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Themed Issue: Role of Epigenetics in Mediating Programming Effects.

REVIEW

Understanding the epigenetics of neurodevelopmental disorders and DOHaD

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The Developmental Origins of Health and Disease (DOHaD) hypothesis refers to the concept that 'malnutrition during the fetal period induces a nature of thrift in fetuses, such that they have a higher change of developing non-communicable diseases, such as obesity and diabetes, if they grow up in the current well-fed society.' Epigenetics is a chemical change in DNA and histones that affects how genes are expressed without alterations of DNA sequences. Several lines of evidence suggest that malnutrition during the fetal period alters the epigenetic expression status of metabolic genes in the fetus and that this altered expression can persist, and possibly lead to metabolic disorders. Similarly, mental stress during the neonatal period can alter the epigenetic expression status of neuronal genes in neonates. Moreover, such environmental, stress-induced, epigenetic changes are transmitted to the next generation via an acquired epigenetic status in sperm. The advantage of epigenetic modifications over changes in genetic sequences is their potential reversibility; thus, epigenetic alterations are potentially reversed with gene expression. Therefore, we potentially establish 'preemptive medicine,' that, in combination with early detection of abnormal epigenetic status and early administration of epigenetic-restoring drugs may prevent the development of disorders associated with the DOHaD.

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Introduction

The brain is the organ that is sensitive to abnormal expression of neurological genes. Either underexpression or overexpression of the same genes encoding proteins related to brain function results in a range of neurological disorders. For example, Pelizaeus–Merzbacher disease, a severe congenital disease is caused by either a deletion, mutation or duplication of the proteolipid protein 1 gene (*PLP1*);[1] lissencephaly, a rare brain formation disorder, is caused by either deletion or duplication of the platelet-activating factor acetylhydrolase 1B subunit alpha gene (*PAFAH1B1*) that encodes a neuronal migration factor;[2,3] Charcot–Marie–Tooth disease, an adult-onset neuromuscular disease is caused by a mutation or duplication of the peripheral myelin protein 22 gene (*PMP22*);[4] and Parkinson's disease is caused by a mutation or multiplication of the α-synuclein gene (*snca*).[5] Because these are all neurological disorders and such examples have not been observed in other clinical fields, the brain is thought to be extremely sensitive to perturbations in gene regulation. In other words, the brain is an organ that requires a proper control system for gene expression. Epigenetic mechanisms are one of the ways by which gene expression is controlled in higher vertebrates.

The term 'epigenetics' was originally used to describe 'the causal interactions between genes and their products, which bring the phenotype into being.'[6] This definition initially referred to the role of epigenetics in embryonic development, in which cells develop distinct identities despite having the same genetic information. However, the concept of epigenetics has changed to refer to 'the heritable changes in gene expression that occur independent of changes in the primary DNA sequence during DNA replication at the step of cell division,'[7] and is known to be associated with a wide variety of biological processes, such as genomic imprinting,[8–13] inactivation of the X chromosome,[14,15] embryogenesis[16] and tissue differentiation.[17] It is known that abnormalities in these biological processes cause a subset of congenital neurodevelopmental disorders; therefore, understanding epigenetic mechanisms, based on DNA methylation and histone modifications, is important for elucidating the pathogenic pathways involved in congenital neurodevelopmental disorders.[8–14]

It is thought that epigenetic modifications are more susceptible to environmental stresses, such as malnutrition and mental stress,[18–20] than are nucleotide sequences, and that epigenetics is one of the underlying mechanisms proposed by the Developmental Origins of Health and Disease (DOHaD) hypothesis,[18,19] in which epigenetic changes induced by various environmental factors during fetal and neonatal periods can cause alterations of epigenetic patterns.

