ENVIRONMENTAL EPIGENETICS

REVIEW ARTICLE

Epigenetic alterations induced by environmental stress associated with metabolic and neurodevelopmental disorders

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Abstract

Epigenetics is a gene regulation mechanism that does not depend on genomic DNA sequences but depends on chemical modification of genomic DNA and histone proteins around which DNA is wrapped. The failure of epigenetic mechanisms is known to cause various congenital disorders. It is also known that the failures of epigenetic mechanisms causes various acquired disorders since epigenetic modifications of the genome (i.e., "epigenome") are more vulnerable to environmental stress, such as malnutrition, environmental chemicals, and mental stress, than the "genome," especially during the early period of life. However, the epigenome has a reversible property since it is based on removable residues on genomic DNA. Thus, environmentally induced epigenomic alterations can be potentially restored. In fact, some medicines, especially for psychiatric diseases, are known to restore an altered epigenome, resulting in the correction of gene expression. Several lines of evidence suggest that environmentally induced epigenomic alterations are not erased completely during gametogenesis, but are transmitted to subsequent generations with disease phenotypes. In accordance with these understandings, I would like to propose the development of epigenomic-based preemptive medicine that consists of the early detection of the developmental origins of diseases using epigenomic signatures and the early intervention that take advantages of the use of epigenomic reversibility.

Key words: neurodevelopmental disorder; metabolic disorder; environmental stress; epigenetics: epigenome; preemptive medicine

Introduction

Diabetes mellitus (DM) comprises a group of heterogeneous metabolic disorders that share an increase in the concentration of blood glucose. Both environmental and genetic factors are thought to contribute to the occurrence of DM. A number of studies have demonstrated that various environmental factors including overeating, passive smoking in those who are not themselves active smokers, and ambient air pollution such as by $PM_{2.5}$ induce systemic insulin resistance as a predisposition to type 2 DM (T2DM) [1, 2].

As for genetic factors associated with DM, including maturity onset diabetes of the young (MODY), several causative

genes have been identified and >75 genetic variants. However, mutations in genes associated with MODY are rare and whether the identified common variants are causal and how these genetic variants exert their effect on the pathogenesis of T2DM is largely unknown [3, 4].

Several lines of evidence suggest that epigenetic alterations induced by environmental factors (e.g. nutritional factors and mental stress) during the fetal and neonatal periods are underlying mechanisms of the predisposition to T2DM [5–9].

A number of environmental factors are also known to be involved in the pathogenesis of neurodevelopmental disorders (NDs), such as inappropriate child rearing (e.g. child abuse and malnutrition by the parents with mental problems) [10–13], viral infections with rubella and cytomegalovirus, which induce immunological reactions in the brain [14–19], and environmental chemicals such as endocrine-disrupting chemicals e.g. tobacco, air pollutants, solvents, metals, pesticides, flame retardants, non-stick chemicals, phthalates, and bisphenol A (BPA) [20].

As for genetic factors associated with NDs, causative genes associated with brain function have been identified. Mutations in genes encoding secreted proteins (e.g. *RELN*), cell adhesion molecules (e.g. *NLGN3* and *NLGN4*), receptors and transporters (e.g. *GRIN2A*), synaptic scaffolding proteins (e.g. *SHANK3* and *LIN7B*), and actin cytoskeleton dynamics (e.g. *TSC1* and *TSC2*) [21–27]. These findings suggest that NDs can be recognized as "synaptic disorders" [21, 28] (Fig. 1).

Unexpectedly, mutations have also been identified in chromatin-remodeling factors that are apparently not involved directly in brain function. These include methylated CpG-binding proteins [e.g. *MEPC2* associated with Rett syndrome (RTT)], DNA methyltransferases (e.g. *DNMT3A* associated with intellectual disability with overgrowth), histone methyltransferase (e.g. *EHMT1* associated with Kleefstra syndrome), and chromatin remodeling proteins (chromodomain helicases) (e.g. *CHD8* associated with an autistic disorder) [29–33]. These findings suggest

that NDs can also be recognized as "chromatin (a unit of DNA and histone proteins that are chemically modified) disorders" [24–35] (Fig. 1).

Recent studies revealed that ASC2 (a protein involved in cortical neuronal migration and neurogenesis), which is associated with a subtype of NDs binds to Polycomb repressive complex 1 (a chromatin remodeling protein) and controls the expression of genes (e.g. neurocan) involved in axon guidance in the developing forebrain [36–40], suggesting that a close interaction between neuronal molecules and chromatin molecules is essential for brain development and failure of this interaction leads to misregulation of brain development-associated genes, resulting in NDs.

