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Future of Environmental Research in the Age of Epigenomics and Exposomics

Nina Holland

Children's Environmental Health Laboratory, School of Public Health, University of California, Berkeley, CA, USA

Abstract

Environmental research and public health in the 21st century face serious challenges such as increased air pollution and global warming, widespread use of potentially harmful chemicals including pesticides, plasticizers, and other endocrine disruptors, and radical changes in nutrition and lifestyle typical of modern societies. In particular, exposure to environmental and occupational toxicants may contribute to the occurrence of adverse birth outcomes, neurodevelopmental deficits, and increased risk of cancer and other multifactorial diseases such as diabetes and asthma. Rapidly evolving methodologies of exposure assessment and the conceptual framework of the Exposome, first introduced in 2005, are new frontiers of environmental research. Metabolomics and adductomics provide remarkable opportunities for a better understanding of exposure and prediction of potential adverse health outcomes. Metabolomics, the study of metabolism at the whole-body level, involves assessment of the total repertoire of small molecules present in a biological sample, shedding light on interactions between gene expression, protein expression and the environment. Advances in genomics, transcriptomics and epigenomics are generating multidimensional structures of biomarkers of effect and susceptibility, increasingly important for the understanding of molecular mechanisms and the emergence of personalized medicine. Epigenetic mechanisms, particularly DNA methylation and miRNA expression, attract increasing attention as potential links between the genetic and environmental determinants of health and disease. Unlike genetics, epigenetic mechanisms could be reversible and an understanding of their role may lead to better protection of susceptible populations and improved public health.

Keywords

Metabolomics; miRNA expression; environmental health; phthalates; DNA methylation; personalized medicine

1. Emerging Risk Factors and Public Health

The greatest public health accomplishments of the 20th century, according to the Report of the Centers for Disease Control (CDC), include healthier mothers and children due to a decrease in maternal mortality during child birth, better control of infectious diseases, and

Corresponding Author: Nina Holland, PhD, 733 University Hall, School of Public Health, UC Berkeley, CA 94720-7360, Phone: 510-665-2200, Fax: 510-665-2202, ninah@berkeley.edu.

increased access to immunizations and family planning (1–2). Tobacco has been recognized as a health hazard, and significant strides have been made to protect against smoke exposure in public places. Other accomplishments ranged from motor vehicle and workplace safety; declines in deaths from heart attack and stroke; safer and healthier food and fluoridation of drinking water. Despite this progress, environmental research and public health in the 21st century face serious challenges including increased air pollution and global warming, widespread use of potentially harmful chemicals including pesticides, plasticizers, and other endocrine disruptors, and radical changes in nutrition and lifestyle typical of modern societies (3).

Many factors of environmental pollution, such as air and water pollution, as well as industrial pollution, are especially prevalent in rapidly developing economies such as China, India and some countries of Eastern Europe, Africa and South America (3). However, the impact of this pollution spreads beyond the local, and is now recognized as a driver of global climate change. Environmental and occupational exposures to toxicants may contribute to the occurrence of adverse birth outcomes, neurodevelopmental deficits, and increased risks of cancer and other common health conditions such as cardiovascular diseases, asthma, diabetes and obesity (4). These risks are not distributed evenly among populations and countries around the world, and can be modified by age, genetic makeup, SES and other factors (5–6).

2. Children are at Higher Risk

Children are more susceptible to environmental factors than adults, and fetal exposures can be especially detrimental (4). Children eat, drink and breathe more per unit of body weight than adults, and they explore their environment orally with extensive hand-to-mouth behavior (7). Moreover, newborns and young children have much lower levels of some enzymes than adults (8). For example, the paraoxonase (PON1) enzyme, initially named for its ability to hydrolyze organophosphate esters, cholinesterase inhibiting compounds often used in pesticides, is found at significantly lower levels in young children than in adults (9). Importantly, PON1 enzyme activities and genotypes have been associated with oxidative stress-related health conditions, including neurodegenerative disorders, diabetes, cardiovascular diseases, and obesity (10–13). A number of studies suggest a relationship between some *PON1* polymorphisms and low PON1 protein levels with adverse development and cognition in children (14–16).