Based on these findings, we introduce possible epigenetic mechanisms associated with congenital neurodevelopmental disorders, acquired neurodevelopmental disorders induced by environmental factors, epigenetic treatments that take

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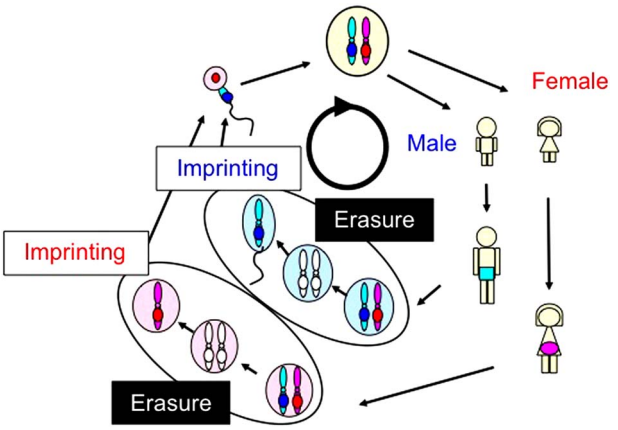

Fig. 1. Erasure and establishment of genomic imprinting. Inherited maternal and paternal imprints are erased and new imprinting is established according to the individual's sex during the processes of spermatogenesis and oogenesis.

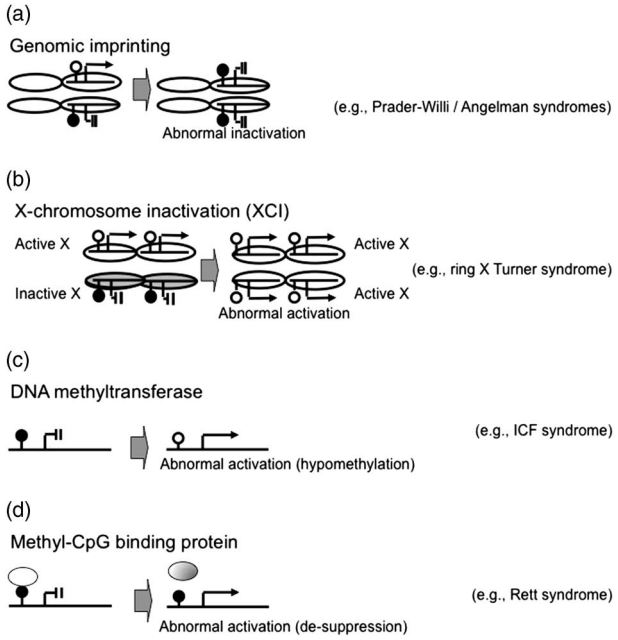

Fig. 2. Neurodevelopmental disorders caused by epigenetic abnormalities. (a) Abnormal suppression of the active allele of imprinted genes causes genomic imprinting disorders. (b) Abnormal activation of the inactive X chromosome in females causes X-chromosome inactivation disorders. (c) Mutations in genes encoding a DNA methyltransferase produces a deficiency resulting in insufficient DNA methylation, which in turn leads to aberrant expression of the target genes. (d) Mutations in genes encoding methyl-CpG binding proteins causes abnormal regulation of the target genes.

advantage of their reversibility and the significance of transgenerational epigenetic inheritance.