In this review, I introduce various congenital disorders caused by epigenetic misregulation and disorders caused by acquired epigenetic misregulation and discuss epigenomic-based preemptive medicine taking advantage of the use of the epigenetic reversibility for patients with metabolic and NDs and for future generations in terms of transgenerational epigenetic inheritance.

Congenital Disorders Caused by Epigenetic Misregulation

RTT is a representative ND characterized by repetitive and stereotypic hand movements, seizures, gait ataxia, and autistic features, which is caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2) [29]. Since RTT is an X-linked dominant disorder, the affected patients are females. In males, the disorder is thought be embryonic lethal, although in rare cases, male RTT patients have been reported [41].

The MeCP2 protein binds methylated DNA regions and controls the expression of a number of genes including synapse-associated genes such as *BDNF, DLX5, ID, CRH, IGFBP3, CDKL1, PCDHB1,* and *PCDH7* by interacting with histone deacetylases in
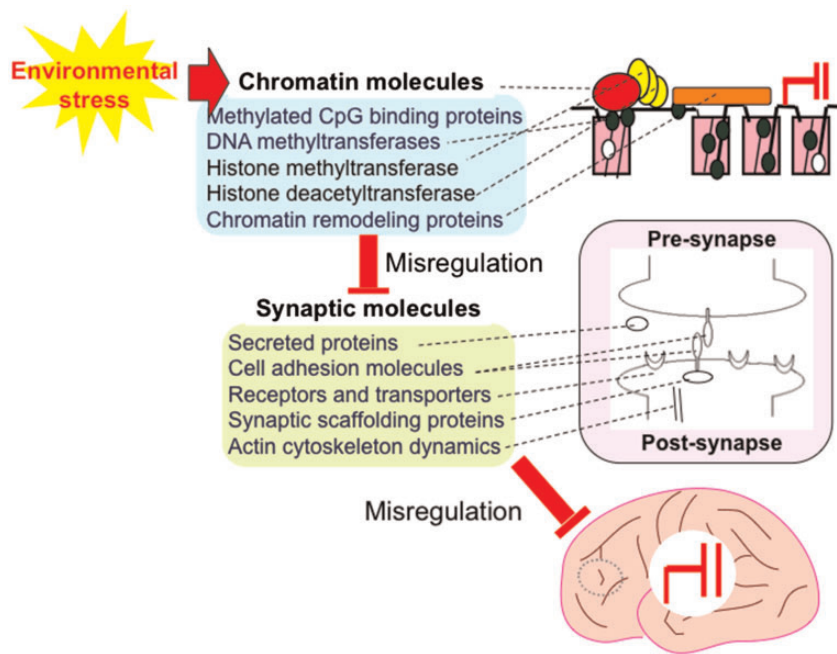

Figure 1: Mutations in the genes encoding proteins associated with synaptic function are found in a subset of patients with NDs. Mutations in the genes encoding chromatin-associated proteins are found in a subset of patients with NDs via misregulation of synapse-associated genes. Various types of environmental stress affect the function of chromatin-associated genes. All of these genetic alterations and epigenetic misregulation by environmental stresses lead to the misregulation of brain function

neuronal cells and brain tissue [42–52], resulting in the regulation of excitatory synaptic strength [53] (Fig. 1).

Instead of studying the inaccessible brain cells of RTT patients during development, neural cells can be generated by using induced pluripotent stem cell (iPSC) technology. Several iPSC studies demonstrated that RTT neurons have abnormalities in maturation [54–56] and differentiation, in which a subset of glia cell-specific genes, such as *GFAP*, are aberrantly expressed due to de-suppression because of a deficiency of MeCP2 [57] (Fig. 2).

The brain is a gene-dosage-sensitive organ in which either under-expression due to mutation or deletion of a gene or over-expression due to duplication of the same gene results in neurological abnormalities. The effects of aberrant gene expression are exemplified by conditions such as Pelizaeus–Merzbacher disease, a severe congenital myelination disorder associated with deletion, mutation, or duplication of *PLP1* [58], lissencephaly, a severe congenital neural migration disorder associated with either deletion or duplication of *LIS1* (*PAFAH1B1*) [59, 60], Charcot–Marie–Tooth disease, an adult-onset neuromuscular disease associated with mutation or duplication of *PMP22* [61], and Parkinson's disease associated with either mutation or multiplication of *SNCA* [62].

