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Prenatal environmental exposures, epigenetics, and disease

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Abstract

This review summarizes recent evidence that prenatal exposure to diverse environmental chemicals dysregulates the fetal epigenome, with potential consequences for subsequent developmental disorders and disease manifesting in childhood, over the lifecourse, or even transgenerationally. The primordial germ cells, embryo, and fetus are highly susceptible to epigenetic dysregulation by environmental chemicals, which can thereby exert multiple adverse effects. The data reviewed here on environmental contaminants have potential implications for risk assessment although more data are needed on individual susceptibility to epigenetic alterations and their persistence before this information can be used in formal risk assessments. The findings discussed indicate that identification of environmental chemicals that dysregulate the prenatal epigenome should be a priority in health research and disease prevention.

Keywords

BPA; DNA methylation; Environmental chemicals; Environmental tobacco smoke; Epigenetics; Fetus; Polycyclic aromatic hydrocarbons; Transgenerational

1. Introduction

Following a brief summary of the role of epigenetics in early development and disease, this review focuses on the evidence that the prenatal/fetal period is highly susceptible to epigenomic dysregulation with implications for health, both lifelong and transgenerationally. We then offer examples of developmental exposure to various environmental pollutants shown to induce epigenetic changes and neurodevelopmental deficits and diseases. Interactions between toxic and environmental exposures and genetic, nutritional and social factors that can exacerbate effects are then described. Finally, two case studies are provided to illustrate the strengths and limitations of available epigenetic data and the potential of using epigenetic markers to forge causal links between toxic environmental exposures and neurodevelopmental outcomes. In this section, we summarize evidence that epigenetic alterations in endocrine and immune pathways are directly involved in the adverse neurodevelopmental effects associated with *in utero* exposure to the two classic endocrine disruptors, polycyclic aromatic hydrocarbons (PAHs) and bisphenol A (BPA).

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2. The role of epigenetics in early development and disease: the prenatal/ fetal window of susceptibility

Epigenetics is the study of heritable changes in gene expression or phenotype occurring without changes in DNA sequence [1]. For general reviews, see [2–4]. The genetic information in DNA has been likened to the notes of an orchestral score and epigenetics to the conductor who interprets the score and controls the dynamics of the symphonic performance [5]. While new epigenetic mechanisms are being uncovered, the best characterized are DNA methylation, changes in histone proteins around which DNA is packaged, and expression of non-coding RNAs (see [6–9] for review). Interactions between these epigenetic mechanisms generate diversity of cell types during development and then maintain the expression profiles of the different cell types throughout life [6]. The term "environmental epigenomics" reflects the constant interplay between the environment, which includes both endogenous (such as hormone levels or immune status) and exogenous factors (such as nutritional and chemical exposures), and the epigenome. The best characterized epigenetic events in early mammalian development are genomic imprinting (the silencing of one parental allele at a single locus, which occurs in the parental germ stem cells) resulting in monoallelic gene expression and x-chromosome inactivation (silencing of one of the two X chromosomes in mammalian females) occurring in early embryogenesis (reviewed in [6]). Dysregulation of imprinted genes during early development is involved in disorders such as Angelman's, Prader-Willi and Beckwith-Wiederman Syndromes, certain cancers, and possibly in autism and other neurological syndromes [10].

Gene expression can be regulated by epigenetic processes. Two examples include coordinated epigenetic modifications of chromatin by DNA methylation and post-translational covalent modifications of histone proteins [4,11,12] and micro-RNA-induced suppression of gene expression during development [13]. DNA methylation is the most extensively investigated of the epigenetic mechanisms and involves the addition of a methyl group at the carbon-5 position of cytosine in CpG dinucleotides. While CpG dinucleotides are underrepresented in mammalian genomes overall, and usually exist in a methylated state, proximal gene promoter regions often overlap with CpG rich regions known as "CpG islands" that are typically unmethylated. In these regions, cytosine methylation serves a regulatory function [14]. By extending into the major groove of DNA, the methyl group of 5-methylcytosine (5-mC) interferes with transcription binding proteins, inhibiting transcription, and effectively silencing the gene [7]. More importantly, DNA methylation acts as a docking site for methyl-DNA binding proteins that recruit other chromatin remodeling proteins. The importance of methylation changes at non CpG islands is now being recognized [15]. Both hypermethylation and hypomethylation of DNA can result from exposure to exogenous chemicals. For some genes, even a small change in the level of DNA methylation at a few CpG sites might subtly alter gene expression and increase disease risk [16,17].