Epigenetic mechanisms associated with congenital neurodevelopmental disorders

Genomic imprinting is an epigenetic phenomenon initially discovered in mammals that results in monoallelic gene expression. The inherited maternal and paternal imprints are erased in the germ line and a new imprinting pattern is established in a parent-of origin-specific manner according to the sex of the individual (Fig. 1). This phenomenon underlies a subset of neurodevelopmental disorders, such as Prader–Willi syndrome (PWS), Angelman syndrome (AS) and Beckwith–Wiedemann syndromes (BWS).[8–13] PWS, characterized by hypotonia in infancy, hyperphagia, obesity and mental retardation, is caused by either paternal chromosome 15q11-q13 deletion or uniparental maternal disomy (Fig. 2a). All these genetic abnormalities lead to loss of function of multiple paternally expressed imprinted genes within the 15q11-q13 region.[8–9] Conversely, AS, characterized by intractable epilepsy, severe mental retardation and an inappropriate happy demeanor such as frequent laughing, is caused by either maternal 15q11-q13 deletion, uniparental paternal disomy or *UBE3A* mutation. All these genetic abnormalities lead to loss of function of the maternally expressed imprinted *UBE3A* within the 15q11-q13 region.[9] A recent study has demonstrated that PWS is caused by defect in the SNORD116 cluster of small nucleolar RNA genes within the paternal 15q11-q13 region, indicating that the cluster region is the smallest critical region for PWS.[10] Another recent study has shown that AS is associated with unbalanced expression between the maternally expressed *UBE3A* transcript and the paternally expressed *SNURF-SNRPN* transcript (antisense transcript of *UBE3A*), which is a new pathogenic mechanism based on antisense RNA for AS.[11] BWS, characterized by macroglossia, omphalocele and embryonal tumors, is caused by either paternal uniparental disomy for chromosome 11p15, gain of methylation at imprinting center 1 within the maternal 11p15 region or loss of methylation at imprinting center 2 within the maternal 11p15 region. All these genetic abnormalities perturb expression of imprinted genes within the 11p15 region.[12,13]

In mammals, the X chromosome is much larger than the Y chromosome and carries substantially more active genes. Consequently, females ought to have greater gene expression from their two X chromosomes than males do from their single X. However, this potential imbalance between females and males is prevented by the epigenetic inactivation of one of the two X chromosomes in females. If X-chromosome inactivation (XCI) does not occur properly, it can be lethal for in the affected female embryo; this effect is evident in mouse embryonic clones produced by somatic nuclear transfer in which a majority of clones abort due to failure of XCI[21] (Fig. 2b). If one of the two X chromosomes is very tiny due to a chromosome rearrangement (e.g. a small ring-shape X chromosome with a centromere), then this tiny X chromosome may escape XCI. In this case, the female has a normal X chromosome and a small ring X chromosome that are both

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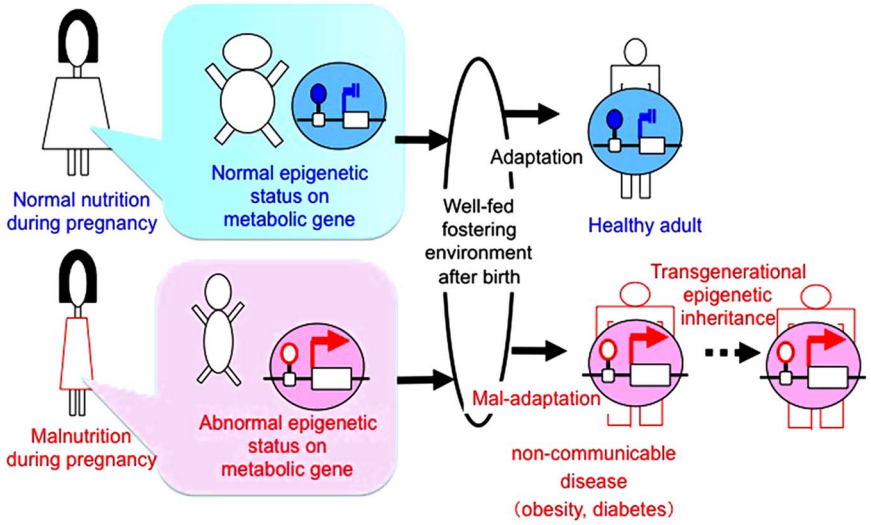

Fig. 3. Epigenetic basis of the linkage between maternal nutrition and predicting future neurodevelopmental outcomes in the offspring. Maternal malnutrition (especially folic acid deficiency, a methylation residue) induces a low DNA methylation status of metabolic genes in the liver of the fetus, which causes overexpression of the target genes and development of an origin of obese in the fetus. This status is good for survival of the fetus in the malnutritional environment, but if it then nurtured in a well-fed society after birth, it will develop obesity and diabetes mellitus during its adult period. A recent report demonstrated that the *in utero* malnutrition-programmed liver lipid metabolism can be inherited by the second generation, suggesting that the nutritional environment-induced 'DOHaD nature' can be transmitted to the descendants.

active. Such genotypes do not always cause embryonic lethality, but they are associated with extremely severe neurodevelopmental delay,[14,15] indicating that proper epigenetic chromosome inactivation is essential for normal development.

