs contribute to the epidemics of obesity and diabetes through epigenetic mechanisms.

Phytoestrogens exert endocrine disruption through their actions as epigenome modifiers (Siow and Mann 2010; Zhang and Chen 2011). Their epigenetic functions are best studied in endocrine-related cancers (Hardy and Tollesfsbol 2011). Population studies have consistently demonstrated genistein, a major component of soy, to have protective effects against prostate cancer, with epigenetics playing a significant role (Molinie and Georgel 2009). In breast cancer cells, both genistein and daidzein were shown to reverse DNA hypermethylation and restore the expression of the tumor suppressors BRCA1 and BRCA2 (Bosviel et al. 2012). In prostate cancer cells, the two phytoestrogens exerted similar action on *BRCA1*, *GSTP1*, and *EPHB2* promoters (Adjakly et al. 2011). In addition, because genistein has both DNMT inhibitory and histone modification action, it was found to reactivate tumor suppressor genes such as *p21WAF1/CIP1* (Majid et al. 2008) and *p16INK4a* (Kikuno et al. 2008) and *BTG3* in prostate cancer cells (Majid et al. 2010). In animal models, neonatal exposure to genistein induced unscheduled expression of Nsbp1 by hypomethylation of its promoter in the mouse uterus (Tang et al. 2008), whereas coumestrol and equol silenced H-ras expression by promoter hypermethylation in the rat pancreas (Lyn-Cook et al. 1995). Similarly, pre- and postnatal dietary exposure to soy phytoestrogens advanced sexual maturation and induced aberrant promoter methylation of skeletal α-actin (*Acta1*), estrogen receptor-α, and *c-fos* (Guerrero-Bosagna et al. 2008).

The best-documented EDC with a transgenerational epigenetic effect is the fungicide vinclozolin, which has been shown to induce epigenetic changes that can be transmitted through the sperm (Anway et al. 2005, 2008; Crews et al. 2007, 2012; Skinner 2011). After a one-time transient exposure of pregnant rats to vinclozolin, three generations of male offspring exhibited a broad array of disorders, including male infertility, accelerated aging, behavioral abnormality, and prostate diseases, which was accompanied by epigenetic, trancriptomic, and genetic changes that persisted through all three generations. In addition to vincozolin, the model has recently been used to compare the transgenerational effects of different EDCs (Manikkam et al. 2012). Different EDCs were found to induce different gonadal abnormalities and unique patterns of DNA methylation changes that persist in F1 through F3 offspring in this model. Future investigations are needed to further unravel

how these epimutations are transmitted through generations, and the implication of these transgenerational epigenetic inheritance are only beginning to be understood (McCarrey 2012).

Tobacco Smoke

Exposure to tobacco smoke can cause numerous adverse health effects, including various cancers, cardiovascular disease, and pulmonary disease through DNA damage, oxidative stress, and inflammatory responses (Centers for Disease Control and Prevention 2010). The epigenetic effects of tobacco smoke in these various diseases are less well known and have yielded inconsistent results. Epigenetic patterns from tobacco smoke have been associated with specific patterns of gene hypermethylation; these have been seen in animal models of lung cancer that could serve as biomarkers for the disease (Mathers et al. 2010). In non-small-cell lung cancer, tobacco smoke caused hypermethylation of the *p16* gene promoter region that was significantly associated with packs per year smoked and duration of smoking (Kim et al. 2001). Similar relationships were also observed for other tumor suppressor genes, including *APC*, *RASSF1A*, and *MTHFR* (Toyooka et al. 2004; Vaissiere et al. 2009). Hypermethylation, however, is not the only effect of tobacco smoke on genes. Tobacco smoke was found to cause global DNA hypomethylation in specific cancers, such as colorectal adenoma and cancer (Pufulete et al. 2005). In lung cancer cells, cigarette smoke extract induced aberrant expression of the prometastatic oncogene synuclein-gamma (SNCG) through demethylation of a promoter CpG island and inhibition of *DNMT3B* expression (Liu et al. 2007). These divergent responses may reflect that epigenetic modifications in response to an environmental exposure are gene- and disease-specific, a postulate that needs further research for substantiation.

Tobacco smoking can also interfere with histone function. In A549 and Calu-6 lung cancer, cell lines exposed to tobacco-smoke condensate increased tumorigenesis in nude mice through the repression of the Dickkopf-1 gene by recruitment of the polycomb repression complex (SIRT1, EZH2, SUZ12, and BMI-1). This occurred without hypermethylation within the promoter region that coincided with decreased H4K16Ac and increased H3K27me3 levels (Hussain et al. 2009).

