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Placental Epigenetics in Children's Environmental Health

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Abstract

There is a growing interest in understanding the mechanisms that drive the developmental origins of health and disease, and the role of epigenetic regulation has risen to the forefront of these studies. In particular, the placenta may be a model organ to consider as a mediator of the impact of the environment on developmental programming of children's health, as this organ plays a critical role in directing development and regulating the fetal environment. Several recent studies have begun to examine how environmental toxicant exposures can impact the placental epigenome, focusing on studies of DNA methylation and microRNA expression. This review highlights several of these studies and emphasizes the potential the placenta may hold on the broader understanding of the impact of the intrauterine environment on long-term health.

Keywords

placenta; DNA methylation; fetal programming; biomarker; developmental origins; microRNA

The theory of developmental origins of health and disease (DOHaD) posits that the environment encountered during gestation impacts fetal development to allow elaboration of the single fetal genome to accommodate variation in phenotypes which are responsive or adaptive to the predicted external environment. Elegant epidemiologic studies have taken advantage of natural experiments, including the Dutch Famine of World War II and the Quebec ice storm of 1998 to demonstrate the impact of extreme environmental conditions on infant, childhood, and long-term health outcomes.[1–8] Birth weight, as a marker of the quality of the intrauterine environment, has also been linked to adult diseases and disorders including metabolic syndrome, cardiovascular disease, obesity, diabetes, and mental health conditions.[9–13]

Building on this research, contemporary studies are aiming to elucidate how specific environmental factors, including maternal nutrition, psychosocial profile, drugs, xenobiotics and environmental contaminants, maternal metabolic status, and infection, can impact early childhood and long-term health. Importantly, these studies are also beginning to enumerate mechanisms underlying these effects in the hopes that interventional efforts may become

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apparent. This review will focus on such studies, specifically those focusing on environmental contaminants and the utility of the placenta and epigenetic biomarkers in the placenta to contribute to the understanding of the mechanisms underlying gestational environmental contribution to long-term health.

The Placenta's Role in DOHaD

Central to understanding the mechanisms underlying DOHaD is the placenta. David Barker, who delineated the "Thrifty Phenotype" giving rise to the current concept of DOHaD, devoted much of his work to linking gross placental characteristics such as placental size to adult metabolic outcomes as well as understanding the predictors of those placental measures.[14–18] Such work continues, and new visual morphometric tools are being used to demonstrate how morphologic and pathologic variation of the placenta can influence childhood growth and potentially other outcomes.[19–21] Understanding molecular features of cells responsible for placental function, though, holds additional promise in providing fundamental insights into the effects of environmental contaminants and their effects.

The critical roles of the placenta in fetal development make it an excellent organ of focus to consider as a mediator of the environment on fetal, infant, and potentially lifelong health. The placenta sits at the interface of the maternal and fetal environment, controlling fetal development and environment through a variety of critical functions (Table 1). It is the first complex organ to form during development, and can be impacted at the earliest stages by maternal environmental factors leading to adaptations which can both positively and negatively impact the course of gestation. Environmental toxicants can significantly impact fetal development by impairing or altering the placenta's ability to perform these functions.[22,23]

Appropriate placental gene expression is paramount to fetal regulation during pregnancy, and alterations from this have been linked to preeclampsia, intrauterine growth restriction, gestational diabetes mellitus, and trophoblastic disease.[25–29] While characterizing gene expression patterns can aid in pinpointing critical pathways involved in disease pathogenesis, an additional layer of examination, considering how these expression patters become impacted is necessary to fully describe toxicant effects on the placenta and thus impacting health.

Epigenetic Mechanisms and the Placenta

Epigenetic mechanisms are those which control gene expression or gene expression potential in a mitotically stable fashion without altering the underlying sequence of the DNA. Fundamentally, epigenetic mechanisms regulate the conformation and accessibility of chromatin to transcription factors and the transcriptional machinery's ability to generate RNA from the DNA sequence.