Similarly, not only mutations in *MECP2* but also duplication of *MECP2* cause severe mental retardation especially in males [63] and cognitive impairment with learning difficulties and speech delay in females [64]. The over-dosage effect of *Mecp2* has been found in transgenic mice and monkeys that show motor coordination deficits, heightened anxiety, and impairments of learning and memory. These animals also exhibit various behavioral problems such as a higher frequency of repetitive circular locomotion, increased stress responses, stereotypic cognitive behaviors, and reduced interactions with other animals [65, 66].

These findings results from genetic and epigenetic studies suggest that the brain is extremely sensitive to the dosage of proteins associated with synaptic or neuronal function, such as BDNF and LIS1, and is also sensitive to the dosage of proteins associated with chromatin structure or epigenetic gene regulation such as MeCP2, and further indicate that the brain is an organ that requires strict gene control to maintain the corrected levels of proteins associated with brain function.

ICF syndrome, which is characterized by Immunodeficiency (e.g., IgG and IgA), Centromere instability (breakage of the pericentric heterochromatic regions of chromosomes 1, 9, and 16 due to abnormally low levels of DNA methylation), and Facial anomalies, is a congenital autosomal recessive disorder caused by mutations in the DNA methyltransferase gene, DNMT3B, which lead to de-suppression due to hypomethylation of genes [67, 68] (Fig. 2). A recent study demonstrated a hypomethylation pattern in mesenchymal stem cells differentiated from iPSCs of ICF patients, which is potentially associated with immunological pathogenesis [69].

Prader–Willi syndrome (PWS) is a congenital epigenetic disorder characterized by muscle hypotonia during infancy, cryptorchidism (in boys), short stature, small hands and feet, hyperphagia starting from childhood and subsequent obesity and T2DM in adulthood, and various neurodevelopmental features such as obsessive–compulsive disorder. PWS is not caused by abnormalities in a single epigenetic molecule, but is caused by an abnormal epigenomic pattern in which the expressed paternal genes, located on chromosome 15q12, are missing physically or functionally due to paternal deletion or uniparental maternal disomy, respectively [70–73]; PWS patients have only maternally inherited genes on chromosome 15q12 that are imprinted (methylated) and are thus not expressed (Fig. 2).

Angelman syndrome, characterized by severe intellectual disability and intractable epilepsy with puppet-like ataxic movements and paroxysms of laughter, is another epigenetic disorder caused by an abnormal epigenomic pattern in which the expressed maternal allele of *UBE3A*, located on chromosome 15q12, is missing physically or functionally due to maternal deletion or uniparental paternal disomy, respectively [74]. Conversely, over-dosage of the expressed genes located on the maternal chromosome due to chromosomal duplication or triplication causes autistic-like features [75]. Is interesting to note that assisted reproductive technologies (e.g. *in vitro* fertilization and intracytoplasmic sperm injection), which are used widely due to increases in age at the time of conception of the first child, alter DNA methylation status at loci and are potentially involved in an increased risk of Beckwith–Wiedemann syndrome, a congenital epigenetic disorder characterized by overgrowth in the fetal period with an increased risk of childhood cancer [76, 77].
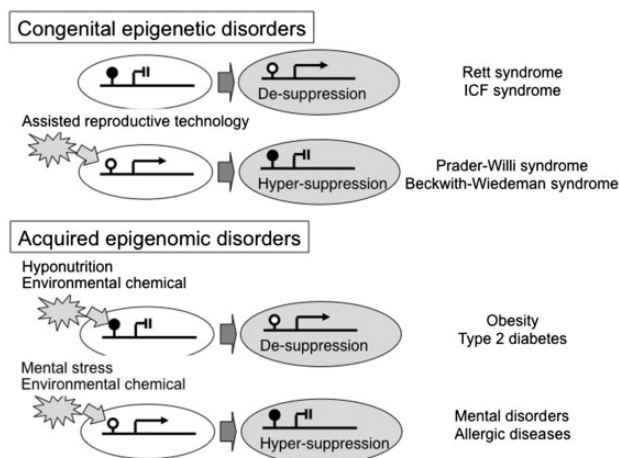

