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REVIEW

Epigenetic regulators sculpt the plastic brain

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BACKGROUND: Epigenetic regulation is a level of transcriptional regulation that occurs in addition to the genetic programming found in biological systems. In the brain, the epigenetic machinery gives the system an opportunity to adapt to a given environment to help not only the individual but also the species survive and expand. However, such a regulatory system has risks, as mutations resulting from epigenetic regulation can cause severe neurological or psychiatric disorders.
OBJECTIVE: Here, we review the most recent findings regarding the epigenetic mechanisms that control the activity-dependent gene transcription leading to synaptic plasticity and brain function and the defects in these mechanisms that lead to neurological disorders.
METHODS: A search was carried out systematically, searching all relevant publications up to June 2017, using the PubMed search engine. The following keywords were used: "activity induced epigenetic," "gene transcription," and "neurological disorders."
RESULTS: A wide range of studies focused on the roles of epigenetics in transgenerational inheritance, neural differentiation, neural circuit assembly and brain diseases. Thirty-one articles focused specifically on activity-induced epigenetic modifications that regulated gene transcription and memory formation and consolidation.
CONCLUSION: Activity-dependent epigenetic mechanisms of gene expression regulation contribute to basic neuronal physiology, and defects were associated with an elevated risk for brain disorders.

Keywords epigenetic, activity-dependent gene expression, memory, neurological diseases

Introduction

The central nervous system is a dynamic system. For any stable dynamic system, a stimulus triggers a response to activate an "engaged" state and then the system returns to a normal state. For example, at the level of the neural circuit, stimuli trigger a chain reaction of neuronal firing; however, even the most extensive stimuli-induced neuronal firing in the brain would not last long. After the stimulus, an inhibitory circuit or a homeostasis regulatory network would be engaged and balance the network activity, thus helping the circuit to return to a state of normal activity. At the cellular level, stimuli induce a chain reaction of cell signaling molecules to activate the cell and produce the energy needed for the stimuli-induced neuronal firing. Stimuli-induced responses also remodel the cellular structure, including pruning excessive synapses and building new synapses. By any means, molecular activation in the cell would eventually return to a normal state.

The brain is not like other stable dynamic systems in that external stimuli can gradually optimize the system to function efficiently within the external environment. One essential feature of the brain is that it can remember past experiences and optimize its responses to stimuli according to prior experiences. In other words, instead of producing one stable point in a dynamic system, the brain can create a chain of stable points according to the history of each individual (Fig. 1). This feature requires additional regulatory mechanisms as well as the genetic programming. Such a regulatory mechanism must have the following three properties: be long-lasting, so that experiences can be memorized; have a capacity to be switched on and off by environmental signals; and create a stable point in the dynamic system that requires a feedback loop to maintain this regulatory state.

Accumulating evidence suggests that epigenetic regulation is a candidate mechanism for a second level of response regulation in the central nervous system. Epigenetic regulation has been found to be essential for maintaining cell fate after differentiation during neural development and for

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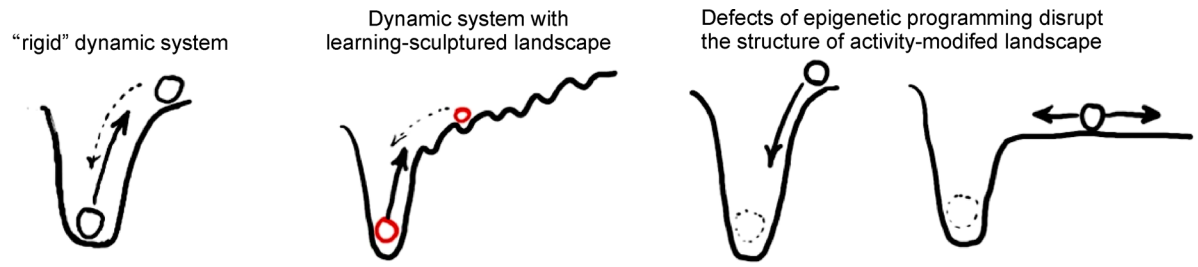

Figure 1 Epigenetically regulated stable dynamic system in the brain. Scheme shows the transcriptional state of the cell in the brain is engaged by signal input and the sculptured epigenetic landscape.

regulating learning and memory in the mature brain. Epigenetic regulation can even modulate brain function via transgenerational inheritance.

