Review Article

Epigenetics in Neurodevelopmental and Mental Disorders

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Key Words

Epigenetics · Neurodevelopmental disorder · Mental disorder · Environment · Rett syndrome · MeCP2

Abstract

Epigenetic mechanisms are essential for normal development during embryogenesis and for differentiation of neural cells. Thus, precise understanding of epigenetic mechanisms, including DNA methylation and histone modification, is important to elucidate the pathogenic pathways in neurodevelopmental disorders. These include various congenital disorders caused by failures of genomic imprinting, X chromosome inactivation, and mutations of the proteins associated with epigenetic gene regulation. Several lines of evidence have suggested that various environmental factors, including insufficient nutrition, drugs, and mental stress, can alter epigenetic gene regulation in the brain, which potentially cause autism and adult mental disorders. However, epigenetic mechanisms are reversible mechanisms based on the attachment and detachment of modification factors onto DNA and histone proteins. Furthermore, recent studies indicate that epigenetic proteins, such as MeCP2, act as ‘lubricants’ rather than essential parts that make up the brain structure, which works at a relatively later period of brain development. Therefore, making use of this epigenetic reversibility, the correction of abnormal epigenomic patterns and the administration or upregulation of epigenetic molecules will potentially be useful therapies for neurodevelopmental and mental disorders caused by epigenetic abnormalities.

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Introduction

The brain is a gene dosage-sensitive organ in which underexpression or overexpression of the same genes encoding proteins related to brain function results in a range of neurological disorders. The effects of aberrant gene expression are exemplified by conditions such

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as Pelizaeus-Merzbacher disease, a severe congenital disease associated with a deletion, mutation, or duplication of the proteolipid protein 1 (*PLP1*) gene [1], lissencephaly, a rare brain formation disorder associated with deletion or duplication of the platelet-activating factor acetylhydrolase 1B subunit alpha (*PAFAH1B1*) gene that encodes a neuronal migration factor [2, 3], Charcot-Marie-Tooth disease, an adult-onset neuromuscular disease associated with a mutation or duplication of the peripheral myelin protein 22 (*PMP22*) gene [4], and Parkinson's disease, which can have a mutation or multiplication of the α -synuclein (*SNCA*) gene [5]. These clinical findings suggest that the brain is extremely sensitive to perturbations in gene regulation. Furthermore, they indicate that 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. These mechanisms are essential for normal development during embryogenesis [6] and for differentiation of neural cells [7] and other cell types [8]. Understanding of epigenetic mechanisms, including DNA methylation, histone modification, and regulation by microRNAs, will be important for elucidating the pathogenic pathways in neurodevelopmental disorders [9–12].

In this short review, we provide a brief and basic description of congenital neurodevelopmental disorders caused by epigenetic abnormalities. Moreover, we also consider acquired neurodevelopmental disorders caused by environmentally induced epigenetic alterations. Finally, we discuss future directions in medicine for these disorders based on recent advances in our understanding of epigenetic mechanisms.

Basic Mechanisms of Congenital Neurodevelopmental Mental Disorders Caused by Epigenetic Abnormalities

The epigenetic phenomenon was initially discovered in humans through the studies of genomic imprinting. It is a parent-of-origin control of gene expression now known to be associated with various human disorders. In an imprinted gene, one of the two parental alleles is active and expressed and the other is inactive and not expressed. This difference in activity is based on differential epigenetic tagging of the alleles through a mechanism such as DNA methylation. Mutation or deletion of the active allele at an imprinted locus causes a failure of gene expression despite the presence of a normal gene at the inactive allele (fig. 1a). A classic example of this phenomenon occurs in the neurodevelopmental disorders Prader-Willi and Angelman syndromes [13].