Cigarette smoke can also induce chronic obstructive pulmonary disease, which is associated with the induction of a proinflammatory state that is, in part, caused by epigenetic reprogramming of inflammatory cytokines. In rat lungs, exposure to smoke increased phospho-acetylation of histone 3 and acetylation of histone 4 but decreased the activity of histone deacetylase 2, leading to an increase in the transcription of proinflammatory genes in the lung (Marwick et al. 2004). In another study, cigarette smoke induced the activation of IκB kinase α (*IKKα*) and consequent phosphorylation of ser10 and H3K9 acetylation on

IL-6 and *MIP-2* gene promoters and lys310 RelA/p65 acetylation in lungs of C57BL/6J mice (Yang et al. 2008).

Exposure to tobacco smoke is also a major risk factor for the development of asthma (McLeish and Zvolensky 2010). Some of the epigenetic actions of tobacco smoke on asthma pathogenesis include chromatin remodeling and HAT and HDAC homeostasis in alveolar macrophages (Ito et al. 2001), DNA hypomethylation of the *MAOB* gene promoter region in peripheral blood mononuclear cells of smokers compared with nonsmokers that lasts for years after the cessation of smoking (Launay et al. 2009), and DNA methylation patterns at specific gene promoters including *p16*[*INK4a*] (Digel and Lubbert 2005; Kim et al. 2001), *CYP1A1* (Anttila et al. 2003), *RASSF1A* (Kim et al. 2003), and *FHIT* (Kim et al. 2004). However, it is unclear whether some of these epigenetic changes are caused by cigarette smoking or by pathological changes associated with disease development.

Because epigenetic mechanisms control embryonic development, stem-cell programming, and differentiation, maternal exposure to tobacco smoke can have significant implications for a developing fetus (Logrieco 1990). Prenatal exposure to cigarettes can lead to increased risk of asthma, pulmonary diseases, and cardiovascular disease later in life (Breton et al. 2009; Pattenden et al. 2006). Prenatal exposure to tobacco smoke is associated with gene-specific differences in DNA methylation patterns, including demethylation of *AluYb8* and an increase in methylation of *AXL* and *PTPRO* genes, indicating that altered DNA methylation may result in lifelong effects (Breton et al. 2009). More recently, maternal tobacco smoke was associated with modest epigenome-wide reprogramming of placental DNA methylation in a CpG site-specific manner with concomitant alterations in gene expression profile in the fetus (Suter et al. 2011). In addition to DNA methylation, placental downregulation of miR-16, miR-21, and miR-146a has been associated with maternal cigarette smoking during pregnancy (Maccani et al. 2010). Alterations of these regulatory epigenetic mechanisms in utero can increase the risk for various diseases later in life, and thus their study is of high importance for preventing disease in future generations.

Polycyclic Aromatic Hydrocarbons

It is well known that PAHs are the most widespread organic pollutants found in the environment. PAHs are present in coal, crude oil, and tar deposits and also come from the burning of fossil fuels, forest fires, and volcanic eruptions. Other sources of human exposure to PAHs are automobile exhaust, cigarette smoke, dietary fats, cooking oils (Simon et al. 2008), industrial exposure at coal-tar production plants, coking plants, aluminum production plants, and municipal trash incinerators. There is surmounting evidence that chronic exposure to PAHs is linked to many diseases, including cancers such as those of the lung and bladder (Boffetta et al. 1997; Bosetti et al. 2007), asthma (Perera et al. 2009), obstructive lung disease (Burstyn et al. 2003), fatal ischemic heart disease (Burstyn et al.

2005), and cognitive defects and fetal growth impairment with in utero exposure (Choi et al. 2006; Perera et al. 2005).