The epigenome is susceptible to dysregulation throughout life; however, it is thought to be most vulnerable to environmental factors during embryogenesis, which is a period of rapid cell division and epigenetic remodeling [16,18]. Following a complex choreography, following fertilization, DNA methylation patterns are largely erased and established early in mammalian development (reviewed in [7,19]). Fig. 1 illustrates the normal timetable for reprogramming of methylation of non-imprinted and imprinted genes during early development, beginning with the primordial germ cells (PGCs) of each of the parents (F_0) through gametogenesis, fertilization, the embryonic period of the offspring (F_1), followed by the maintenance of methylation in somatic cells and the development of germ cells that will become F_2 [7,20,21]. These dynamic stages represent windows of potential vulnerability to epigenetic dysregulation [7]. While the maintenance of imprinted genes throughout the

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preimplantation period is essential for normal embryonic development, demethylation of other genes is needed to make the genome broadly available to the developing embryo. Thus, after fertilization and prior to implantation, the embryo undergoes genome-wide demethylation, with the exception of imprinted genes (which retain the methylation profile of the parent-of-origin) and some retrotransposable elements [16]. Beginning when the embryo is in the blastocyst stage (starting day 5 post fertilization for humans) and before implantation into the uterine wall (about 7 days post fertilization), methylation patterns in non-imprinted genes are reestablished *de novo* by the DNA methyltransferases DNMT3a and DNMT3b and their cofactor DNMT3L [20,22]. DNA methylation patterns are maintained by DNMT1, which restores full methylation to hemi-methylated CpG sites following DNA replication; this maintenance is critical for normal development [20,23].

As noted, imprinted genes do not undergo genome-wide demethylation before implantation but maintain their methylation patterns throughout this period of reprogramming, allowing for the inheritance of parental-specific monoallelic expression in somatic tissues throughout adulthood [20]. Primordial germ cells (PGC) (the precursor cells that develop into spermatogonia and oogonia) have differential methylation by parent-of-origin at imprinted genes until they enter the genital ridge, when their DNA undergoes global demethylation of both imprinted and non-imprinted genes [24,21]. Remethylation of imprinted genes occurs in a sex-specific manner during gametogenesis (the division of gametocytes into haploid sperm and oocytes by meiosis) [19,20]. Imprints are established perinatally in the male germ line and are maintained throughout the mitotic divisions of the spermatogonial stem cells [20,21,48]. In the female germline, imprints are established during oocyte growth while they are arrested during the meiotic prophase I and are erased soon thereafter in the primordial germ cells of the next generation [25,26]. It can be seen from this brief summary that, prior to complete cell differentiation and the persistence of a stable epigenetic pattern, there is an opportunity for prenatal endogenous and exogenous exposures to alter the elaborate DNA methylation patterning required for normal tissue development [18]. Imprinted genes may be a particularly susceptible target for environmentally induced epigenetic effects [27]. The early developmental period is thought to be the most susceptible to epigenetic insults because the DNA synthesis rate is high and the elaborate DNA methylation patterning and chromatin structure required for normal tissue development is established at that time [28]. However, after birth, somatic cell methylation patterns continue to adjust in response to developmental and environmental factors [2,3,29].

In 1992, Barker and colleagues laid the groundwork for the “fetal basis of adult disease” (FEBAD) hypothesis, postulating that, because organs undergo developmental programming *in utero* that predetermines subsequent physiologic and metabolic adaptation during adult life, prenatal insults such as nutritional deprivation or environmental exposures that disturbed developmental programming could lead to a higher risk of disease in adulthood. They showed that abdominal fatness in adult men, an indicator of increased risk of cardiovascular disease and diabetes independent of body mass, was associated with retarded fetal growth, suggesting a persisting response to adverse conditions in fetal life [30]. Since 1992, the evidence has grown that developmental plasticity allows the fetus to make anticipatory responses to the external environment by altering the course of cellular and organ differentiation *in utero* in order to gain adaptive advantage for later life challenges [31,32]. However, a mismatch between the prenatal and the postnatal environment or synthetic environmental agents that mimic internal or natural cues can result in disease. The FEBAD hypothesis has been supported by evidence that fetal nutrient availability, other intrauterine factors, and external environmental factors can cause serious consequences in later life by permanently reprogramming the functional capacity of organs. Classical examples include the association of low or lower birth weight with increased risk of adult

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onset cardiovascular disease [31], type 2 diabetes mellitus, osteoporosis [33], depressive disorders [34] and certain cancers [35].

There is compelling evidence that epigenetic dysregulation underlies the observed associations between adult disease and adverse environmental/nutritional conditions early in development. For example, Heijmans and colleagues reported that individuals who were periconceptionally exposed to famine during the Dutch Hunger Winter in 1944–1945 had, six decades later, significantly less DNA methylation of the imprinted insulin-like growth factor II (*IGF2*) gene compared to their unexposed same-sex siblings [36]. *IGF2* is a key factor in human growth and development and is maternally imprinted. Diseases that have been associated with early gestational exposure to famine include schizophrenia and coronary heart disease – diseases in which *IGF2* may play a role.

In addition, a series of elegant studies in mice has shown that prenatal exposure to dietary methyl-donor supplementation with folic acid, Vitamin B12, choline, and betaine not only increased DNA methylation at specific CpG sites but also altered subsequent phenotypes such as coat color and obesity in the A^{vy} mouse model (reviewed in [7]). The fact that CpG sites were altered in tissues derived from the ectodermal, endodermal, and mesodermal lineages indicates that methylation profiles were changed early in embryonic development [7,18,37].

Another often-cited illustration of the importance of methylation changes attributable to environmental factors, albeit one involving neonatal exposure, is the work of Weaver et al. [38,39] showing that maternal stress and subsequent nurturing behaviors alter the epigenotype in rodent offspring, affecting their glucocorticoid receptor (GR) expression and behavior. The epigenetic changes could be reversed in adulthood by administering methionine or histone deacetylatase (HDAC) inhibitor. These epigenetic effects are not germline inherited but are passed on to the offspring directly from the mother through her behavior during the first week of postnatal life [40,29]. In a related study, newborns of mothers who had symptoms of depression during pregnancy had increased methylation of the glucocorticoid receptor gene in umbilical cord blood cells and the infants had elevated salivary cortisol concentrations at three month of age [41].