Figure 2: Epigenetic misregulation in congenital epigenetic disorders and acquired epigenetic disorders. (**A**) Abnormalities in a methylated CpG binding protein or a DNA methyltransferase result in Rett syndrome or ICF syndrome, respectively. An aberrant genomic pattern due to failure of genomic imprinting results in Prader-Willi syndrome. (**B**) Environmental factors alter epigenomic status, resulting in predispositions to various common disorders

Acquired Disorders Caused by Epigenetic Misregulation

In the concept of gene–environment interactions for common diseases including metabolic and NDs, the combination of heritability (G: genetic factor such as a single nucleotide polymorphism) and experience (E: environmental factor), that is, the "G × E" model, has been used where G and E contribute independently to disease occurrence. I would like to propose an "E × G" model, in which E changes G dynamically, where G is not a genomic DNA sequence (i.e. the genome) but genomic DNA and histone protein modifications (i.e. the epigenome) [78]. I would like to show examples that underlie this new model, in which environmental factors alter the epigenome of individuals, changing their health status.

Epidemiological studies of populations affected by famines in the Netherlands and China demonstrated that the generation with a lower birth weight than normal had an increased risk for

obesity, DM, and mental disorders [79, 80]. These studies suggested that the number of patients with DM and an ND might increased in Japan because the rate of low birth weight infants has increased over the past 30 years due to the increase of young women who diet even while pregnant and the directions of obstetricians to minimize pregnancy weight gain to avoid a hard labor and reduce the risk of gestational DM [79]. Furthermore, recent epigenetic studies demonstrated that malnutrition with insufficient folic acid intake during pregnancy induced lower DNA methylation in genes (e.g. *PPARα*) in the liver of rat offspring [5, 6]. Similar low levels of DNA methylation were observed in the peripheral blood of individuals who lived through the Dutch famine [81]. Conversely, periconceptional micronutrient supplementation, including folate, zinc, and vitamins A, B, C, and D, increased DNA methylation levels in human offspring [82]. This kind of scientific study to clarify the mechanism of the occurrence of "adult diseases" during the early period of life for early intervention is referred to as "Developmental Origins of Heath and Disease" [83].

In addition to malnutrition, a number of environmental chemicals have been shown to alter the epigenome. For example, prenatal exposure to BPA, a chemical with reproductive toxicity that induces growth alterations and immune dysregulation, alters DNA methylation in fetal brain and in mast cells and liver of offspring [84–86]; prenatal exposure to polybrominated diphenyl ethers, which are used as flame retardants, decreases DNA methylation of *TNFα* and increases TNFα (a proinflammatory molecule) expression in cord blood [87]; prenatal exposure to tobacco smoking alters DNA methylation of *AHRR*, *MYO1G*, *CYP1A1*, and *CNTNAP2* in cord blood; and these altered DNA methylation patterns were observed in the peripheral blood of their children born to smoking mothers at the age of 17 years and may be associated with diseases, such as bronchial asthma [88]. These findings suggest that DNA methylation is changeable during the early periods of life, and these changes can persist for a long period after birth and can be associated with disease phenotypes.

Similar to patients with DM, the number of children with NDs has increased in England [89] (prevalence from 1/2,500 to 1/86) and other countries over the last 50 years. The rate of affected children has reached 100 (range, 34–264) per 10 000 children [90–94]. For these increases, twin studies have implicated the influence of environmental factors in the development of NDs [95–97].

The epigenome, characterized by epigenetic mechanisms, acts as a "physical receptor" for environmental stresses. In fact, epigenomic differences are more markedly different in older monozygotic twins than in younger monozygotic twins [98], and differential epigenomic patterns have been observed between discordant monozygotic twins with RTT, a representative ND as mentioned above, in which abnormal epigenomic patterns that lead to aberrant synaptic gene expression were observed in the RTT twin with the more severe phenotype [99]. A previous rat study demonstrated that exposure to short-term postnatal stress by separating offspring from their mother induced hypermethylation within the promoter region of *NR3C1*, which encodes a glucocorticoid receptor hormone associated with resilience, in the hippocampal region of the offspring, which leads to life-long abnormal behavior [7]. Furthermore, recent human studies also demonstrated that ice storm stress in 1998 in Quebec during pregnancy altered DNA methylation of immunological genes in the peripheral blood of the offspring [100], and severe maternal stress that causes depression during pregnancy alters DNA methylation in imprinted *IGF2* and

GNASXL in cord blood [101] and in *NR3C1* and *BDNF* in the buccal mucosa of 2-month-old infants [102, 103].