One of the most sensitive periods for PAH exposure is early-embryonic development. In a longitudinal cohort study involving 700 children, the epigenetic effects of transplacental exposure to traffic-related PAHs were studied (Perera et al. 2009). Maternal airborne PAH-exposure resulted in hypermethylation of the acyl-CoA synthetase long-chain family member 3 (*ACSL3*) promoter (Perera et al. 2009), which positively correlated with prevalence of parent-reported asthma symptoms in children aged 5 years. In a separate study, global DNA methylation and adduct formation in cord blood was analyzed and compared (Wu et al. 2011). Prenatal exposure to PAHs was reported to be associated with global hypomethylation of cord blood DNA and PAH adduct accumulation. A recent study on the same cohort reported hypermethylation of the interferon-γ (*INF-γ*) promoter to be associated with PAH levels in cord blood of offspring of the exposed mother (Tang, Levine, et al. 2012). Long interspersed nuclear element-1 (*LINE-1*) is greatly regulated during development, as it is highly expressed in early embryogenesis and silenced during cellular initiation. Exposure of HeLa cells to benzo(*a*)pyrene, however, leads to premature chromatin remodeling of H3K4Me3 and H3K9Ac and hypomethylation of CpG islands at the *LINE-1* promoter due to reduced *DNMT1* expression (Teneng et al. 2011).

PAH exposure is known to induce the formation of PAH DNA adducts, which have a tendency to accumulate in specific cell types (Pratt et al. 2011). Only recently has this formation been recognized as a mechanism to trigger site-specific epigenetic modification. In breast cancer MCF-7 cells, benzo(*a*)pyrene exposure caused DNA adduct formation at CpG dinucleotides expressing aberrant methylation changes (Sadikovic et al. 2007). Furthermore, the presence of PAH DNA adducts and aflatoxin B1 may be associated with *RASSFIA* hypermethylation in hepatocellular carcinomas (Feng et al. 2011). Industrial coke oven workers chronically exposed to PAHs exhibited increased methylation levels of *Alu* and *LINE-1* as well as abnormal DNA methylation patterns at specific sequences of the *p53* gene promoter that correlated with levels of PAH exposure (Pavanello et al. 2009). Finally, in firefighters, whose occupation puts them at risk of routine exposure to incomplete combustion products including PAHs, had a higher level of *DUSP22* promoter hypomethylation in blood DNA when compared with nonfirefighting controls (Ouyang et al. 2012). Furthermore, the occupation exposure–related *DUSP22* promoter methylation correlated with the duration of service year but not with age, suggesting cumulative exposure could be measured by an epigenetic signature.

Given the widespread exposure of human populations to PAHs, both outdoors and indoors, inhaled, ingested, or dermal adsorption, and the complex composition of this class of compounds, future research should focus on the epigenetic effects of mixtures such as PAHs, which are ubiquitous in many environmental settings.

Infectious Pathogens

Inflammation and oxidative stress are integral components of many health conditions and disease states, including type 2 diabetes, cardiovascular disease, cancer, neurodegenerative diseases, immunodeficiency, aging, and asthma (Ho 2010; Hussain and Harris 2007; Scrivo et al. 2011). Chronic inflammation has been associated with DNA methylation and induction of specific miRNAs in cancer (Hussain and Harris 2007; Schetter et al. 2010). As a common response to many adverse environmental exposures, inflammation and oxidative stress after exposure often act as indirect epigenetic modulators. Exposure to infectious pathogens, particularly bacterial and viral, causes inflammation and oxidative stress (Minarovits 2009; Stein 2011), which could, in turn, trigger epigenetic events in host cells or organs.

Bacterial infection with *Helicobacter pylori* is a high-risk factor for gastric cancer and was found to be associated with hypermethylation of specific CpG islands in gastric mucosa, which is consistent with aberrant DNA methylation marks seen in gastric cancer (Maekita et al. 2006). Furthermore, *H. pylori* was shown to induce DNA hypermethylation of the E-cadherin promoter (Chan et al. 2003), which is an adhesion molecule involved in tumor invasion and metastasis, and *RUNX3* (Kitajima et al. 2008), which is a potential tumor suppressor gene. Viruses are known to induce various cancers (Fernandez and Esteller 2010), and some of their regulatory epigenetic mechanisms have been elucidated. The link between the hepatitis B virus and hepatocellular carcinoma has been known for decades (Kew 1986; Sherman and Shafritz 1984) and is now believed to occur in a multistep manner, with the majority of the epigenetic changes occurring in the earlier stages (Um et al. 2011). Many epigenetic alterations have been identified in hepatitis B virus X protein–induced carcinogenesis, including DNA hypermethylation of *p16[INK4a]* and subsequent transcriptional activation of *DNMT1* in HepG2 cells through the *p16(INK4a)*-cyclin D1-cyclin–dependent kinase (CDK) 4/6-retinoblastoma protein *(pRb)-E2F1* pathway (Jung et al. 2007), hypermethylation of multiple specific CpG islands occurring in a stepwise manner (Um et al. 2011), including aberrant methylation of the E-cadherin, *RASSFIA* (Zhong et al. 2003), and *GSTP1* (Zhong et al. 2002) promoters, histone deacetylation of E-cadherin, and downregulation of miRNA-373 (Arzumanyan et al. 2012). The human papillomavirus is linked to cervical cancers and head and neck, skin, and other cancers (zur Hausen 2009). It has been known for decades that human papillomavirus is associated with DNA hypermethylation, which may prove to be a useful biomarker for cancer (Cao et al. 2008; Fernandez and Esteller 2010; Wentzensen et al. 2009). In addition to methylation, human papillomavirus E7 has the ability to bind and regulate the enzymatic activity of DNMT1 (Burgers et al. 2007) and has also been shown to perturb the chromatin