Bagot and Meaney conclude that epigenetic remodeling can occur both during early and later stages of development in response to environmental events that regulate development and function, with increased risk for psychopathology [42]. Most studies have focused on the influence of the maternal environment and maternal-infant interactions. However, recent evidence suggests that paternal factors (nutritional, toxicological, age, and phenotypic variation) can affect offspring and in some cases grandoffspring [43].

With respect to the lifecourse, a well studied example of an exogenous *in utero* exposure affecting adult disease is diethylstilbesterol (DES), the estrogenic pharmaceutical agent. This non-genotoxic, epigenetic carcinogen induced reproductive disorders and cancers in daughters exposed *in utero* and even in their granddaughters (reviewed in [44]). DES has been shown to alter gene methylation in mice exposed *in utero* suggesting that epigenetic mechanisms are involved [45].

An indirect mechanism by which environmental toxicants may increase propensity to adult disease is through the induction of changes in gene expression in response to IUGR (see review by Joss-Moore and Lane [4,12]. Among the epigenetic environmental exposures that have been associated with IUGR are air pollution [46–50], organochlorine pesticides [51], and possibly trihalomethanes or other water disinfection byproducts [51,52]. IUGR affects organ systems by interrupting developmental processes such as apoptosis or altering levels of homeostatic regulation factors [4,12]. Epigenetic dysregulation is at least partially

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responsible for these effects, as IUGR can induce changes in gene expression accompanied by changes in levels and activities of chromatin modifying enzymes such as DNMT1 and HDAC1, global DNA hypomethylation, and increased histone H3 acetylation [53,54]. IUGR-related adult morbidities include metabolic disorders (dyslipidemia, fatty liver, obesity) and non-metabolic disorders (chronic lung disease, neurodevelopmental disorders) [4,12]. Recent studies suggest that mechanisms altering epigenetics help drive disease processes. For example, transdifferentiation processes have been implicated in diabetes [55,56].

3. Prenatal exposure to environmental pollutants, related health effects, and epigenetic dysregulation

As reviewed by Baccarelli and Bollati [57], studies in adults have demonstrated epigenetic changes related to environmental exposure to metals, air pollution, benzene and persistent organic pollutants. For example, in a study of adult coke oven workers and controls, global and IL-6 hypermethylation and *p53* hypomethylation were associated with PAH exposure [58]. In workers exposed to the leukemogen, benzene, epigenomic data showed effects of benzene on DNA methylation of a number of specific genes [59].

With respect to prenatal exposures, there is an increasing body of evidence that diverse pollutants alter epigenetic programming and disease risk in the F_1 and even F_2 and F_3 generations. These include arsenic, tobacco smoke, air pollutants, and endocrine disrupting chemicals.

3.1. Arsenic

The long-term consequences of *in utero* and early childhood arsenic exposure in human populations include increased mortality from lung cancer and bronchiectasis in young adulthood [60]. In rodent models, *in utero* arsenic exposure resulted in a sharp increase in hepatocellular carcinomas in exposed offspring and also changed the expression of genes involved in cell proliferation, stress and cell-to-cell communication. These gene expression changes were evident when the offspring reached adulthood [61].

Extending this experimental work, Fry and colleagues [61] have reported that, among 32 newborns born to arsenic-exposed and arsenic unexposed mothers in Thailand, gene expression changes in cord blood were highly predictive of *in utero* arsenic exposure. Arsenic exposure was associated with robust activation of an integrated network of pathways involving the gene *NF-κB* (nuclear factor kappa-light-chain-enhancer of activated B cells), inflammation, cell proliferation, stress, and apoptosis. This finding is biologically plausible because *NF-κB* regulates a large number of genes critical for apoptosis as well as inflammation-driven tumor progression.

Few studies have directly linked epigenetic or gene expression changes induced by arsenic to adverse health outcomes in a human population and none has examined the link between prenatal arsenic exposure, methylation, and disease. However, a population-based study of human bladder cancer found that arsenic exposure, measured as toenail arsenic, was associated with promoter methylation of the candidate tumor suppressor gene RASSF1A in human bladder tumors. These results suggest that bladder carcinogens induce epigenetic alterations important in bladder cancer causation [62]. Another study of adults in Bangladesh found that arsenic exposure was associated with increased genomic methylation of leukocyte DNA but that genomic hypomethylation of leukocyte DNA was associated with increased risk for arsenic-induced skin lesions [63]. In a nested case-control study of 274 cases who developed lesions two years after recruitment and 274 controls matched to

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cases for sex, age, and water arsenic, the odds ratio for development of skin lesions among participants with hypomethylated leukocyte DNA at recruitment was 1.8 (95% confidence intervals (CIs)).

3.2. Tobacco smoke

Prenatal exposure to active or passive maternal tobacco smoking has been associated in some studies with lower pulmonary function, increased risk of asthma [64], cancer [65,66], obesity [67,68], type II diabetes [69], and low birth weight which is associated with coronary heart disease, obesity and type II diabetes [70].