Mutations in the genes that encode proteins associated with the epigenetic gene control machinery can also cause congenital neurodevelopmental disorders. For example, DNA methyltransferases (DNMTs) mediate addition of a methyl group (CH_3) to CpG dinucleotides. Mutations in *DNMT3B*, a *DNMT* gene, cause ICF syndrome, characterized by immunodeficiency, centromere instability, facial anomalies, and mild mental retardation.[22–24] Thus, dysregulation of gene expression as a result of a DNMT mutation may cause the features of this syndrome (Fig. 2c). A recent report indicates that mutation in another DNMT gene, *DNMT3A*, also causes an overgrowth syndrome with intellectual disability.[25]

Methyl-CpG-binding domain proteins (MBDs) also play an important role in epigenetic gene regulation. Mutation of *MECP2*, an *MBD* gene, causes Rett syndrome, characterized by seizures, ataxic gait, language dysfunction and autistic behavior.[26,27] A recent study showed that MeCP2 controls expression of neuronal genes,[28] suggesting that dysregulation of multiple neuronal genes may cause the neurological features of this syndrome (Fig. 2d).

Epigenetic mechanisms of acquired neurodevelopmental disorders

Epigenetic controls of gene expression are generally very stable; thus, DNA and histone modification patterns within the genome are faithfully reconstructed after DNA replication (i.e. cell division). The only exception to this expected stability are the changes associated with carcinogenesis, in which defects in the epigenetic mechanisms are thought to be induced by lifelong environmental stimuli.[7] Although epigenetic mechanisms are generally stable, they can also be altered by certain conditions of short-term stress. Epidemiological studies of populations affected by famines in the Netherlands and China demonstrated that the offspring born to the mothers exposed to famine during their first and second trimester had lower birthweights than offspring born to the mothers not exposed to famine,[29] and the offspring had increased risks of metabolic disorders (e.g. obesity, diabetes mellitus) and mental disorders.[30,31] A similar phenomenon appears to be occurring in Japan where birth weights have decreased over the last 30 years due to intentional dieting in young Japanese women, which has resulted in fetal malnutrition.[32]

Short-term stress-related epigenetic changes due to malnutrition during the fetal period underlie the DOHaD. Recent studies in rats demonstrated that malnutrition during the fetal period decreases DNA methylation and increases expression of the peroxisome proliferator-activated receptor alpha gene (*PPARa*) in the liver, which may increase risks of metabolic disorders (Fig. 3).[18,19] Indeed, altered DNA methylation status was identified in the whole blood of individuals who suffered malnutrition during a period of famine in the Netherlands, in which the methylation of *INSIGF* was lower among individuals who were periconceptionally exposed to the famine compared with their unexposed same-sex siblings, whereas methylation of *IL10*, *LEP*, *ABCA1*, *GNASAS* and *MEG3* was higher.[33] It was also reported that assisted reproductive technologies (e.g. *in vitro* fertilization and intracytoplasmic sperm injection),

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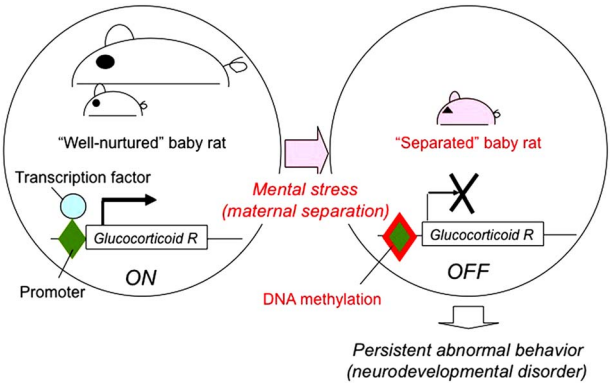

Fig. 4. Epigenetic mechanism that bridges mental stress and neuronal gene function. Environmental factors (e.g. maternal separation-stress during the 1st week of life) can alter the epigenetic status (e.g. DNA methylation) in a neuronal gene (e.g. the glucocorticoid receptor gene promoter) in the rat brain, which leads to persistent gene expression changes, that result in abnormal behavior throughout the lifespan of the individual.