remodeling machinery, such as histone deacetylase activity (Brehm et al. 1999), histone acetylase activity (Peng et al. 2000), and acetyltransferase domain of pCAF (Avvakumov et al. 2003). The Epstein-Barr virus is associated with naso-pharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, and lymphoproliferative tumors (Fernandez and Esteller 2010; Minarovits 2009). Epigenetic modifications of Epstein-Barr virus include DNA methylation (Fernandez et al. 2009), histone remodeling (Countryman et al. 2008; Fejer et al. 2008; Gerle et al. 2007), and the aberrant expression of distinct miRNAs (Cai et al. 2006). An Epstein-Barr virus–encoded oncoprotein, latent membrane protein 1 (LMP1), upregulates *DNMT1*, *DNMT3a*, and *DNMT3b,* resulting in a phenotype similar to that of *H. pylori,* with hypermethylation of the E-cadherin promoter (Tsai et al. 2002). In addition to bacteria and viruses, microbes such as protists, fungi, and archaea, have been suggested to partake in disease pathogenesis through epigenetic regulation (Minarovits 2009). However, little is known in this area of microbial epigenetics of disease.

Upon microbial recognition, Toll-like receptors (TLRs[1]) in the host initiate an immune response that results in increased expression of inflammatory genes and upregulation of many specific miRNAs, including miRNA-21, miRNA-146, and miRNA-155 (Quinn and O'Neill 2011). MiRNAs are important components of both innate and adaptive immunity. *INF-γ* is normally suppressed by miRNA-29 through direct targeting of *INF-γ* mRNA in natural killer cells and T cells in mice, but upon bacterial infection with *Listeria monocytogenes* or *Mycobacterium bovis* bacillus Calmette-Guerin, the miRNA is downregulated (Ma et al. 2011). Aberrant or chronic regulation of specific miRNAs has been associated with chronic inflammation, autoimmunity, and cancer (O'Connell et al. 2012; Quinn and O'Neill 2011). In addition to host miRNAs, many viruses have also been found to contain their own set of miRNAs, including Epstein-Barr virus and other herpes viruses, simian virus 40, and human adenovirus, which potentially affect the human immune response by downregulating specific defense genes (Cullen 2006; Taganov et al. 2007).

Understanding microbe-induced epigenetic modifications may have a therapeutic benefit because of the reversibility of epigenetic processes through RNA therapy strategies and the possibility of preventing microbe provocation of disease development.

Particulate Matter, Diesel Exhaust Particles, Ozone, and Other Outdoor Pollutants

Epidemiologic studies involving particulate matter (PM[1]) or other outdoor pollutants such as ozone and nitrogen dioxide have provided evidence for causal adverse health effects, including asthma (London and Romieu 2009; Peden 2011), chronic respiratory diseases (Grigg 2009; Kelly and Fussell 2011; Soto-Martinez and Sly 2010), cardiovascular diseases (Brook et al. 2010; Franchini et al. 2012; Zanobetti et al. 2011), type 2 diabetes (Coogan et al. 2012), and diseases of the central nervous system, including neurodevelopmental

disorders, stroke, Alzheimer's disease, and Parkinson's disease (Genc et al. 2012).

Exposure to fine urban PM in mice and in mouse alveolar epithelial cells increased *DNMT1* transcription and methylation of the *p16* promoter (Soberanes et al. 2012). Because *p16* suppression or inactivation has been found in roughly 50% of all cancers, this epigenetic effect potentially links chronic PM exposure to carcinogenesis (Li, Poi, et al. 2011).