Although genetics strongly influence *PON1* expression, it is clear that other factors such as epigenetics may be involved in control of PON1 enzyme variability. It is feasible that low developmental expression of the *PON1* gene could be controlled by epigenetic mechanisms. The promoter polymorphism, $PON1_{-108}$, was strongly associated with methylation, particularly for CpG sites located near the CpG island (17). Causal mediation analysis demonstrated statistically significant indirect effects of methylation, providing evidence that DNA methylation mediates the relationship between $PON1_{-108}$ genotype and *PON1* expression. These findings show that integration of genetic, epigenetic, and expression data can shed light on the functional mechanisms involving genetic and epigenetic regulation of candidate susceptibility genes like *PON1*. It also shows the effective application of a novel

systems biology approach that relies on integration of the multidimensional data obtained by omics methodologies.

3. New Research Technologies and Environmental Health

Rapid evolution of molecular biology and genomics at the second half of the 20th century created a strong foundation for an explosion of various omic methodologies, as well as novel approaches to exposure characterization and understanding molecular mechanisms leading to human disease in the 21st century. Following the completion of the Human Genome Project in April 2003 (18), a pursuit of more powerful methodologies of sequencing the entire genome resulted in improvements to all steps of the sequencing pipeline, from bench work to bioinformatics. With a highly competitive market, innovative sequencing hardware and services advanced rapidly with increasing accuracy and decreasing costs. Sanger sequencing, or the so-called “First Generation Sequencing” that played a critical role in the completion of Human Genome Project, was an important start for the currently available techniques. The Second Generation Sequencing platforms, such as Roche 454, Illumina (MiSeq and HiSeq) and ABI SOLiD, require Polymerase Chain Reaction (PCR) in their pipeline (19). These platforms significantly improved the throughput, read length and quality of the sequencing hardware from their initial products. Recently, Illumina released the HiSeq 4000, further increasing throughput and lowering the cost per Gb of sequencing data in comparison with its competitors. The Second-Generation Sequencing platforms raised the data output from 84 kb in 2005 (first generation) to 1.8 terabases of data in a single sequencing run (Illumina 4000). HiSeqXTM Ten, released in 2014, can sequence over 45 human genomes in a single day, and new technologies promise to sequence 1000 or more genomes a day (20).

Current efforts by the genetics community to catalog genetic data worldwide have resulted in sharing data through repositories such as HapMap and the 1000 Genomes Project. These initiatives allow researchers and clinicians to determine the relative frequencies of variants in their samples compared to reference populations. For example, a GWAS study of asthma published in 2010 described location, allele frequency and local haplotype structure of approximately 15 million SNPs, 1 million short insertions and deletions and 20,000 structural variants using a whole genome sequence strategy (21). Nowadays, with existing high-throughput sequencing methodologies, an amazing amount of data can be generated. This scope of information comes with challenges in developing the best methods specific for filtering and ranking genetic variants, as well as handling the analysis of rare variants for disease and gene-by-environment (GxE) analysis.

4. Exposomics and Metabolomics

The concept of the Exposome was first introduced by Chris Wild in 2005 and has since received a lot of attention as a new approach for integral comprehensive characterization of exposure to a wide variety of nutritional, lifestyle, environmental chemicals and biological toxins (22–26). A person’s exposome is the sum total of the many exposure factors that fill the days, months, and decades of that person’s lifetime including exposures to chemicals, radiation, heat/cold, noise, food, stress, and other environmental agents; their health

behaviors and activities; and the unique profile of their microbiome. Instead of characterizing exposures “one by one”, or less commonly by combined exposure to 2–3 chemicals at once, the goal is to simultaneously account for numerous factors ranging from chemical to nutritional, behavioral and environmental. As stated by Rappaport et al 2012, “Given the poor state of knowledge about health-impairing environmental exposures, epidemiologists continue to pursue narrow hypotheses that largely skirt disease etiology in favor of known environmental risk factors, even when the attributable risks are small. Although such hypothesis-driven studies confirm some environmental sources of disease, they offer only fragments to our understanding of the major causes and mechanisms of chronic diseases (27).” Methodologies for more complex assessment of total exposures are only beginning to emerge, and still have to reach the stage of development and validation enjoyed by modern genomic research.