Histones, the proteins which constitute the nucleosome core, represent the most active sites of epigenetic regulation, as tails of these proteins which are accessible from the nucleosome core can be posttranslationally modified with a variety of moieties leading both to changes in the physical accessibility of the DNA they encase, and also to signaling to transcriptional

activators and repressors to control transcription. The histone modification landscape, although highly relevant in controlling gene expression patterns in the placenta and all other tissues, has been less well characterized, particularly in human studies, as the methodologies required for its characterization are thus far not amenable to large-scale population studies. Chromatin immunoprecipitation techniques required for colocalizing modified histones with their coincident DNA rely on antibodies which can have challenges in their reproducibility, as well as access to pristine, freshly collected, and fairly large quantities of samples, which may not be feasible in epidemiologic contexts.

On the other hand, modification of the DNA itself, in the form of cytosine methylation, has been well characterized in human studies. DNA methylation often occurs coincidentally with repressive histone modifications, and in the context of CpG methylation within promoter or proximal promoter region, CpG-rich (CpG island) areas can signal gene silencing. DNA methylation can be interrogated using sodium bisulfite modification of genomic DNA.[30] This technique leads to the deamination of all unmethylated cytosines in the genome to uracil, while methylated cytosines are retained. Following amplification, the methylation status can be determined by methylation-specific PCR or sequencing strategies, including short-read quantitative pyrosequencing or mass spectrometry–based techniques as well as next-generation sequencing technologies, simply by denoting the presence or absence of cytosine in the sequence. It is worthy to note that when performed quantitatively, the percent methylation being reported at any site is really a reflection of the number of methylated alleles within a given sample, and is more reflective of the number of cells demonstrating a methylated state, as any one allele can be only methylated or not.

There is a growing literature of studies examining the DNA methylation status of specific candidate genes, as well as markers of global DNA methylation, and variation in genome-wide DNA methylation in the placenta.[31] Owing to the importance of the placenta in development, links have been made between variation in placental DNA methylation and newborn outcomes including growth and birth weight, gestational age, and behavior.[32–36] In addition, various pregnancy conditions and complications, including preeclampsia, gestational diabetes, and maternal obesity, have been linked to placental DNA methylation profiles.[37–44]

An additional level of epigenetic control, at the posttranscriptional level, is directed by noncoding RNA, and specifically microRNA (miRNA). MiRNAs are small, approximately 22 nucleotides, noncoding RNA molecules, which are highly ubiquitous and possess conservation across many species.[45] MiRNAs posttranscriptionally regulate gene expression by base-pairing to the 3′-untranslated region of a target mRNA resulting in either translational repression or direct degradation of the mRNA, the exact mechanism of which depends largely on the degree of complementarity of the miRNA to its mRNA target. Because partial complementarity of a miRNA to an mRNA target can still lead to translational repression, a single miRNA has the capability of regulating a large number of genes.[46] MiRNAs have been implicated in regulating numerous cellular processes and play a critical role in mammalian development.[47,48] Highly conserved clusters of primate-specific miRNA are expressed in the placenta and other tissues[49,50] and interestingly, similar patterns of regulation of these conserved miRNA have been described in placenta

and brain.[50] Altered miRNA expression has been linked to several maternal–placental conditions such as preeclampsia[51– 55] and growth restriction,[56] reinforcing the role for placental miRNA as clinical biomarkers of exposure or disease.[57] In fact, the C19MC miRNA cluster plays critical role in placental trophoblast migration, maternal immune system regulation, possibly through their secretion as exosomes acting as intercellular signals.[49,58–61]

As it is clear that maternal factors can contribute to the epigenomic landscape of the placenta, and that this level of epigenetic regulation can impact placental function and children's health, there is a growing interest from the environmental epidemiology community to consider placental epigenetics as a mediator of the maternal toxicant environment on children's health outcomes. This more complete understanding of the central role of the placenta and its molecular landscape holds the hope of providing risk predictors and biomarkers to help clinicians better diagnose and treat complex disease and to provide insights to the pathologic process. In the following sections, we highlight recent work considering the impacts of selected environmental toxicants on placental epigenetic profiles and how these link to important newborn and early life outcomes.