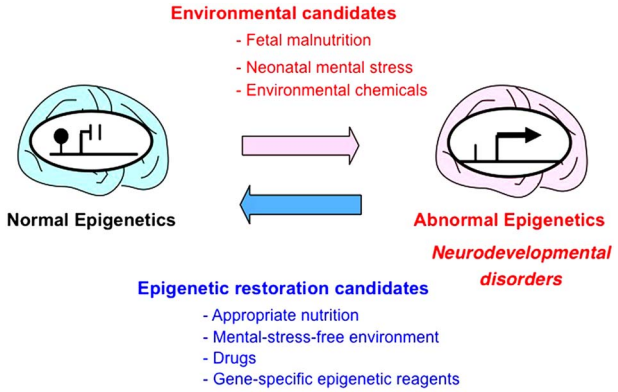

Fig. 5. Current understanding of extrinsic mechanisms of acquired neurodevelopmental disorders. Acquired neurodevelopmental disorders may be caused by dysregulations of epigenetic mechanisms due to harmful environmental factors; these failures might be reversed by favorable factors that restore the normal epigenetic mechanism.

which are now widely used due to increases in maternal and paternal ages, lead to a decrease in the DNA methylation status at multiple maternally methylated imprinted loci.[34,35] Another example in which short-term stress induces epigenetic changes is that mental stress within the 1st week of life in neonatal rats alters the pattern of DNA methylation in the promoter region of the glucocorticoid receptor gene (*Gr*; also known as *NR3C1*) in the brain, resulting in long-term abnormal behavior. The level of *Gr* methylation normally decreases in the brains of offspring given high maternal care in the 1st week after parturition[20](Fig. 4 left). By contrast, rat pups separated from their mothers during this period show aberrant hypermethylation of the *Gr* promoter and repression of *Gr* expression in the hippocampus[20] (Fig. 4 right). This observation may hint at a possible mechanism for the etiology of neurodevelopmental abnormalities associated with neonatal and childhood neglect and maltreatment in humans. The ability of stress to induce long-term changes was supported by *postmortem* brain analyses of suicide victims with a history of childhood abuse; in these individuals, hypermethylation of the neuron-specific promoter of *NR3C1* as well as reduced expression were observed in the hippocampus.[36] Overall, there is growing evidence that mental stress in early life can induce long-lasting epigenetic changes that have a lifelong effect on personality.[37] Taken together, these human and animal findings suggest that the DNA methylation changes due to assisted reproductive technologies, fetal malnutrition and neonatal stress possibly contribute to recent rapid increase of children with mild neurodevelopmental disorders, which is reported in many countries, including Korea.[38]

In addition to malnutrition during the fetal period and mental stress during the neonatal period, several lines of evidence suggest that *extrinsic* (environmental) factors, such as drugs,[39–43] mental, neuronal stimulation[44] and environmental chemicals, such as via smoking,[45,46] alter the epigenetic status and thereby affect brain function. Therefore, it is intriguing to speculate that acquired neurodevelopmental disorders, including autistic disorders, may be the result of epigenetic dysregulation caused by environmental factors (Fig. 5).