Alterations in DNA methylation patterns in genomic DNA from buccal cells of children were associated with *in utero* exposure to maternal smoking such that prenatally exposed children had significantly lower levels of global methylation as well as increased methylation of several genes compared to children without exposure [71]. Adjustment for postnatal ETS exposure did not appreciably change the results. The finding of an association between prenatal tobacco smoke exposure and global hypomethylation was observed for ALuY68 but not LINE 1, possibly reflecting their different control mechanisms and transcription patterns in response to cellular stressors [72]. In contrast, Terry et al. [73] reported that prenatal exposure to maternal tobacco smoking was associated with higher levels of global methylation in mononuclear blood cells from adult women. The inconsistencies may reflect the different assays, tissues, and age of subjects. If confirmed, the finding of global hypomethylation in children exposed prenatally to tobacco smoke is of concern since the trend of global hypomethylation with region or gene-specific hypermethylation has been observed previously in cancers [57,74]. Global hypomethylation is thought to result in chromosomal instability and increased mutational events, while promoter hypermethylation can silence expression of tumor suppressor genes [75].

In addition to the observed effects of F_0 exposure during embryonic development of the F_1 generation, environmental exposures during gestation have been shown to influence disease risk in the F_2 generation. For example, grandmaternal smoking during the mother's fetal period was associated with a greater risk of asthma in the grandchildren (F_2 generation), independent of maternal smoking [76]. Risk was further increased if both the grandmother and the mother smoked during pregnancy. Epigenetic mechanisms have been proposed for this phenomenon [76]. Another example of F_0 exposure affecting the F_2 generation is provided by experimental studies of DES and uterine cancer [77–79].

3.3. Air pollution/PAHs

Benzo[a]pyrene (BaP) and other PAHs exert both genotoxicity (inducing DNA damage, DNA adducts, and mutations) and epigenetic toxicity. Certain PAHs resemble steroid hormones and are considered endocrine disruptors. They are lipid soluble, accumulate in adipose tissue, and are transferred across the placenta and the fetal blood brain barrier (reviewed in [80,81]). In the Columbia Center for Children's Environmental Health (CCCEH) New York City (NYC) cohort, prenatal exposure to PAHs produced by burning of fossil fuel and other organic material has been associated with multiple adverse effects including fetal growth reduction [82] and IUGR [46] in African Americans, as well as developmental delay [83], reduced IQ [84], and behavioral disorders (in preparation) in both African Americans and Dominicans. In a parallel cohort study of Polish Caucasians, adverse effects were also observed on fetal growth [85], cognitive development [86], and behavioral disorders.

In a subset of the NYC cohort, prenatal PAH exposure was significantly associated with genomic hypomethylation in umbilical cord white blood cell (UCWBC) DNA. Newborns in

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the highest prenatal PAH exposure group had an average decrease of 0.42 ng/100 mg total DNA compared to newborns in the lowest prenatal PAH exposure group ($p < 0.01$) [87]. In the same 159 cohort children, the persistence of global methylation pattern was evaluated by comparing methylation measured in cord blood to methylation measured in blood collected at age 3. Global DNA methylation levels in cord and 3-year blood were significantly correlated ($r = 0.82$, $p < 0.01$), suggesting that changes in cord blood epigenetic markers due to prenatal PAH exposure may be stable alterations that persist in blood through early childhood [87].

In order to explore the association between prenatal PAH exposure, epigenetic changes and childhood asthma, methylation sensitive restriction fingerprinting was used to analyze umbilical cord white blood cell (UCWBC) DNA of 20 CCCEH cohort children [88]. Over 30 DNA sequences were identified whose methylation status was dependent on the level of maternal PAH exposure. Six of the 30 DNA sequences initially identified were found to be homologous to known genes having one or more 5′-CpG island(s) (5′-CGI). Of these, acyl-CoA synthetase long-chain family member 3 (*ACSL3*), which belongs to the acyl-CoA synthetase long chain (ACSL) family of genes which encodes key enzymes in fatty acid metabolism, exhibited the highest concordance between the extent of methylation of its 5′-CGI in UCWBCs. The level of gene expression in matched fetal placental tissues in the initial 20 cohort children. In a larger sample of 56 cohort children, hypermethylation of the *ACSL3* 5′-CGI was found to be significantly associated with maternal airborne PAH exposure exceeding 2.41 ng/m^3 (OR = 13.8; $p < 0.001$) and with a parental report of asthma symptoms in children prior to age 5 (OR = 3.9; $p < 0.05$). Hypermethylation of this gene in T helper cells or lung tissues is expected to diminish fatty acid utilization and beta-oxidation-energy production, and possibly influence membrane phospholipid composition. Thus, if validated, methylated *ACSL3* 5′ CGI in UCWBC DNA may be a surrogate endpoint for transplacental PAH exposure and/or a potential biomarker for environmentally related asthma and may provide mechanistic support for the FEBAD hypothesis.

3.4. Phthalates

The phthalates are ubiquitous industrial plasticizers and include agents such as di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP), which are classified as endocrine disruptors because of their anti-androgenic or pro-estrogenic effects [89,90]. They are used to soften polyvinyl chloride and are found in adhesives and glues, agricultural adjuvants, building materials, personal care products, medical devices, detergents, packaging, children’s toys, pharmaceuticals, food products, and textiles [91]. Exposure to phthalates can occur through diet, inhalation, or dermal exposure.