Metabolomics has been proposed as a valuable approach to address the challenges of exposomics. Metabolomics, the study of metabolism at the whole-body level, involves assessment of the entire repertoire of small molecules present in a biological sample, shedding light on interactions between gene expression, protein expression, and the environment (28–31). Metabolomics (also known as metabonomics) allows for the full characterization of biochemical changes that occur during xenobiotic metabolism, and can therefore contribute to understanding the impact of environmental chemical exposures on human health. Recent technological developments enable comprehensive simultaneous analysis of all metabolites present in small volumes of a sample, allowing for the assessment of system-wide metabolic changes that occur as a result of an exposure or in conjunction with a health outcome (32).

Targeted metabolomics refers to methods in which specific metabolites are measured in order to characterize a pathway of interest, whereas untargeted metabolomic assays look for as many metabolites as possible on a global scale without bias (34). Transient perturbations to the transcriptome or proteome that occur in response to environmental exposures may be magnified at the level of the metabolome, making metabolomics a promising methodology for characterizing the molecular changes induced by xenobiotics and identifying new biomarkers of effect (29, 33–34). Among “omics” methodologies, metabolomics interrogates the levels of a relatively lower number of features and thus has strong statistical power compared to genome-wide and transcriptome-wide studies (35). Metabolomics is therefore a potentially sensitive method for identifying biochemical effects of external stressors. Though the developing field of “environmental metabolomics” seeks to employ metabolomic methodologies to characterize the effects of environmental exposures on organism function and health, the relationship between most of the chemicals and their effects on the human metabolome have not yet been studied (36).

For example, phthalates, endocrine disrupting chemicals that are widely used as additives in industrial and consumer products such as plasticizers, stabilizers and solubilizing agents, have been detected indoors in household air and dust, as well as in food, milk and drinking water (38). Phthalate metabolites, especially monoethyl phthalate (MEP), are commonly found in shampoos, detergents, and cosmetics (38–39). Exposure may occur through a variety of routes, including ingestion, inhalation, and dermal contact (40). Almost all U.S.

residents have measurable amounts of phthalate metabolites in their urine, indicating chronic and pervasive exposure and similar exposures are reported in many other countries (41–43). Fetal exposure to phthalates is also widespread, as more than 98% of pregnant women tested have detectable levels of phthalate metabolites according to NHANES (43). Phthalates have been found in amniotic fluid, meconium, and placenta, demonstrating that phthalates cross the maternal-fetal placental barrier (43–44). Prenatal and lactational exposures have been associated with endocrine disrupting effects in animals and adverse birth outcomes in humans, strongly suggesting that early life phthalate exposures may contribute to the fetal origins of disease (41, 45–46). A number of studies have reported that levels of phthalate metabolites in the urine of pregnant women are associated with biomarkers of oxidative stress, such as isoprostane and malondialdehyde (47–48). However, limited knowledge is available on the relationship between traditional measures of phthalate exposure, characterizing up to 17 metabolites and parent compounds (49), and metabolomic markers in the same specimens as measured by targeted or untargeted methodologies.

Though phthalate metabolomic data in humans are very limited, research in animal and *in vitro* models suggests that metabolomic profiling can serve as a biomarker of phthalate exposure. Studies in mice and rats exposed to different dietary or prenatal doses of phthalates have demonstrated that metabolic profiles in a variety of tissues can indeed distinguish dosage groups and that profiles differ by animal sex, with male animals appearing more susceptible to metabolic dysregulation (50–52). Sumner et al. demonstrated that urinary profiles in prenatally-exposed rats could differentiate pups with or without observable reproductive effects even three weeks after exposure, indicating the potential usefulness of metabolomics as a biomarker of both exposure and effect (53).

Metabolomics research in environmentally-exposed populations may demonstrate similar effects of phthalate exposure in humans. A recent study in a Chinese male cohort used metabolomics as a tool to identify exposure biomarkers in urine. This study reported that low-level environmental phthalate exposures (DBP & MEHP) were associated with increased oxidative stress and fatty acid oxidation, and decreased prostaglandin metabolism (54). Recent discoveries using metabolic mapping technologies have helped to uncover novel pathways and metabolite-mediated posttranslational modifications, as well as their impact on physiology and disease (55).