Since the X chromosome carries more genes than the Y chromosome, females (XX) have more genes than males (XY). This potential sex-related imbalance in gene expression is avoided by the inactivation of one of the two X chromosomes in females through an epigenetic mechanism [14]. If X inactivation does not occur properly in a female fetus, the fetus dies in utero and is aborted (fig. 1b). The role of an epigenetic mechanism in the X inactivation is supported by the observation that cloned animals produced by somatic nuclear transfer abort their embryos following failure of the X chromosome inactivation [15, 16]. Even if one of the X chromosomes is extremely small due to large terminal deletions and the dosage effect of X-linked genes is small, the female fetus shows severe congenital neurodevelopmental delay [17]. This effect is further supported by the suggestion that proper epigenetic control of gene expression is essential for normal brain development.

DNA methylation is achieved by the addition of a methyl group (CH₃) to CpG dinucleotides in a reaction that is mediated by DNA methyltransferases. Defective activity of DNA (cytosine 5-)-methyltransferase 3 beta (*DNMT3B*) causes ICF syndrome, which is charac-

Fig. 1. Epigenetic abnormalities associated with neurodevelopmental and mental diseases.

terized by immunodeficiency, centromere instability, facial anomalies, and mild mental retardation (fig. 1c) [18–20].

Methyl CpG-binding proteins, which bind to the methylated DNA region of genes, are also important molecules for control of gene expression. Mutations in the methyl CpG-binding protein 2 (*MeCP2*) gene cause Rett syndrome, which is characterized by seizures, ataxic gait, language dysfunction and autistic behavior [21, 22]. It is thought that mutation of *MeCP2* results in a dysfunctional protein, and the failure of MeCP2 to bind to the methylated regions of genes causes the inappropriate suppression of gene expression in the brain and leads to the manifestation of Rett syndrome (fig. 1d). Recent studies have shown that MeCP2 controls the expression of neuronal genes, such as brain-derived neurotrophic factor (*BDNF*), distal-less homeobox 5 (*DLX5*), insulin-like growth factor-binding protein 3 (*IGFBP3*), and the protocadherins *PCDHB1* and *PCDH7* (neuronal cell adhesion molecules) [23–27]. These findings suggest that not only mutations [28], but also epigenetic dysregulation of genes encoding synaptic molecules is associated with the genesis of neurodevelopmental disorders. It has been found that both deficiency or excess of MeCP2, such as through duplication of the *MECP2* genomic region, can lead to neuropsychiatric outcomes [29].

Acquired Neurodevelopmental Disorders Caused by Environmentally Induced Epigenetic Alterations

In England, the number of children with neurodevelopmental disorders, especially autistic spectrum disorder, has increased by 30-fold (prevalence from 1/2,500 to 1/86) in the last 50 years [30]. Worldwide, the rate of affected children is currently estimated at 100 (range 34–264) per 10,000 children [31–35]. Therefore, precise understanding of the etiologies of these disorders is important.

Various environmental factors have been implicated as contributors to the pathogenesis of autistic spectrum disorder [36]. However, recent genetic studies in a subset of autistic children [28] have also revealed mutations in genes encoding proteins that are associated with synaptic function, including synaptic scaffolding proteins, receptors, transporters on

Fig. 2. Current understanding of intrinsic and extrinsic factors that influence neurodevelopmental and mental diseases.

synapses and neuronal cell adhesion molecules. This evidence indicates that autism is a disorder of the synapse [37].

Nevertheless, the increase in the incidence of autism cannot be solely attributed to these genetic factors because it is unlikely that mutation rates have suddenly increased in the recent years. Therefore, environmental factors are more likely to be the cause of this increase. Some support for this conclusion comes from a study in twins that identified the influence of environmental factors on the occurrence of autism [38, 39].

Recent studies have shown that the epigenome (DNA and histone modifications) is more sensitive to environmental factors than the genome (DNA sequences) (fig. 2) [9]. Mental stress, such as maternal separation, changed the pattern of DNA methylation of the glucocorticoid receptor gene promoter in the mouse hippocampus during the first week of life [40]. Such environmentally induced DNA methylation changes can be transmitted across generations and induce abnormal behavior in later generations [41].