While not all studies have been consistent, prenatal exposure to phthalates has been associated with shortened gestational age [92,93] and with a number of adverse reproductive and developmental effects including decreased anogenital distance among newborn boys [90], undescended testis (exposure to a combination of phthalates and anti-androgenic pesticides) [94], and adverse neonatal neurodevelopment among girls [95]. Phthalate exposure has also been associated with elevated body mass index (BMI) during the first three years of life [96].

Phthalates are epigenetically toxic. In MCF7 breast cancer cells, treatment with BBP led to the demethylation of estrogen receptor (ER) alpha promoter-associated CpG islands, suggesting that altered ER mRNA expression by BBP might be related to aberrant DNA methylation in the promoter region of the receptor [89]. Exposure to DEHP during sexual differentiation of rats caused male reproductive tract malformations and abnormal expression of insulin-like growth factor-(IGF-1), *c-kit ligand* (KITL), and leukemia

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inhibitory factor (LIF), genes that may contribute to the reproductive toxicity of phthalates [97].

3.5. Bisphenol A (BPA)

BPA is also considered an endocrine disruptor and can accumulate in adipose tissue [98]. BPA is used in the production of plastics and resins which are used in food and drink containers, flame retardants, dental sealants, and in the recycling of thermal paper. Almost all exposure, including that to children, has been thought to occur through diet [99,100]. Recent studies, however, have suggested that non-dietary sources may be important as well [101,102]. In experimental models BPA has been associated with adverse reproductive effects in females [103] and with an increased susceptibility to cancer [104].

Developmental (neonatal) exposure of rats to BPA resulted in increased incidence of prostate intraepithelial neoplasia (PIN) when followed by prolonged estradiol and testosterone exposure in adulthood [35]. The prostate tissues showed consistent methylation changes as a result of neonatal estrogen or BPA exposures. The phosphodiesterase Type 4 variant 4 (PDE4D4) gene showed hypomethylation of the 5′CpG island, resulting in increased PDE4D4 expression in the adult prostate [105]. These findings jointly suggest that the prostate epigenome is permanently altered by early exposure to BPA and that the epigenetic alteration may lead to heightened risk of prostate cancer with aging.

4. Case studies: a proposed epigenetic mechanism for the neurodevelopmental effects of *in utero* exposure to PAHs and BPA

The prior section has reviewed the evidence that diverse prenatal environmental exposures increase risk of various diseases in the offspring and in some cases their grandchildren, that they also alter the epigenome, and that epigenetic dysregulation may mediate their adverse health effects. In contrast, in the following section we present two case studies in which we propose that epigenetic alterations in endocrine and immune pathways are directly involved in the neurodevelopmental effects associated with *in utero* exposure to PAHs and BPA. This section illustrates both the limitations of available data and the potential of using epigenetic markers to forge links in the causal chain for a particular exposure and a specific health outcome.

PAHs have been shown to be neurotoxic and affect gene expression in humans. Laboratory studies exposing experimental animals to PAHs during the prenatal and neonatal periods have reported neurodevelopmental and behavioral effects including depression-like symptoms and memory impairment in the absence of other overt toxicological effects [106–111]; others have shown that exposure affects neurotransmitter levels and gene expression patterns in the brain [80,112–114]. For example, prenatal treatment of rats with BaP impaired memory and ability to learn, consistent with alterations in the expression profile of glutamate receptor (GluR) subunits, which are key genes involved in long-term potentiation (LTP), considered the cellular correlate of learning and memory [81,111].

Many studies have shown that PAHs such as BaP are endocrine disruptors, affecting gene expression in hormonal regulatory pathways important in early brain development. Gene targets include the aryl hydrocarbon receptor (AhR) [115–117], *CYP1A1* and *CYP1B1* and *CYP19A1*; these genes are expressed in the fetal brain and peripheral lymphocytes [118–123]. In experimental studies, BaP caused alterations in levels of noradrenaline, dopamine, and serotonin and/or their metabolites in discrete brain regions [112–114]. In gestationally exposed rats, BaP caused significant reductions in expression of the N-methyl-D-aspartic acid (NMDA) glutamate receptor subunit *NMDAR2B* [81,111,124], and reduced LTP across the perforant path granular cells synapses in the hippocampus [125]. These data indicate that

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BaP and other PAHs disrupt the glutamate pathway and the dopaminergic and serotonergic systems, consistent with observed disturbances of learning and emotional behavior [113,125].

In addition, PAHs are immunotoxic contaminants known to affect expression of pro-inflammatory cytokines including interleukin-1beta, tumor necrosis factor-alpha (TNFα) IFN-γ and the chemokine CCL1 and [126,127]. Cytokines are also produced by CNS tissue and peripheral leukocytes [128]. These cytokines are among those most often implicated in neurodevelopment [129–131].

Finally, exposure to BaP upregulated *COX-2*, a key enzyme involved in inflammation and associated with reactive oxygen species (ROS) production, in rat astrocytes [132,133] in human cells and rats exposed to BaP or its main metabolite BPDE [133–136]. Residents of cities with severe air pollution had significantly higher expression of *COX-2* in the frontal cortex and hippocampus compared to controls at autopsy [137].