Environmental Exposures and DNA Methylation

Endocrine disrupting chemicals (EDCs) are generally considered to be a wide-ranging group of compounds that, at certain doses, act to alter the function of hormones within mammals.[62] Common chemicals with broad use and so nearly universal exposure that fall within this category include phenols such as bisphenol A (BPA), or phthalates, which are important plasticizers used often in food packaging. In most cases, the toxic activity of EDCs is not entirely through their hormonal effects, and there remain significant questions regarding how they impact wide-raging human health conditions particularly during the prenatal period.[63] Experimentally in a murine model, BPA has been shown to affect the epigenome through alteration of the DNA methylation status of the metastable Agouti allele in mice, a phenomenon which can be reversed by nutritional supplementation with methyl donors (folic acid).[64] Importantly, animal models have demonstrated that the liver's ability to metabolize BPA into its inactivated state is reduced by 40% during pregnancy,[65] suggesting an acute susceptibility to endocrine disruptors during this period for both the mother and fetus. Human studies mimic these findings, demonstrating that pregnant women excreted 26% greater levels of BPA in their urine as compared with pre-pregnancy.[66]

Recent work has begun to examine the potential epigenetic effects of EDCs in human populations. Nahar et al demonstrated that in utero exposure to BPA altered expression of xenobiotic metabolizing enzymes (XMEs) in human fetal liver tissue through site-specific methylation of the Catechol-*O*-methyltransferase (*COMT*) genes and average methylation differences of the sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1 (*SULT2A1*) gene by BPA exposure level.[67] Increasing maternal levels of the sum of phthalate metabolites assessed in maternal urine were negatively correlated with placental methylation of the imprinted genes *H19* and insulin-like growth factor 2 (*IGF2*).[68] *H19* and *IGF2* form a gene cluster on human chromosome 11, and have been shown to be heavily regulated by epigenetic mechanisms (common among imprinted genes)

with *IGF2* acting as an important fetal growth factor.[69] Together, these preliminary findings suggest that EDC exposure has the potential to impact fetal and child health through variation in placental methylation, though a more thorough investigation is required.

Many metals and metalloids found in the environment, including cadmium, and mercury pose potential health hazards, and are becoming increasingly studied for their effects during gestation. In many cases, the toxic mechanisms of these exposures are unclear and epigenetic effects have become increasingly investigated as the potential pathways through which these exposures impact human health.

Cadmium exposure primarily occurs through cigarette smoke and dietary intake, with high levels found in offal meats, crustaceans, mollusks, and some leafy greens.[70,71] Cadmium is a transplacental toxic metal, accumulating in and passing through the placenta to the fetal circulation, and has been implicated as a potential cause of adverse birth outcomes, including birth weight and head circumference, although this effect may be sex specific.[72]

The epigenetic influence of this metal is now a topic of study, including work in a rat model, where prenatal exposure to cadmium altered methylation of the hepatic glucocorticoid receptor.[73] This parallels human in vitro data demonstrating an altered glucocorticoid response in human placental trophoblasts following cadmium exposure.[74] In cord blood DNA, cadmium exposure could be associated with variable DNA methylation which also demonstrated sex specificity. Correlations between exposure levels and methylation in boys were predominantly positive (96% of the top 500 CpG sites), while in girls only 29% of the top 500 correlated CpG sites showed a positive relationship. In addition, the genes showing strong correlations to cadmium levels differed between the sexes, as girls were predominantly affected in genes related to organ development, while changes in boys were in cell-death–related genes. Though the authors had previously described an inverse relationship between cadmium and birth weight in girls, this study was unable to identify specific CpG sites affecting birth weight.[75]