All of these findings indicate that the epigenome is vulnerable to environmental stress during the early period of life, environmental stress-induced epigenomic alterations can alter or modify phenotypes, and the recent increase of ND patients may be caused by epigenomic alterations induced by environmental and social stress to children and/or mothers.

Epigenomic-Based Preemptive Medicine

For adult-onset diseases, physicians make a diagnosis based on the guidelines established for each disease. In these cases, diagnosis is made at a later stage of development after the patient fulfills the criteria for each adult disease (e.g. blood sugar and HbA1c levels for T2DM). Furthermore, gold standard therapeutic protocols are strictly determined in the guidelines, regardless of a patient's individual genetic background, which may influence the effectiveness of the administered drugs. In this context, "personalized medicine" has been proposed as the application of treatments that take into consideration each patient's genetic background.

"Preemptive medicine" is a type of personalized medicine that is based on the individual and is thus different from population-based preventive medicine that started as a means to prevent the spread of infectious diseases (it is now moving toward the prevention of adults diseases). In preemptive medicine, a practical approach is to detect high-risk individuals by screening with a blood biomarker, which includes genetic and epigenetic information, and to intervene in high-risk individuals at the preclinical stage to prevent serious events, such as T2DM, Alzheimer's disease, osteoporosis, and coronary heart disease [104].

Such a preemptive approach based on an epigenomic marker has already been started for PWS, one of the congenital epigenetic disorders mentioned above. High-risk individuals (i.e. PWS patients) are identified by an abnormal pattern of *SNRPN* promoter methylation in peripheral blood during infancy, and a variety of physical and drug treatments are provided to the individuals to prevent future symptoms (e.g. obesity and T2DM).

For example, a program of a well-balanced low-calorie diet and regular exercise is applied to prevent weight gain by hyperphagia and the subsequent development of obesity, which begins at 2–4 years of age [105]. Physical therapy for patients younger than 3 years of age improves muscle strength and encourages the achievement of developmental milestones, and daily muscle training increases physical activity and lean body mass in older patients [106]. Growth hormone treatment normalizes height, increases lean body mass, decreases fat mass, and increases mobility, which are beneficial to weight management [107]; a longitudinal study demonstrated that growth hormone treatment normalized stature and improved weight and body composition in PWS patients compared to non-growth hormone-treated PWS patients [108, 109]. Furthermore, a recent randomized controlled trial revealed that physical training combined with growth hormone further improved muscle thickness, which was matched by an increase in muscle strength and motor development in infants with PWS [110]. Growth hormone treatment further improves language skills in infancy, cognitive skills in childhood, and mental speed, mental flexibility, motor performance and ability to adapt to society in adulthood [111–115]. Therefore, epigenomic-based preemptive

medicine is effective for patients with PWS although the number of PWS patients is limited.

In order to establish a preemptive program for acquired disorders similar to that for PWS, it will be necessary to identify "epigenomic signatures" that are modified by environmental factors and can be detected in peripheral blood. In fact, mental stress-induced hypermethylation of the brain-derived neurotrophic factor (*Bdnf*) gene was demonstrated in the hippocampal region of a mouse model of depression [116]. Subsequently, abnormal DNA methylation of *BDNF* was proposed as an epigenomic blood marker for the individuals with major depression [117]. Abnormal DNA methylation of *FHL2*, *ZNF518B*, *GNPNAT1*, and *HLTF* was also proposed as an epigenomic blood marker for individuals with T2DM [118]. Furthermore, it was demonstrated recently that exposure to BPA during the prenatal period induced lasting DNA methylation changes in *Bdnf* in the hippocampus and blood in mice, and that exposure to high levels of BPA *in utero* induced DNA methylation changes in human cord blood [119]. These findings suggest that methylation in the blood may be used as a predictor of methylation in the brain and indicate that DNA methylation in the peripheral blood can be a useful biomarker for the detection of psychopathology.

It was reported recently that epigenomic restoration of histone acetylation can be achieved by the administration of psychotropic drugs, such as valproic acid and imipramine [116, 120, 121]. A recent epidemiological study further demonstrated that supplementation of folic acid during pregnancy, which is an important nutrient for DNA methylation, reduced the risk of NDs in the offspring [122]. Studies using RTT or *Mecp2*-duplication mouse models have demonstrated that genetic supplementation of MeCP2, bone marrow transplantation, antisense oligonucleotides, or deep brain electrical stimulation after birth successfully attenuates neurological symptoms [123–126]. These findings support the notion that the phenotypes of NDs caused by epigenetic dysregulation are reversible and thus treatable. In this context, drugs are under development by many pharmacological companies taking advantage of the use of epigenomic reversibility.