Epigenetic treatment based on epigenetics' reversibility

We are hopeful that the environmentally induced adverse epigenetic changes can be reversed by appropriate drugs. In fact, some of the drugs used for mental disorders have been found to restore the normal epigenetic status of neuronal genes[39–43] (Fig. 5). Folic acid, for example, is a nutritional component that supplies methyl residues to DNA, RNA and proteins, and its administration to pregnant rats resulted in altered DNA methylation in the offspring.[47] Furthermore, the offspring of rats given folic acid supplementation during pregnancy under malnutrition conditions exhibited higher levels of methylation of a hepatic gene than did offspring of malnourished mothers not given the supplement.[18] Administration of folic acid is known to be beneficial for the treatment of neurodevelopmental disorders (e.g. autistic spectrum disorder) in children, an effect that may be mediated via restoration of the normal DNA methylation status in disease-related gene regions.[48,50] In addition to folic acid, other environmental factors have also been reported to alter DNA methylation and histone modification status in the brain and other organs of mice and other species: royal jelly,[51] drugs for mental disorders,[39–43] environmental chemicals,[52,53] external stimuli (electro-convulsive treatment for psychiatric diseases)[54] and regular exercise.[55]

As described above, mental stress in the 1st week of life can cause epigenetic abnormalities in the brains of mice. Conversely, several mouse studies demonstrated that environmentally stimulating conditions can ameliorate behavior abnormalities. Mice that live in an enriched environment, consisting of larger-sized home

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cages with a variety of objects including running wheels, show improved motor coordination and decreased anxiety-related behavior in heterozygous *Mecp2*$^{+/-}$ female mice, a model of Rett syndrome.[56,57] Enriched environments also improved locomotor activity, reduced ventricular volume and restored the expression of synaptic markers, including synaptophysin and PSD95 in the hypothalamus and syntaxin 1a and synaptotagmin in the cortex of hemizygous *Mecp2*$^{-/Y}$ male mice.[58,59]

It is widely accepted that curing patients with congenital neurodevelopmental disorders is very difficult. However, it was recently demonstrated that the epigenetic disorder Rett syndrome might be an exception to this expectation, partly because *MECP2* does not encode a product required for brain structure, but rather encodes a 'lubricant' that works at a relatively late period of brain development. As a consequence, reintroduction of *MECP2* into *Mecp2*-null mice either before[60] or even after birth was sufficient to rescue Rett-like neurological symptoms.[61] Furthermore, restoration of MeCP2 function in astrocytes restored dendritic morphology and substantially improved locomotion, anxiety levels and respiratory abnormalities in hemizygous *Mecp2*$^{-/Y}$ male mice.[62] These results suggest that upregulation of *MECP2* might help to improve brain function in Rett syndrome patients. Valproic acid, one of the most popular drugs against epileptic seizures and a known HDAC inhibitor, also restore MeCP2 expression;[63,64] similar effects were seen with fluoxetine, a drug for mental disorders, and cocaine.[65] Taken together, these results indicate that neurodevelopmental disorders caused by epigenetic abnormalities are potentially treatable.

Transgenerational epigenetic inheritance

According to current understanding in the field of biology, one's acquired character is not inherited by the next generation of offspring. Based on this notion of Darwinian inheritance, acquired changes induced by harmful habits (e.g. smoking) during one's lifetime should not be transmitted to one's children. However, recent advances in epigenetics have revealed that such undesirable acquired traits (e.g. smoking-induced DNA methylation changes[45,46]) might be transmitted to the next generation.

Epigenetic marks, either DNA methylation or histone modifications, allow the mitotic transmission of gene activity states from one cell to its daughter cells. A fundamental question in epigenetics is whether these marks can also be transmitted meiotically through the germline. In mammals, epigenetic marks should be cleared by demethylating factors such as the cytidine deaminases and re-established in each generation, but this clearing is incomplete at some loci in the genome of several model organisms possibly due to deficient demethylating factors.[66] Therefore, 'transgenerational epigenetic inheritance,' which refers to the germline transmission of an environment-induced epigenetic mark,[67,68] may provide a direct biological proof for Lamarckism, the hypothesis that an organism can pass on to its offspring characteristics that it acquired during its lifetime; that is, an hypothesis of the heritability of acquired characteristics.