Importantly, recent discoveries in many neurological and most psychiatric disorders (De Rubeis et al., 2014; Devor et al., 2017; Stessman et al., 2017) did not identify single dominant genetic mutations but, instead, studies have identified hundreds of genes associated with increased risks for a single disease, implicating that malfunction of the central nervous system can be induced by a combination of concurrent environmental stresses and genetic mutations. Interestingly, many of the risk factors involve epigenetic regulators. Here, we summarize the major findings of epigenetic mechanisms in the central nervous system. We hypothesize that epigenetic regulation is essential in creating a chain of stimuli-engaged stable states in the dynamic system of the brain; defects in mechanisms of epigenetic regulation can lead to either instability of the system or the loss of environmentally engaged stable states, thereby leading to an increased risk of neurological and psychiatric disorders.

Long-lasting epigenetic modifications regulate gene transcription

In the adult brain, epigenetic mechanisms play an important role in generating and maintaining changes in synaptic plasticity and memory formation through the modulation of gene expression (Guan et al., 2009; Gräff et al., 2012). Epigenetic modifications can be defined as the structural adaptations of chromosomal regions to induce changes in the phenotype without a change to the genotype (Bird, 2007; Waddington, 2012). Epigenetic regulation often includes three aspects: 1) modifications at the level of the nucleotides, which includes DNA methylation and RNA interference (RNAi) (Ramsahoye et al., 2000; Bird, 2002; Laird, 2003; Matzke and Birchler, 2005); 2) post-translational modifications at the level of histones (PTMs) and the incorporation of histone variants (Jenuwein and Allis, 2001; Pusarla and Bhargava, 2005; Kouzarides, 2007; Talbert and Henikoff, 2010); and 3) nucleosome remodeling, which refers to ATP-dependent processes that modify the structure of chromatin (Becker and Hörz, 2002; Clapier and Cairns, 2009). These modifications regulate gene transcription and are essential for normal chromosome architecture and function. The epigenetic marks are variable over time and can be remodeled in response to external stimuli (Borrelli et al., 2008). Above all, epigenetics offers potential mechanisms for sustained changes in the transcriptional activity in the central nervous system as induced by neuronal activity (Roth and Sweatt, 2009; Sweatt, 2013; Zovkic and Sweatt, 2015; Sweatt, 2016).

Activity-dependent switch of epigenetic regulation

Transcriptional regulation by three types of epigenetic regulators in the brain

Activity-dependent alterations in the transcriptional program is governed by histone acetylation (Table 1). Histone acetylation is catalyzed by histone acetyl transferases (HATs), and acetyl marks are removed by histone deacetylases (HDACs) (Kouzarides, 2007; Guan et al., 2009). Interestingly, neuronal depolarization leads to a widespread recruitment of CBP, an enhancer that is correlated with an increase in expression of target genes (Kim et al., 2010). High frequency stimulation leads to a global increase in H3 and H4 acetylation on the *reelin* and *bdnf* promoters, correlating with a higher level of targeted gene expression and LTP induction (Sui et al., 2012). Membrane depolarization of cortical neurons increases H3K27ac at a subset of enhancers and regulates activity-dependent transcription (Malik et al., 2014). In the mouse brain, histone acetylation is associated with learning. Object memory formation enriches H3K14ac at the *zif268* promoter and promotes *zif268* expression during memory consolidation (Gräff et al., 2012). Strikingly, light pulse stimulation induced rapid histone acetylation in the promoters of *mPer1* or *mPer2* in the suprachiasmatic nucleus (SCN) and increased mouse Per1 (*mPer1*) expression (Naruse et al., 2004).