For targeted metabolomics, a single-reaction monitoring (SRM) liquid chromatography-mass spectrometry (LC-MS/MS)-based platform, which can quantitate the levels of several hundred representative polar and nonpolar metabolites, is widely used. Other researchers use a nuclear magnetic resonance (NMR) approach (56). One technology that was developed to meet the challenge of the vast number of unknown metabolic pathways is activity-based protein profiling (ABPP) using activity-based chemical probes to assess the functional states of both characterized and uncharacterized enzymes (57–58). While targeted metabolomics is a powerful approach for quantifying changes in the levels of known metabolites in common metabolic pathways, the metabolome likely consists of many more metabolites and pathways that are yet uncharacterized. As such, untargeted and unbiased metabolomic profiling that can identify hundreds of thousand novel biomarkers and uncover unique insights into dysregulated metabolic pathways is necessary.

Adductomics is an area of research that is focused on characterizing adducts from reactions between circulating electrophiles and blood nucleophiles, and an “adductome” is defined as the totality of such adducts within a given target (27). Adducts of hemoglobin and serum albumin appear to be more informative than those of DNA and glutathione for characterizing adductomics because of their abundance and a longer half-life in human blood. So far, adductomic profiles were characterized with regard to benzene exposure, acrylamide and other environmental pollutants (59–61).

Despite exciting advances in the field of Exposomics, much more work is needed, especially with the emergence of more powerful methodologies for adductome and metabolome analysis, and cross validation with the traditional markers of exposure assessment is essential.

5. Epigenetics and Environment

Epigenetic mechanisms influence gene expression without changes in DNA sequences. Unlike genetic mutations, which lead to permanent changes of genes, epigenetic modifications are reversible and responsive to different environmental factors including lifestyle, diet and exposure to chemicals (62–63). The most widely studied epigenetic marks are DNA methylation and histone modifications. Less is known about non-coding RNAs, considered the third type of epigenetic marks (64–66). Increasing evidence has shown that epigenetic modifications, including non-coding RNA, alter or control DNA expression and the degree of DNA transcription as an adaptive response (67–69).

DNA methylation refers to the potential of a cytosine (C) base to be methylated at its 5^{th} carbon if followed by a guanine (G) base in the DNA code, called a CpG site. The human genome contains about 30 million CpG sites distributed throughout several gene regions referred to as CpG islands, shores, shelves, and gene bodies. CpG islands are stretches of DNA with a high frequency of CpG dinucleotides that often occur in proximity to gene promoter regions (70). It was previously believed that the majority of functional changes to the methylome occurred in CpG islands; however, methylation changes along CpG shores (regions within 2kb of islands) and within the gene body may also have functional effects on gene expression (71–72). Rapidly emerging methods for measuring DNA methylation present investigators with a difficult decision in choosing the platform that provides the best balance of accuracy, coverage, reproducibility, throughput and cost (73–74).

Exploratory tools have included methylation-sensitive restriction fingerprinting, methylation-specific microarrays, and next generation sequencing. Bisulfite conversion followed by high-throughput pyrosequencing is considered the “gold standard” method for determining methylation status at specific sites (75–77). The Infinium Illumina Methylation Assay allows both genome-wide and site-specific assessment of DNA methylation. The most commonly used platform interrogates over 450,000 CpG sites (450K BeadChip) (20, 77). An even more comprehensive platform (Epic Beadchip) that covers > 850,000 CpG sites was released in 2016 (78). While Infinium BeadChips do not cover all the CpG sites in the methylome this approach can be relatively cost effective and informative in environmental pollution studies, especially when hits have been validated by other methodologies such as

targeted sequencing, changes of expression and/or confirmation in the in additional cohorts (79).

DNA methylation patterns are established through critical stages of ontogenesis. The role of the prenatal period, when the embryo undergoes genome-wide DNA demethylation and remethylation, is likely to be very important in epigenome integrity and development. Environmental exposure during these sensitive time periods can result in changes, in some cases permanent, in the methylation status of DNA. The amount and patterns of DNA methylation may vary by tissue and cell type (80). Disruption of these methylation patterns has been linked to disease development and to various environmental exposures (62, 81). Some genes may become hypomethylated due to environmental exposure and others may be hypermethylated (82–85).