Mechanisms of mercury toxicity also remain enigmatic, although mercury exposure in early life is associated with adverse neurodevelopmental outcomes,[76,77] including reduced newborn cerebellum size,[78] adverse behavioral outcomes,[79] central nervous system damage,[80] poor psychomotor development,[81] and cognitive developmental delays.[82] Other effects which may not appear until later life, such as increased type II diabetes susceptibility, have also been reported.[83,84]

Mercury crosses the placenta[85,86] and interferes with placental functioning.[87] Twice the concentration of methylmercury, the predominant form of mercury exposure, has been found in placenta compared with maternal blood.[88] A common source of mercury exposure is maternal fish consumption,[89] although maternal dental amalgams with inorganic mercury[89,90] can also increase placental mercury. A single maternal amalgam restoration has been associated with a three- to sixfold increase in placental mercury.[90] There has been limited examination of mercury exposure associated with molecular features of the developing placenta, although a recent epigenome-wide study identified hypomethylation of the *EMID2* gene associated with infant mercury exposure in utero and linked the altered

methylation status of this gene to an adverse neurobehavioral profile characterized by significantly higher arousal, excitability, signs of stress or abstinence, and hypertonic motor tone, with poorer self-regulation and quality of movement compared with non–high-risk infants.[91] Although requiring replication and expansion, these preliminary studies suggest a potential epigenetic mode of mercury's toxic activity which can be considered.

Placental miRNA Expression and Environmental Exposures

Initial studies in lymphoblastoid cell lines demonstrated the potential responsiveness of miRNA expression to cellular stressors, including folate deficiency and arsenic exposure.[92] In vitro studies using placental trophoblast models identified miR-146a to be induced with exposure to BPA, and that the overexpression of this miRNA in trophoblasts led to decreases in cellular proliferation and increased sensitivity to DNA damaging agents, denoting an important potential mechanism for coexposure synergism.[93] Other studies have also demonstrated associations between miRNA expression in human cells and exposure to trace metals (reviewed in Baccarelli and Bollati[94]), including Cd,[95] As, and Pb,[96] and metal-rich particulates.[97] Although a relatively new area in environmental health research, studies focusing on miRNA hold significant potential to improve our understanding of the health effects of various environmental contaminants including the wide-ranging and long-term effects of these exposures.

Conclusion and Future Directions

There is growing interest in studies of the placenta as a mediator of the intrauterine environment, and highlighted here was only a sampling of the work considering the effects of environmental toxicants on the placental epigenome. This complements the work considering the impact of maternal nutrition and health, psychosocial factors, genetics, and drugs including pharmaceuticals, as well as the burgeoning work considering the paternal contribution to children's long-term health. Yet, it highlights the urgent need for cross-disciplinary studies that can more appropriately integrate all of these environmental factors, as none occur in a vacuum, and all, likely, in some way contribute to long-term developmental programming. The placenta and its molecular characteristics can thus potentially serve as an integrated assessment of the complicated interplay of all of these factors, and in so doing not only provided a biomarker of exposure but one of effect to better characterize the mechanisms driving DOHaD. For the long-term implications of the placental epigenome to be fully realized, long-term longitudinal studies linking the placental epigenetic landscape to children's outcomes will be needed. As more studies begin to incorporate placental collections and assessments, there will be growing opportunities to combine resources and develop highly integrated studies to tackle some of the most complicated effects of the intrauterine environment, as well as to inform potential avenues of intervention and prevention.

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Table 1

Key functions of the placenta[24]

Transport
• Nutrients, water, waste, gases
Metabolism
• Glucose, amino acids, lipids
Protection
•Export pumps, xenobiotic metabolism, glucocorticoid regulation, physical barrier, immune regulation
Endocrine
• Estrogens, growth factors, cytokines, chemokines, angiogenic factors, pregnancy hormones, neuropeptides