PM is a mixture of chemicals, but the largest contributors of traffic-related PM are diesel exhaust particles. Many studies have focused on the epigenetic changes in PM or diesel exhaust particle exposure, including changes at repeat elements and specific gene promoter regions, which thus alter expression levels (Baccarelli and Bollati et al. 2009; Baccarelli et al. 2009; Tarantini et al. 2009). We have investigated exposure of diesel exhaust particles in a cohort of children with high risk of allergies and asthma and showed that higher diesel exhaust particle exposure is significantly associated with an increase in global hypomethylation and hypermethylation of the promoter of *IFN-γ* and *FOXP3* in saliva DNA (Brunst et al. 2012). Intriguingly, this diesel exhaust particle–associated global demethylation is significantly intensified by the presence of *GSTP1* or *GSTM1* genetic polymorphisms (Brunst et al., unpublished data). This finding is an excellent example of health outcomes from environmental, genetic, and epigenetic interaction. In another study, diesel exhaust particles were shown to induce COX-1 expression through chromatin modification of H4 near the *COX-1* gene promoter region, as well as HAT and HDAC1 regulation in the human bronchial epithelial cell line, BEAS-B2 (Cao et al. 2007). In human bronchial epithelial cells, diesel exhaust particle exposure induced aberrant miRNA expression in roughly 63% of the 313 detectable miRNAs studied (Jardim et al. 2009). Such changes in bronchial epithelium due to chronic exposure, along with other changes, may potentially cause respiratory disease or cancer. Chronic exposure to diesel exhaust particles in *Aspergillus fumigatus*–sensitized mice induced hypermethylation of the *IFN-γ* promoter and hypomethylation of CpG-408 in the *IL-4* promoter of CD4^{+} cells along with aberrant immunoglobulin E production (Liu et al. 2008). Such alterations in T helper gene expression can potentially be damaging to tissues through chronic inflammation; this knowledge can enhance our understanding of asthma pathogenesis. Further, some of the epigenetic changes caused by diesel exhaust particles have been shown to carry across cell division and are potentially transgenerational (Ji and Khurana Hershey 2012). There is clearly a need for more development and transgeneration epigenetic studies to elucidate this possibility as the United States tackles the epidemics of asthma and other allergic diseases.

Because air pollution increases myocardial infarctions and cardiovascular mortality, a recent cohort study explored the relationship between exposure to air pollution and specific blood markers for immune response as well as subsequent DNA methylation states of specific gene promoters in elderly men (Bind et al. 2012). It found the exposure affected four key biomarkers of inflammation: fibrinogen, C-reactive

protein, ICAM-1, and VCAM-1. Exposure to black carbon and nitrogen dioxide increased fibrinogen, ICAM-1, and VCAM-1 levels in the blood, whereas ozone exposure best correlated with changes in levels of C-reactive protein and ICAM-1. In subjects with higher *Alu* methylation or lower *LINE-1*, tissue factor, or *TLR-2* methylation, the effects of air pollution were more profound, suggesting that epigenetic states play a crucial role in the response to air pollution. This further supports the hypothesis that air pollution–induced epigenetic events that lead to cardiovascular pathogenesis occur through thrombosis, systemic cytokine-mediated inflammation, and endothelial dysfunction.

Dust Mites, Pet Dander, Insects, Fungi, and Other Indoor Allergens

Indoor allergens such as dust mites, pet dander, insect allergens, and fungi have been known to induce sensitization and allergy-related immunologic diseases such as asthma, rhinitis, and atopic dermatitis in susceptible individuals (Bush 2008; Platts-Mills 2007). Some studies have provided evidence for the prevention of sensitization to indoor allergens through avoidance strategies (Baxi and Phipantanakul 2010; Mounier et al. 1992), but these treatment studies have yielded inconsistent and controversial results. Understanding the full mechanism of sensitization and allergic response from indoor allergens is essential for improvement in therapeutics and promotion of safer home environment. On this note, it is unfortunate that little is known about the epigenetic effects of indoor allergens.