Studies using mouse models also suggest that the clinical features of a congenital epigenomic disorder can be ameliorated not only by the administration of "ultimately designed" epigenomic drugs but also by providing a better nurturing environment. For example, environmental enrichment with larger-sized home cages containing a variety of objects including running wheels, improved motor coordination with a slight increase in BDNF protein levels in the cerebellum, rescued memory deficits in the Morris water maze, and decreased anxiety-related behavior in RTT model (heterozygous $Mecp2^{+/-}$) female mice [127, 128]. Similarly, environmental enrichment improved locomotor activity with reduced ventricular volume and decreased the expression of synaptic markers, such as synaptophysin and PSD95 in the hypothalamus and syntaxin 1a and synaptotagmin [129, 130]. The precise molecular mechanism underlying the environmental enrichment effect remains to be elucidated, but it is intriguing to think that the epigenomic status of MeCP2-target synaptic genes may be restored by environmental enrichment.

Conclusions

In this article, I introduced congenital disorders with epigenetic abnormalities caused by genetic alterations such as RTT and PWS and acquired disorders with environmentally induced epigenomic abnormalities. Furthermore, I discussed the concept of epigenomic-based preemptive medicine, taking advantage of the use of epigenomic reversibility.

Several lines of evidence suggest that environmental stress that alters a phenotype affect not only the exposed individual but also subsequent progeny for successive generations. In other words, ancestral experiences could influence subsequent generations, the concept of which is termed "transgenerational inheritance." Furthermore, environmental factors such as endocrine-disrupting chemicals and nutrition do not promote genetic mutations but instead promote epigenetic changes; the permanent programming of an altered epigenome in the germline can allow for the transmission of transgenerational epigenetic phenotypic variations and subsequent disease risk [131, 132].

The evidence supports the theory of Lamarckian inheritance in which an organism can pass on phenotypes that it acquired during its lifetime to its offspring. More precisely, a hypothesis has emerged that environmental stress results in epigenetic changes at some loci in the genome and these can escape the epigenetic reprogramming that normally occurs between generations [133, 134].

Short-term postnatal mental stress by separating offspring from their mother alters DNA methylation not only in the brain but also in the sperm of male offspring, and then, the environmentally induced epigenetic and expression alterations of *Crfr2* are transmitted up to the third generation (F1 sperm and F2 brain) along with behavioral abnormalities [135]. Furthermore, exposure to prenatal stress induces changes in DNA methylation and micro-RNA expression in the placenta and brain, which leads to an increase in risk for NDs, schizophrenia, and anxiety- or depression-related disorders later in life [136].

Exposure to an environmental chemical (e.g. vinclozolin) during embryonic gonadal sex determination can alter male germ-line epigenetics, and the alteration of DNA methylation in the germ line appears to result in the transmission of transgenerational adult-onset diseases, such as spermatogenic defects, prostate and kidney diseases, and cancer [137]. A recent study demonstrated that exposure to BPA in early life induces glucose intolerance and β-cell dysfunction, with hypermethylation and associated decreased expression of Igf2 in the islets of male F2 offspring; this suggests that exposure to BPA during early life can result in the generational transmission of glucose intolerance and β-cell dysfunction through the male germ line by an epigenetic mechanism [138].

However, evidence that such effects persist in subsequent generations has been inconclusive [133, 139, 140]. These effects must be observed in the F3 generation to be considered transgenerational because the *in utero* nature of the ancestral perturbation affects not only the somatic and germ cells of the developing F1 fetus but also the germ cells of the F2 generation [132]. In this context, a recent study demonstrated that !treatment of pregnant mice with methoxychlor altered the methylation of all genes examined in the F1 offspring, but these effects disappeared gradually from F1 to F3 [141]. This suggests that transgenerational epigenetic inheritance is not "solid (complete)" genetic inheritance but "soft (incomplete)" epigenomic inheritance [142, 143]. Nevertheless, epigenomic-based preemptive medicine will be important not only for the exposed first generation but also for subsequent successive generations in terms of disrupting the vertical transmission of epigenomic disorders.

Acknowledgments

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