The rapidly expanding list of environmental exposures associated with epigenetic effects includes organochlorines, bisphenol A, persistent organic pollutants, benzene, metals, air pollution, tobacco smoke, aflatoxin B, ionizing radiation, bacteria (*H.Pylori*) and viruses (HPV, EBV, HBV) (86–87). Dietary and lifestyle factors such as alcohol, traumatic stress, folate deficiency, low methionine intake and aging have also been associated with epigenetic changes (82–83, 88). Limited but growing evidence also indicates that exposure to phthalates results in DNA methylation changes and may be a key mechanism by which these endocrine disruptors impact health (86). Mice exposed prenatally to di-(2-ethylhexyl) phthalate(DEHP) were seen to have increases in global DNA methylation levels and consistent increases in DNA methyltransferase protein levels, showing that *in utero* phthalate exposure has broad effects on DNA methylation (89). *In utero* exposure to DEHP was also reported to decrease androgen formation in fetal and adult rat testes by deregulating the nuclear steroid receptors through CpG hypomethylation (90). Recently, differential DNA methylation of repetitive elements, an epigenetic marker of genome instability, was reported in newborns and children with prenatal exposure to phthalate metabolites (17). These findings suggest that prenatal exposure to some endocrine disruptors may influence DNA methylation, highlighting epigenetics as a plausible biological mechanism through which environmental exposures may affect human health. When DNA methylation is analyzed in the context of population studies, it is prudent to remember that the findings will indicate associations with certain exposures, and detailed mechanistic interpretation would require additional studies in carefully designed experiments with model organisms or cell cultures (91–92).

There is a growing interest in analyzing the role of microRNAs (miRNAs) as a functionally important epigenetic mark (81, 93). MiRNAs are about 18–22 nucleotides in length and play an active role in the epigenetic regulation of gene expression in all living organisms with eukaryotic nuclear DNA (21, 94–95). The miRNAome contains more than 2,500 mature miRNAs that have been identified in humans and deposited in the miRBase (96). The majority of the miRNA target binding sites are not yet known, but putative binding sites within coding sequences can be identified by sequence complementarity to candidate miRNAs (97).

Methodologies currently available for miRNA expression analysis include Affymetrix GeneChip® miRNA 4.0 array, Nanostring and EdgeSeq miRNA whole transcriptome assay (HTG Molecular). Both Affymetrix and HTG platforms use next generation sequencing technology to quantitate miRNA expression of more than 2200 miRNAs. Compared to the arrays, the Nanostring methodology is advantageous as it is more cost effective and more appropriate for analysis of several dozens to several hundred candidate miRNAs.

MiRNAs are an excellent epigenetic biomarker to study because: 1) they are ubiquitously expressed in tissues and body fluids including blood, urine, and saliva (98–99); 2) they are released into the bloodstream from target tissues (i.e. brain, liver) and may reflect profiles of target tissue (100–101); and 3) they are highly stable and resistant to RNase activity as well as effects of pH and temperature in stored specimens over time (102). Accumulated evidence has demonstrated that most of the known miRNAs participate in normal development, as well as disease pathology, and that miRNAs are reliable biomarkers for classifying tumors and identifying tissue injury (103–108).

Although human studies of miRNA expression and environmental exposure are still limited, especially in comparison to DNA methylation, more publications have come out in recent years (87, 109–110). One study found that prenatal arsenic exposure was associated with differential miRNA expression in umbilical cord blood (111). Another study reported that among obese individuals, a conditional indirect effect of exposure to air pollution (PM10) on blood pressure was mediated by miRNA101 in people with lower BMI (112). In another study of the effects of air pollution on several candidate miRNAs, it was shown that PM10 exposure affected miRNAs that are involved in inflammatory and oxidative stress pathways (113). Exposure to black carbon was associated with differential expression of miRNA9 and miRNA96 but it was limited to only one genetic polymorphism XPO5 (114). Blood miRNAs were reported to be a sensitive indicator of environmental and occupational exposure to volatile compounds (115). It appears that the field of environmental research involving miRNA expression is developing rapidly, and these molecular biomarkers have great potential for biomonitoring, diagnostics and understanding of the mechanisms of regulation of gene-environment interactions.