Evidence is growing, however, that the immune response to specific allergens includes multiple, highly regulated epigenetic modifications. In response to allergens, T helper (T_H) lymphocytes are differentiated into T_H2 cells, which express the cytokines interleukin 4, interleukin 5, and interleukin 13, which play a major role in the allergic response through increased histone acetylation. The T_H2 cells maintain their cytokine memory after cell division and are responsive to the allergen. During differentiation, demethylation at the T_H2 locus causes a change in the local chromatin conformation, allowing the DNA to open and recruit transcription factors such as *GATA3* for immediate expression of T_H2 cytokines in response to the allergen (Van Panhuys et al. 2008). In addition, T_H2 polarization in CDT4 cells is associated with *IL-4* expression and *IFN-γ* repression, which occurs through rapid methylation of the CpG island in the -53 position by DNMT3a, inhibiting the transcription factor binding of ATF2/c-Jun and CREB (Jones and Chen 2006). In a more recent epigenome-wide study, methylation patterns in CD19+ B lymphocytes were assessed in healthy and house dust mite–sensitized groups. Differences in DNA methylation were found globally and at specific genetic loci involved in the immune response, including CYP26A1 (Pascual et al. 2011).

Additionally, miRNAs are believed to play a role in the regulation of both innate and adaptive immune responses and the pathogenesis of immunologic diseases (Pauley and Chen 2008). In asthma risk, *HLA-G* is an asthma-susceptibility gene that contains a single nucleotide polymorphism in the 3′ untranslated region that stimulates miRNA targeting of miR-148a, miR-148b, and miR-152 to this gene (Tan et al. 2007). It is not certain whether allergen-induced asthma or other immunologic diseases contain the same complexity of miRNA expression and regulation, but some studies have alluded to this hypothesis. House dust mite antigens activate *TLR-4* from the innate immune response. This response is associated with expression of unique miRNA such as miR-126, which targets T_H2 cell function through *GATA3* regulation (Mattes et al. 2009). With the possibility of more indoor allergen–induced miRNA regulation of the immune response, future treatment strategies could arise from miRNA-based use of oligonucleotides in anti-inflammatory treatments.

Heavy Metals

Metal exposures have been implicated in neurological disease (Edwards and Meyers 2008; Rooney 2011; Zawia et al. 2009), cancers (Christensen and Marsit 2011; Edwards and Meyers 2008; Navarro Silvera and Rohan 2007; Zhitkovich 2011), diabetes (Chen et al. 2009; Edwards and Meyers 2008; Pozharny et al. 2010), and cardiovascular disease (Poreba et al. 2011; Zhang et al. 2009), among others. Traditionally, the effects of metals on disease development were thought to be mediated by DNA damage, which has been studied extensively and reviewed previously (Bal et al. 2011). However, recent epidemiological and experimental research suggests that exposure to metals can cause drastic changes in the epigenome and the effects are persistent. The epigenetic targets of some heavy metals have recently been reviewed (Arita et al. 2009; Cheng et al. 2012; Fragou et al. 2011; Martinez-Zamudio and Ha 2011). Exposure to heavy metals, such as cadmium, was found to induce DNA hypermethylation or hypomethylation, depending on the duration of exposure (reviewed in Cheng et al. 2012). Exposure to chromium, arsenic, nickel, methylmercury, lead, and organotin induces changes in DNA methylation patterns, either at the global or the individual gene level. Moreover, exposure to heavy metals has also been found to result in changes in the histone code, affecting histone methylation, acetylation, ubiquitination, and phophorylation. Nickel, copper, arsenic, and organotin have been shown to cause global histone modifications. Changes in miRNA expression (Ding and Zhu 2009; Marsit et al. 2006; Wang et al. 2012; Zhou et al. 2012) have been demonstrated for cadmium, arsenic, and mercury exposure in various plant species and/or mammalian cancer cells. In conclusion, heavy metals can activate or suppress gene expression through epigenetic modifications, and these changes can last throughout life.