Fewer studies have evaluated methylation changes due to PAHs than have looked at gene regulation or expression. However, in the CCCEH cohort study described above, a number of genes in addition to *ACSL3* were found to be differentially methylated in UCWBC of newborns with high vs. low prenatal PAH exposure [88]. Several are known to be expressed in leukocytes and brain cells and have functions related to inflammatory and or immune pathways. They include *CCL17* (a chemokine also known as TARC) that selectively induces migration of Th2 lymphocytes [138], which is expressed constitutively in thymus and in phytohemagglutinin-stimulated peripheral blood mononuclear cells, and has been found to be overexpressed in autistic brains [139].

The experimental studies described above have drawn an inferential link between PAH-related epigenetic alterations and neurodevelopmental effects, suggesting that alterations in methylation/gene expression mediate the neurodevelopmental effects of PAHs. For example, the observed neurodevelopmental effects of PAHs on learning and memory in humans [83] and the observation that prenatal treatment of rats with BaP impaired their ability to learn [111] are consistent with the observed disruptions of the glutamate pathway [111].

BPA is another endocrine disrupting chemical capable of exerting developmental effects. A recent epidemiological study has linked prenatal exposure to BPA with subtle, gender-specific alterations in behavior of 2-year olds [140]. Experimental evidence indicates that gestational exposure to environmentally relevant doses of BPA abrogates sexual dimorphism in brain structure and behavior and disrupts cognition, social behaviors, and other aspects of brain function [141–143]. Perinatal exposure to BPA altered sex differences in anxiety and depression-like responses in rodents [144–148]. In addition, male mouse offspring of dams treated from mating through weaning with low dose BPA exhibited impairment in memory [149]. Hyperactivity in male mice has also been demonstrated in response to perinatal exposure to BPA (females were not examined) [150]. Importantly, these behavioral changes are induced through low dose exposures to BPA in these experimental models. BPA treatment of pregnant female mice led to disruption in neocortical patterning in offspring during adulthood, possibly by accelerating neuronal differentiation and migration [151], and caused changes in gene expression in the fetal forebrain [152].

As is the case for PAHs, most mechanistic research on BPA, an estrogen-mimicking chemical, has focused on gene expression, rather than DNA methylation. BPA has been shown to interact with estrogen signaling pathways through binding to the estrogen receptors ERα and ERβ [153–155], and is also believed to interfere with non-classical estrogen signaling pathways at very low concentrations [156–158]. Studies in mice have

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shown that perinatal exposure to BPA can disrupt estrogen signaling in the offspring, with changes in gene expression at low doses [159]. Gestational exposure to BPA caused permanent upregulation of ERβ mRNA in the preoptic area of the hypothalamus in male rat offspring [160] and increased ERα and ERβ levels in the dorsal raphe nucleus of male mouse offspring of mice [161].

Prenatal BPA exposure has also been shown to interfere with other endocrine pathways. Prenatal BPA exposure dramatically increased expression levels of AhR in mouse embryonic cerebra, cerebella, and gonads, showing a U-shaped dose–response curve with extremely high response at the lowest dose tested [162]. Prenatal exposure to BPA also interfered with thyroid hormone, required for normal fetal and neonatal brain development [163–165], and increased expression of RC3/neurogranin in the dentate gyrus brain region, suggesting that BPA differentially affects the beta-thyroid receptor (*TRβ*) vs. the alpha-TR (*TRα*) [166] and changes the temporal expression patterns of *TRα* and *TRβ* [152]. Cell-based assays suggest that BPA blocks expression of *TRβ* [167,168].

Prenatal exposure to BPA affects immune cells and the expression of genes involved in inflammation such as IL-4 and INFγ [169,170]. BPA also affects methylation of genes involved in several immune pathways. For example, gestational exposure of rats to BPA caused differential methylation of *Cebpα* [171], which is involved in macrophage differentiation, cytokine signaling, microglial activation, and neuronal signaling [172–175]. As noted above, studies by Ho et al. found that *PDE4D* (involved in macrophage differentiation, neutrophil recruitment in inflammation, responses to oxidative stress, and possibly in regulation of dopaminergic neurotransmission [176–179]) was hypomethylated in the prostates of rats treated neonatally with BPA and also showed increased expression [35]. All of the genes mentioned above are known or believed to be expressed in both the brain and the blood cells.

A number of studies have attempted to link BPA-related changes in gene expression to neurodevelopmental outcomes. *In utero* treatment of mice with BPA eliminated sex differences in the size of the anteroventral periventricular preoptic (AVPV) area, significantly reduced the number of TH (tyrosine hydroxylase) positive neurons in the female AVPV, and abrogated sex differences in the number of TH-positive neurons [143]. In the same study, BPA reduced sexual dimorphism in anxiety-related behaviors in the open-field test. Finally, BPA treatment from mating through weaning both increased levels of neurotransmitter-producing choline acetyltransferase in the hippocampus of male offspring and affected performance on the step-through test, indicating memory impairment as a consequence of BPA exposure [149].