Transgenerational inheritance of epigenetic marks was first demonstrated in a specific mouse strain. The methylation status at the *Axin (Fu)* locus in mature sperm reflects the methylation state of the allele in the somatic tissue of the animal, is linked to the shape of the animal's tail, and does not undergo epigenetic reprogramming during gametogenesis.[69]

Environmental factors, notably the fungicide vinclozilin, stress responses and nutritional challenges, have been associated with transgenerational epigenetic inheritance in animal models. However, it is often difficult to dissect evidence of transmission of epigenetic marks *per se* from transmission of the exposure itself.[70,71] Therefore, transgenerational effects should be distinguished from parental and grandparental effects. In addition to contributing to their DNA, parents can influence their offspring in many other ways: for example, by contributing bioactive molecules in the egg and sperm cytoplasm, and by providing nutrients and hormonal information during embryogenesis. Malnutrition during pregnancy affects not only the pregnant mother and fetus but also the fetus's primordial germ cells, which can lead to phenotypic changes in the grandchildren (second generation). Actually, the specific diet- (supplementation of folic acid) induced methylation status at the *Axin (Fu)* locus linked to hair color of the animal's skin was inherited over two generations, but this status was lost by the third generation.[72] These reports indicated that, while the specific diet leads to parental and grandparental effects, the acquired epigenetic information was not simply inherited transgenerationally, and further suggested that the *Axin (Fu)* locus was resistant to environmentally induced acquisition of new germ-line epigenetic information.[72]

Transgenerational effects of environmental toxins (e.g. the endocrine disruptors vinclozolin, an anti-androgenic compound), and methyoxychlor, an estrogenic compound), were demonstrated in the fourth generation (F4) in rats with decreased spermatogenic capacity and increased male infertility. Moreover, the effects on reproduction correlated with altered DNA methylation patterns in the germ line.[73] It was also demonstrated that plastic-derived endocrine disrupters, including bisphenol-A, increased the risk of pubertal abnormalities, diseases of the testes and ovaries, in the F3 generation in rats, and that differential DNA methylated patterns were identified for the plastic- and control-lineage F3 generation sperm,[74] suggesting the existence of 'true' transgenerational epigenetic inheritance up to the third generation in experimental animals. This observation has also been confirmed in Drosophila, in which an aberrant epigenetic mark (defective chromatin state) induced by environmental stress (e.g. heat shock) was inherited by the next generation.[75]

As described above, short-term mental stress due to maternal-neonate separation immediately after birth alters the epigenetic status in the brain of the neonate and results in persistent abnormal behavior[16] (Fig. 4). It has further been demonstrated that such environmentally induced epigenetic changes occur not only in the brain but also in the sperm and, thus, aberrant environmentally induced epigenetic marks

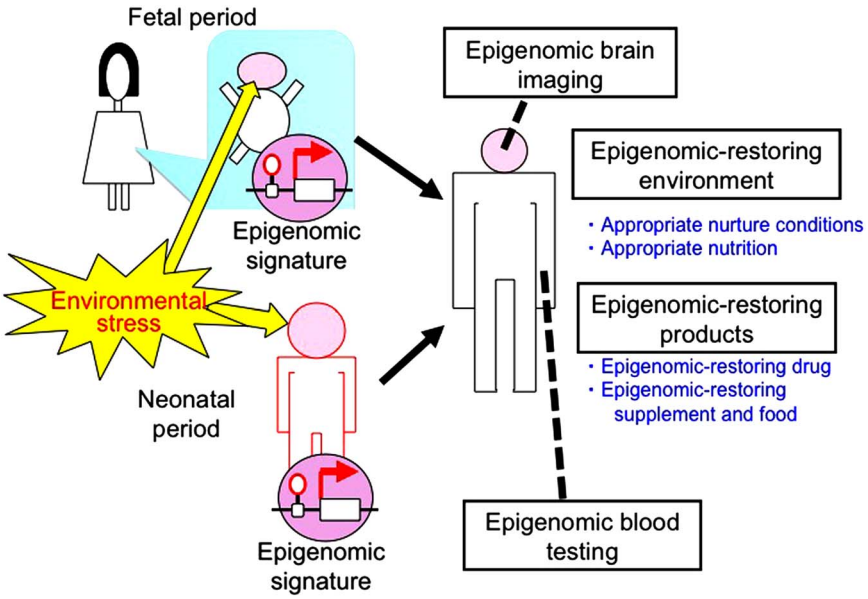

Fig. 6. Epigenetic-based preemptive treatment of neurodevelopmental disorders. Early detection, via blood analyses or neuroimaging, of epigenomic signatures induced by environmental stresses during fetal and infant periods opens a path for early intervention in neurodevelopmental disorders by offering an appropriate environment, nutrition or drugs to restore normal epigenetic patterns.