In humans, there is no direct evidence that environmental factors can alter the epigenomic status. However, older monozygotic twins have more epigenomic differences than their younger counterparts [41]. Likewise, in monozygotic twins with discordant severity of Rett syndrome, the epigenomic patterns of the twins differ and they show differences in the expression of neuronal genes [42]. This indicates that environmental factors may affect the human epigenome and that epigenomic differences induced by environmental factors may contribute to neurodevelopmental phenotypes.

In Japan, another social issue that may be related to epigenomic changes is the decline in birth weights during the past 20 years. This trend is thought to be a result of the popularity of dieting among young women and of the recommendation by obstetric physicians to minimize pregnancy weight gain in order to reduce the risk of gestational diabetes mellitus [43]. Based on current epidemiological studies of populations affected by famines in the Netherlands and China [43, 44], the generation with lower birth weight is expected to have an increased risk for obesity, diabetes mellitus and mental disorders in the future years in Japan; this is referred to as the Developmental Origin of Health and Diseases (DOHaD) [45, 46]. Recent studies have demonstrated that malnutrition during the fetal period causes a hypomethylation imprint on the peroxisome proliferator-activated receptor alpha (*PPARα*) gene in the rat liver [47]. Similar DNA methylation changes have been identified in the peripheral tissues of people who suffered malnutrition during a period of famine in the Netherlands [48].

It has also been reported that assisted reproductive technologies (for example, in vitro fertilization and intracytoplasmic sperm injection), which are now widely used due to increases in age at the time of marriage, decreased the status of DNA methylation at multiple maternally methylated imprinted loci [49, 50].

The Future of Epigenetic Medicine for Neurodevelopmental Disorders

It has been reported that administration of folic acid to pregnant rats alters the DNA methylation status in the offspring [51]. Another study has demonstrated that folic acid supplementation to pregnant rats under malnutrition conditions prevents hypomethylation of a hepatic gene in the offspring [52].

In addition to folic acid, a number of environmental factors, such as the nutritional supplement royal jelly [53], drugs for mental diseases [54–56], environmental chemicals [57, 58], and external stimuli (electroconvulsive treatment for psychiatric diseases) [59], have also been reported to alter DNA methylation or histone modification status in mice or other species.

As mentioned above, mental stress in the first week of life causes epigenetic abnormalities in the brains of mice. Conversely, several mouse studies have demonstrated that appropriate educational conditions may ameliorate features of neurodevelopmental disorders. In a mouse model of Rett syndrome, environmental enrichment, consisting of larger-sized home cages with a variety of objects, including running wheels, improved motor coordination and decreased anxiety-related behavior in heterozygous *Mecp2*^{+/-} female mice [60, 61]. Environmental enrichment also improved locomotor activity with reduced ventricular volume, and restored the expression of synaptic markers, such as synaptophysin and PSD95 in the hypothalamus and syntaxin 1A and synaptotagmin in the cortex of hemizygous *Mecp2*^{-/y} male mice [62, 63].

It is generally thought to be difficult to cure patients with congenital neurodevelopmental disorders caused by mutations that encode neuronal molecules, since the distribution of gene products to the appropriate brain regions and at the appropriate time of brain development is complex. However, it has been recently demonstrated that the epigenetic disorder Rett syndrome may be an exception, partly because MeCP2 does not encode a product required for brain structure, but rather it encodes a ‘lubricant’ that works at a relatively late period of brain development. Therefore, reintroduction of MeCP2 into *Mecp2* null mice not only before birth [64], but also after birth, is sufficient to resolve Rett-like neurological symptoms [65]. Furthermore, restoration of the MeCP2 function in astrocytes substantially improves locomotion, anxiety levels, and respiratory abnormalities in hemizygous *Mecp2*^{-/y} male mice along with restoring dendritic morphology [66]. These results suggest that upregulation of *MECP2*, possibly mediated by drug treatment, might help to improve the brain function of Rett syndrome patients. Additionally, these results indicate that neurodevelopmental disorders caused by epigenetic abnormalities can be treatable.

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