Future Directions and New Research Opportunities

It is clear that this review is by no means exhaustive in details. Instead, one of its intents is to bring up untapped areas of
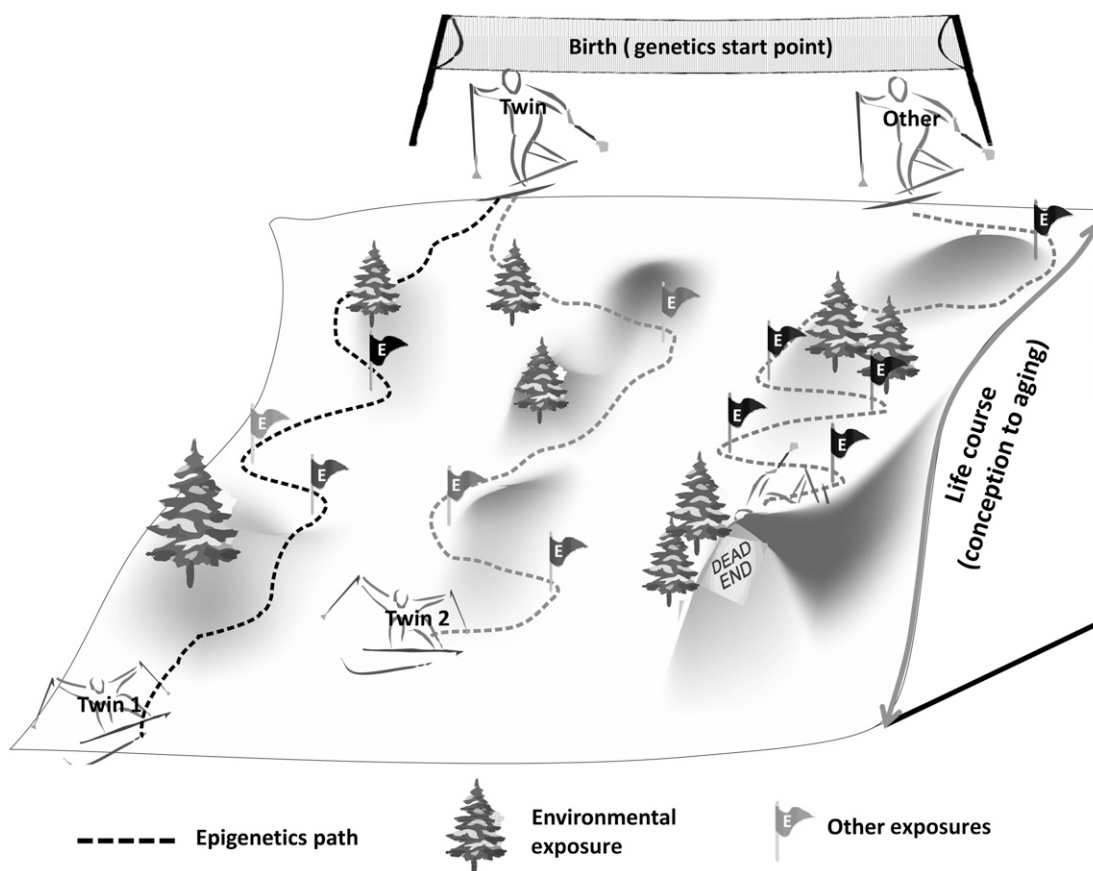
Figure 1 Every individual starts with a defined genetics, which may predispose an individual to certain diseases. During the life course, every individual is exposed to multiple divergent external environment factors (tree) and internal environment factors (lifestyle; flags), leading to different health issues. Depending on the exposures, the magnitude of the epigenomic signature within each individual will differ, leading to changes in the transcriptome. Although some individuals may not advance to the next life stage because of the deadly exposure (dead end), most of them will finish the life journey with differing burden of diseases, depending upon the environment–epigenome interactions that evolve during the life course (e.g., twins will have dissimilar exposures and disease outcomes). The "exposome" is the summation of all exposures an individual experiences over his or her lifetime.

research and unique opportunities for future investigations in environmental epigenetics, which we believe has great potentials to enhance our understanding of disease risk and health outcome.

First, most environmental exposures involve mixtures. This is true for indoor and outdoor pollutants, PAHs, diesel exhaust, PM, EDCs, tobacco smoke, and smoke from incomplete combustion. Thus, the classical toxicology approach that focuses on the health effects of environmental agents, one compound at a time, and on the exposure period to a particular life stage needs to be re-evaluated. In the past, this traditional approach made significant impacts in the field. Examples are the progress made in understanding the health effects of lead exposure on children (Lanphear et al. 2005) and the causal relationship between diisocyanate exposure and adult occupational asthma (Bernstein et al. 2011). However, with the advent of mass spectrometry and other detection technologies, hundreds of chemicals or metabolites can be measured simultaneously with high accuracy. Hence, the field of exposure science has shifted its attention to the biological responses of mixtures. The paradigm-shifting concept of defining environmental