As we have seen, genes in inflammatory/immune and endocrine pathways are targets for PAHs and BPA in the context of neurodevelopmental effects. As discussed by Tian [180], genes involved in inflammation and immune response may be common targets for diverse epigenetic environmental agents; and multiple disease endpoints may be affected. Examples include AhR, a pleiotropic ligand-activated transcription factor whose ligands include many natural and synthetic compounds (such as dioxin and PAHs) and NF-κB, a pleiotropic factor that regulates many physiological and pathophysiological processes. Interactions between AhR and NF-κB pathways are potentially important mechanisms for chemical-induced immune dysfunctions, carcinogenesis, alteration of xenobiotic/pollutant metabolism and other pathological responses induced by environmental insults.

5. Transgenerational effects of prenatal exposures

As we have seen, the role of prenatally acquired somatic epigenetic alterations in disease has been quite widely studied, mostly in experimental models. Less well characterized are

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epigenetic events that are inherited through the germline from parent to child and transmitted to subsequent generations [181].

There is growing evidence that environmental variations experienced by both fathers and mothers may lead to phenotypic variation in the development and behavior of offspring resulting from transmission through the germline [182]. Transmission can result either from altered programming within germ cells of the epigenome of the retrotransposons and imprinted genes or through altered expression of RNA within gametes. “Transgenerational epigenetic inheritance” refers to the transmission of a biological trait to subsequent generations via epigenetic modifications in the germline [7]. As elaborated by Jirtle and Skinner [7], in order to consider transgenerational effects on the epigenome to be a plausible mechanism for a disease phenotype, the epigenetic changes and the disease phenotype must be observed in the F_3 generation. This is because gestational exposure of an F_0 female directly exposes both the F_1 embryo and the F_2 germline. Therefore, phenotypes in the F_1 and F_2 generations may be due to their direct exposure to the environmental factor rather then germline transmission (see Fig. 2).

While multi-generational effects involving direct exposure have been observed for a number of agents [183], there are fewer examples of transgenerational phenotypes occurring in the absence of direct exposure. The best developed example of transgenerational effects of environmental chemicals comes from the classic experiment by Anway et al. [184,185]. These investigators exposed male rats to vinclozolin (an antiandrogenic fungicide) or methoxychlor (an estrogenic organochlorine insecticide) during the period of gonadal sex determination. Exposure resulted in reduced sperm count and viability and increased rates of infertility in adulthood. This loss of fertility was perpetuated through the male germline for four generations. Investigation of the mechanism for the transgenerational phenotype found that endocrine disruptors reprogrammed the male germline during development and induced heritable methylation changes that were stably transmitted through the male germline [186]. Another example is perinatal exposure to BPA shown at environmentally relevant doses of BPA to affect the male germ line, leading to impairment in the fertility of male offspring over three generations [187]. A study of TCDD exposure has demonstrated reduced fertility and an increased incidence of premature birth in F_1 mice exposed *in utero* to this chemical as well as in three subsequent generations [188].

6. Emerging evidence that nutritional, genetic and psychosocial factors may influence DNA methylation by environmental toxicants

Experimental animal studies have shown that the epigenetic reprogramming by behavioral factors is reversible by nutritional factors. For example, Weaver and colleagues showed that the programming of the GR exon 1 promoter associated with low grooming maternal care, as well as the resulting stress response and behavioral phenotypes, were reversible by administration of a methyl donor precursor or a histone deacetylase (HDAC) inhibitor [189]. Other investigators have shown that the effects of maternal exposure to BPA on the offspring, mediated in part by hypomethylation of DNA, are prevented by maternal dietary supplementation [28].

With respect to genetic susceptibility, as noted above, Breton and colleagues observed a significant interaction between the GSTM null genotype of the child and the prenatal exposure to tobacco smoke on global methylation in the child [71]. Foley et al. [16] have reviewed other genetic factors that directly affect DNA methylation. These include the C-to-T substitution at nucleotide 677 of the methylene tetrahydro-folate reductase (MTHFR) gene: TT homozygous individuals have lower levels of DNA methylation than CC homozygous individuals. In addition, variants of the DNMT gene family discussed earlier

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have been associated with diseases including cancer [190]. As another example, a specific variant (C > T) in the O-6-methylquanine-DNA transferase (MGMT) tumor suppressor gene has been associated with O-6-methylguanine-DNA methyltransferase promoter methylation and gene silencing. Wright [191] has reviewed the evidence that psychosocial stressors and physical environmental toxicants play a joint (synergistic) role in disrupting immune and endocrine pathways involved in respiratory and cognitive development and function. She notes that oxidative stress pathways that may influence health are disrupted by both psychological stressors and environmental pollutants such as tobacco smoke and air pollution, all of which generate reactive oxygen species. Further, by causing dysregulatory behavioral states such as depression and anxiety, psychosocial stressors may produce long-lasting effects on shared physiologic processes and thereby increase risk from pollutant exposures [192]. Wright suggests that both factors may be acting through early life reprogramming of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system which are particularly susceptible to both stress and physical environmental toxicants.

Examples of joint effects of the social and physical environment include the interaction between traffic-related air pollution (NO_2) and elevated social stress on risk for childhood asthma, whereby effects were seen only in children with both exposures [193], and the interaction between traffic related pollution and stress on increased asthma symptoms and inflammatory markers in adolescent asthmatics [194]. Another example of joint effects concerns neurodevelopment and cognition of young children in the CCCEH cohort, in which prenatal material hardship modified the response to maternal ETS exposure during pregnancy, as evidenced by reduced scores on the Bayley Scales of mental development at age 2 [195]. Because social and physical environmental toxicants tend to cluster in the most socially disadvantaged populations, understanding of these complex interdependencies may help explain and ultimately prevent health disparities [196]. Both animal and human studies have also shown that environmental enrichment can reverse the effects of early stress [196].