Circular RNAs (also known as exonic circular RNA or circRNA) represent another exciting epigenetic mark that recently received great attention (116). It is a type of covalently closed non-colinear RNA that are linked to physiological development and various diseases (117–118). The presence of abundant circRNAs in saliva, exosomes and blood samples will make them potential diagnostic or predictive biomarkers for diseases, particularly for cancer development, progression and prognosis. Based on the current knowledge of circular RNAs, these molecules have the potential to be the "next big thing" in the omics research (119–120).

6. New Technologies in the Pipeline

A new set of sequencing technologies is rapidly replacing certain types of genomic and epigenomic microarrays as the technology of choice for quantifying and annotating different

elements of the transcriptome and epigenome since they can reliably detect gene variations, gene expression and the expression of novel or known microRNAs.

For example, targeted next-generation bisulfite sequencing using library-free bisulfite padlock probes (BSPPs) will allow us to validate candidate genes and expand interrogation of CpG sites across functional gene sub-regions of interest. SNPs could be identified by using BisReadMapper software, allowing for analysis of allele specific methylation. This approach is one of the most accurate methods for bisulfite sequencing to emerge in a field undergoing rapid innovation (121). Illumina's EPIC TruSeq Methyl Capture panel (released in 2016), an enrichment-based bisulfite sequencing method, offers another way to expand upon 850K EPIC BeadChip findings.

Given that omic research in human populations generates amazing amount of data, computationally efficient methods of integrating these datasets are becoming increasingly important (79, 122). They require a special training in bioinformatics for researchers in the environmental and public health, as well as creating an adequate, sophisticated infrastructure to meet these computational challenges.

7. Environmental Research and Personalized Medicine

Advances in genomics, transcriptomics and epigenomics are generating multidimensional structures of biomarkers of effect and susceptibility, which is increasingly important for our understanding the molecular mechanisms underlying the effects of environmental exposures and is shaping the emergence of personalized medicine (123–127). A critical aspect of understanding the role of epigenetics in gene-environment (GxE) interactions as a key mechanism of effects of environmental exposures on human health is related to differential susceptibility that may be defined by genetic make-up, age or sex. (63). Recently, the NIH Roadmap Epigenomics Consortium generated the largest collection to-date of human epigenomes for primary cells and tissues. The consortium showed that disease and trait-associated genetic variants are enriched in tissue-specific epigenomic marks, revealing biologically-relevant cell types for diverse human traits and providing a resource for understanding the molecular basis of human disease (126–128). Importantly, epigenetic marks are pliable and may be an excellent potential tool for prevention and intervention through development of new types of epigenetic drugs.

Application of novel biomedical developments, including exposomics and epigenomics, to gain a dynamic system-level and human-specific understanding of the causes of disease (128) is an important development that should enhance the contributions of toxicology and environmental research to the 21st Century paradigm in medical science and public health. This new approach can generate a more comprehensive "big picture" by linking environmental sciences with medical research through shifting the focus from animal studies and simplistic cell models to a systems biology framework (129–132).

A very promising contribution of novel omics advances is the emergence of personalized medicine. The 2015 NIH initiative on Precision Medicine is designed to "dramatically improve and encourage creative evidence based approaches" to clinical practice and disease

prevention through taking advantage of molecular biology, genomics, and bioinformatics techniques (133). Currently a two-step strategy for Precision Medicine is proposed: 1. near-term focus on cancers; and 2. long-term objective to generate knowledge applicable to the whole range of health and disease. Another important aspect of the Precision Medicine Initiative is protection of sensitive sub-populations, such as pregnant women and children, from the effects of environmental exposures, drugs, poor diet, and stress. Regular comprehensive monitoring of levels of nutrients and toxicants through optimized non-invasive metabolomics or sensor-based devices already in the works by biotech companies can become a new norm in the not so distant future. Assessing differential risk will require an improved understanding of the role of genetic make-up and gene-environment interactions. This will become feasible as the efficiency and cost of these genome-wide analyses continue to improve.

In conclusion

New Age technologies and approaches can contribute to environmental research, through significantly improving biomonitoring and identification of metabolites and other chemicals, and to Precision Medicine through prevention and intervention.

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