exposure as an "exposome" (Wild 2005) has recently emerged. The term refers to the summation of all exposures an individual experiences over his or her lifetime, from conception to advanced age. Insults or cues from the external environment constantly modify the internal milieu; the combined exposure to both the external and internal changes defines the ultimate exposure. It was further argued that one's internal exposome may provide a better estimate of the ultimate exposure, which may be difficult to measure (Rappaport and Smith 2010). It is important to note that the composition and temporal sequence of these exposures are equally important in determining their effects. Thus, the degree of interactions could be infinite and tends to multiply over time as the individual ages. Furthermore, the nature of these interactions can be synergistic, antagonistic, combinatorial, attenuating, summation, subtractive, opposite, and more. In the context of system biology, the biological effects of an exposome can be defined by its emergent properties (O'Connor 1994; Upinder and Iyengar 1999). In other words, the consequences can only be viewed in its entirety and no single component of the exposome (i.e., a single exposure, a window of susceptibility, a dose or a route, the

frequency of exposure, or a target alone) can predict the disease or health outcome.

With this concept in mind, genetics, epigenetics, transcriptomics, proteomics, metabolomics, bioinformatics, demographic informatics, exposomics, and the entire life-course forms a multidimensional "interactome" that integrates the internal and external environment to determine the health or disease outcomes of an individual. No solitary constituent of this environmental interactome has the predictive value of the whole. As mechanisms underpinning these interactions become understood, phenomena such as nonmonotonic response, developmental origin of disease, continued editing of epigenetic marks, windows of susceptibility, and transgenerational epigenetic inheritance can be better explained. This new knowledge and insight will help inform the public, health-care professionals, and policy makers. Future research directed toward understanding the emergent properties of various environmental interactomes should have significant impacts on the field of environmental epigenetics and its implication on human health and disease variability.

Because it is still difficult to measure external and/or internal exposures over the lifespan, research can perhaps focus on epigenetic biomarkers as either causal or surrogate barometers for environmental diseases. Epigenetic biomarkers that associate with an exposure and/or with the exposure-induced environmental disease will provide invaluable tools for the prediction of risk or for early triage of at-risk groups into surveillance or intervention programs. In this regard, persistent epigenetic memories may serve as risk predictors for devising primary prevention strategies, whereas more nimble marks that respond in a quantitative manner to the changing environment may be useful in monitoring countermeasures. A study on hypermethylation of the DSUP22 promoter as a predictor for the duration of service in firefighting (Ouyang et al. 2012) as well as a study on ASCL3 promoter hypermethylation as an indicator for PAH-induced asthma in childhood (Perera et al. 2009) are early proof-of-principle examples. Future research should focus on the identification of a panel of markers or epigenetic signatures that has high sensitivity and specificity for a mixture or an entire exposome. The challenge may reside in devising noninvasive approaches to find these signatures for population studies in which only surrogate tissues samples are available. Along the same vein, for certain tissues such as the brain, validation of these surrogate epigenetic markers will have to rely on functional imaging. Nevertheless, research in these directions may have huge benefits in meeting the needs of managing health and treating diseases that are affected by the environment. In summary, epigenetic marks that represent broad or narrow, long- or short-term "memories" of exposure may be invaluable for unraveling the consequences of combination exposures over multiple life stages.

Conclusion

The health outcomes resulting from environmental exposure(s) are highly varied and remarkably complex. To advance the

field of environmental epigenetics and deepen our understanding of the detrimental effects of various environmental factors, we need to conduct future studies using the "interactome" approach. This requires consideration of the multidimensional corroborations between genetics, epigenetics, exposomics, and demographics of the study subjects or the populations. Research focuses need to be sharpened to elucidate the unique, but still poorly understood, attributes of epigenetics–environment interaction. These may include early-life reprogramming, windows of susceptibility, nonlinearity of the dose–response relationship, continuous alteration of the epigenome throughout life, the mechanism of transgenerational transmission, and whether specificity exists for the various exposure(s). The potential reversibility of epigenetics affords opportunities for primary prevention of environmentally induced disease either through removal of the adverse exposure(s) or implementation of countermeasures such as one-carbon metabolism-based therapies or oligonucleotide therapies targeting miRNA regulatory circuitries. Because the exposome results from the cumulative effect of epigenetic modifications induced by multiple environmental exposures accrued over time, it is difficult to measure. Therefore, epigenetics biomarkers may provide better readouts of one's past exposome to predict future disease risk and devise effective countermeasures.

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