acquired in one generation can be inherited by the next generation.[76] In other words, chronic maternal separation altered behaviors and DNA methylation of the promoter of several genes in the germline of maternally separated mice; the altered epigenetic changes were then observed in the brains of the offspring along with altered gene expression, including decreases in the expression of the corticotropin releasing factor receptor 2 gene (*Crfr2*) in the amygdala and hypothalamus.[76] In this study, abnormal behavior was observed even in the third generation and altered DNA methylation in the CpG islands of *Mecp2*, the cannabinoid receptor-1 gene (*Cb1*), and *Crfr2* were observed in F1 sperm and F2 brain.[76] In a separate study, chronic maternal separation increased cytosine methylation of the estrogen receptor-alpha1b gene promoter, indicating that individual differences in maternal behavior are epigenetically transmitted from the mother to her female offspring.[77] A recent study also suggested that abnormal liver lipid metabolism programmed by *in utero* undernutrition was transmitted to the next generation with hypomethylation of the liver X receptor alpha gene (*Lxra*) in sperm from F1 to F2 in mice.[78,79] These findings provide biological evidence suggesting that environmental factors, including undernutrition during the fetal period and traumatic experiences in early life, are risk factors for the development of behavioral and emotional disorders not only in one generation but also in the successive generations.

Future perspectives

It was believed that environmentally induced epigenetic alterations were thoroughly erased during the two large waves of resetting of epigenetic marks at gametogenesis, which establishes a new imprinting pattern, and after fertilization, which establishes tissue-specific epigenomic patterns as described above (Fig. 1). However, as discussed, several lines of evidence suggest that environmentally induced epigenetic alterations are not completely erased but are at least partially maintained at gametogenesis, and thus such information (epigenomic signature) is transmitted to the next generation. It is therefore important to detect epigenomic signatures (epigenetic alterations induced by environmental factors) during early postnatal life to allow preemptive treatments, including early intervention by supplying appropriate nurturing, nutrition and drugs (e.g. HDAC inhibitor[39,40,80,81]) to restore the normal epigenetic patterns (Fig. 6). To identify epigenomic signatures (e.g. changes in DNA methylation), methylation arrays or next-generation sequence-based techniques are powerful and useful. Once several genomic regions that are useful for assessing health or diagnosing diseases are identified, simple and cost-effective detection methods, such as pyrosequencing/mass spectrometry-based methods and HPLC columns for detection of DNA methylation alteration (Miyake, Kubota *et al.* manuscript in preparation) will be useful. Also, the integration of neuroimaging methods with 'epigenomic signature' analyses to detect epigenetic abnormalities in the brain in 'real-time' will be essential.[82–85]

In conclusion, epigenetic modifications can be altered by various environmental factors, such as nutrition, mental stress and environmental chemicals. Therefore, targets for the screening of epigenomic signatures will be individuals who previously suffered from these environmental factors as well as their descendants. Furthermore, because altered epigenetic modifications are reversible, epigenomic signatures are potentially useful

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not only as disease-diagnostic markers but also as therapeutic markers. To date, objective markers are not available for neurodevelopmental disorders; thus, the establishment of epigenomic signature for these disorders holds the promise of preemptive treatment for the patients. Moreover, healthcare based on epigenomic signatures will be important because it not only treats the patient, but can also has an impact on potential future generations.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides on the care and use of laboratory animals (University of Yamanashi) and has been approved by the institutional committee (University of Yamanashi).

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