7. Implications for prevention of childhood, adult and multigenerational disease: conclusions

Most of the research to date has focused on the critical role of epigenetics in mediating the effects of social experience and nutrition [197,198]. However, there is also compelling human and experimental evidence that prenatal environmental exposures to endocrine disruptors and other environmental xenobiotics, acting alone or in combination with genetic, nutritional, or psychosocial factors, adversely affect human development and health in childhood and possibly over the lifecourse, and that a primary mechanism is epigenetic dysregulation. Because epigenetics programming determines the state of expression of genes, epigenetic differences could have the same consequences as genetic polymorphisms [197]. Moreover, there is experimental evidence that exposures during the prenatal window can influence disease risk transgenerationally through epimutations in the germline. The research reviewed here has potential implications for risk assessment; although more data are needed on individual susceptibility to epigenetic alterations and their persistence before this information can be used in formal risk assessments.

Reviewers have tended to emphasize the potential reversibility of epigenetic dysregulation and related phenotypes as encouragement for pharmacological and cognitive-intervention [7,199]. Often cited in this regard are studies with animal models showing that supplementation with folic acid during pregnancy or after weaning alters the phenotype and epigenotype induced by maternal dietary deficiency during gestation [200]. A cautionary note is that pharmacologic or dietary interventions would require a gene-specific approach based on a complete understanding of the epigenetic events involved in fetal adaptation to

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adverse or suboptional conditions [201]. Global epigenetic modifying agents such as histone deacetylase inhibitors would pose potential risks by modifying epigenetics of multiple genes, with unpredictable consequences. However, the data strongly encourage preventive policies to reduce early life exposure to epigenetically toxic agents as a priority in public health. Such policies could have both immediate and long-term benefits for human health by preventing disease and developmental disorders in childhood, over the lifecourse, and even in future generations [202].

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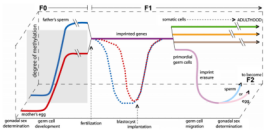

Fig. 1.

There are multiple periods during which environmental exposures could affect the F_1 individual's methylation status, potentially affecting the F_1 phenotype. The first window is during F_0 (parental) germ cell development when methylation is reprogrammed following imprint erasure in the father's sperm (solid blue line) and the mother's egg (solid red line) The second window is post-conception, during F_1 embryonic development, when all but imprinted genes are demethylated, with the male germ line (dashed blue line) demethylating more quickly, followed by the female germ line (dashed red line). Imprinted genes (purple line) maintain their methylation marks throughout this reprogramming, allowing for the inheritance of parental-specific monoallelic expression in somatic tissues throughout adulthood [203]. All of the non-imprinted genes are subsequently remethylated once the embryo reaches the early blastocyst stage. During the gonadal sex determination of the F_1 embryo, primordial germ cells undergo epigenetic reprogramming, where parental imprinting is erased, as the germ cells of the F_1 individual mature (solid light blue or pink line). To determine whether epigenetic alterations are transmitted transgenerationally, the F_3 generation must be studied (see text and Fig. 2) [7]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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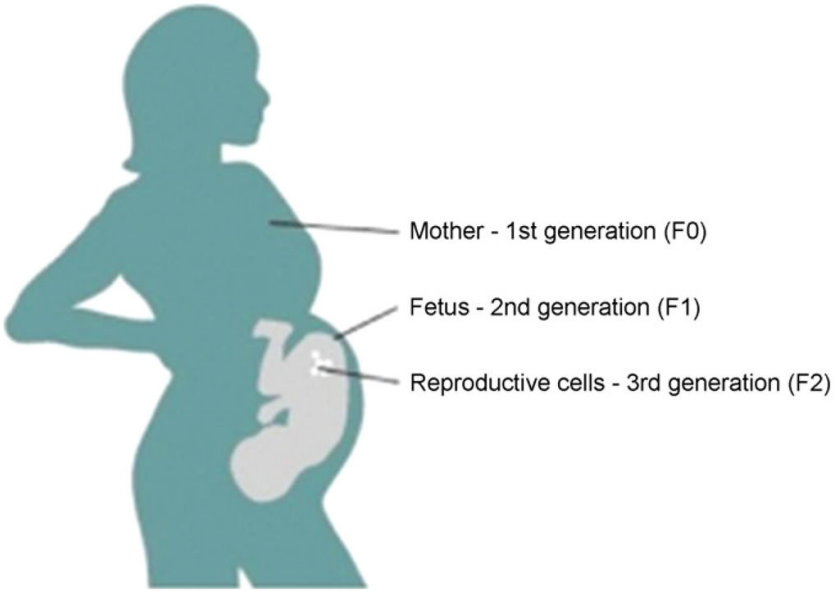

Fig. 2.
Three generations at once are exposed to the some environmental conditions (diet, toxics, hormones, etc.). In order to provide a convincing case for epigenetic inheritance, an epigenetic change must be observed in the 4th generation.