Histone methylation is also regulated by neural activity and causes bi-directional effects on chromatin structure and transcriptional activity (Kouzarides, 2007). Contextual fear learning increases global levels of H3K9me2 in area CA1 and the EC (Gupta-Agarwal et al., 2012) and increases H3K4me3

Table 1 Activity induced epigenetic modification and its readout

Epigenetic modification	Readout
Depolarization induced a decrease in CpG methylation within the regulatory region of the *bdnf* gene	Increased *bdnf* transcription (Martinowich et al., 2003)
Activity-dependent CBP binding at neuronal activity-regulated enhancers	Increased RNAPII binding, eRNA synthesis, mRNA synthesis (Kim et al., 2010)
Synchronous neuronal activation induce active demethylation or de novo methylation in 1.4% of 219,991 CpGs in DG	Methylation changes located in TSS upstream regions were modestly but significantly anticorrelated with changes in gene expression (Guo et al., 2011)
Increased H3K14ac, H3K36me3 in object memory consolidation	Increased *zif268* expression and promoted memory consolidation (Gräff et al., 2012)
Kainic acid induce H3S10 phosphorylation in hippocampal neurons	Increase of *c-fos* transcription (Crosio et al., 2003)
Contextual fear conditioning increases acetylation of histone H3	Required for memory formation (Levenson et al., 2004)
A nighttime light pulse induce H3S10 phosphorylation in SCN clock cells	*c-fos* and *Per1* induction (Crosio et al., 2000)
A light pulse induce histone acetylation within the promoters of *mPer1* or *mPer2* in SCN clock cells	Increased *Per1* expression (Naruse et al., 2004)
Electroconvulsive stimulation increases acetylation of histone H4 at the *c-fos* promoter in hippocampus	Increased *c-fos* expression (Dyrvig et al., 2012)
High-frequency stimulation induced demethylation, H3 and H4 acetylation at the *reelin* and the *bdnf* promoters in the mPFC	LTP induction and increased *reelin and bdnf* expression (Sui et al., 2012)
Contextual fear conditioning increased H3K4me3	Increased *zif268* expression and promoted memory consolidation (Gupta et al., 2010)
Contextual fear learning increased global levels of H3K9me2 in area CA1 and the EC	LTP and memory formation (Gupta-Agarwal et al., 2012)
Contextual fear conditioning increase histone H3 phosphorylation in area CA1	Memory formation (Chwang et al., 2006)
Fear conditioning induced methylation of the memory suppressor gene *PP1,* and demethylation of the synaptic plasticity gene *reelin*	Increased *PP1* expression, decreased *reelin* expression and promoted memory consolidation (Miller and Sweatt, 2007)
Contextual fear conditioning induced exon-specific methylation in *bdnf* gene	Increased *bdnf* gene expression and memory formation (Lubin et al., 2008)
Learning induces persistent DNA methylation of memory suppressor *CaN* in the prefrontal cortex	Decreased *CaN* gene expression and preserved long-term memory (Miller et al., 2010)
Electroconvulsive treatment induced DNA demethylation at *bdnf* and *FGF-1B* promoter in hippocampus	Increased *bdnf and FGF-1B* gene expression and adult neurogenesis (Ma et al., 2009)
Membrane depolarization triggers release of MeCP2 from *bdnf* promoter III	Facilitate *bdnf* transcription (Chen et al., 2003)
Synchronized synaptic activity induced by chemoconvulsants triggers MeCP2 S421 phosphorylation in the brain	Increased *bdnf* transcription and spine maturation (Zhou et al., 2006)
Neuronal activity decreased *TET1* expression	Global alteration of modified cytosines after neuronal activity (Kaas et al., 2013)
Neuronal activity–regulated H3K27ac dynamics at enhancers	Regulate the expression of targeted genes (Malik et al., 2014)
Neuronal activity triggered binding of Ash1L to the promoter and enriched the histone marker H3K36me2 at the *Nrxn1α* promoter region	Repression of *Nrxn1α* transcription (Zhu et al., 2016)
Learning increased H3K9me3 in *Nrxn1* SS4 region	*Nrxn1* SS4 inclusion and memory preservation (Ding et al., 2017)
Electroconvulsive stimulation induced widespread chromatin accessibility changes	Regulate the expression of targeted genes (Su et al., 2017)
Activity-regulated demethylation of *Npas4*	Increased *Npas4* transcription and memory extinction (Rudenko et al., 2013)
Using an HDAC2-targeting inhibitor (HDACi) during remote memory reconsolidation	Increased expression of neuroplasticity-related genes and attenuate remote memory (Gräff et al., 2014)
Fear conditioning induced Histone H2A.Z subunit exchange in the hippocampus and the cortex	Mediates gene expression and restrains the formation of recent and remote memory (Zovkic et al., 2014)
Globe DNA methylation changes during memory acquisition and system consolidation	Alter the expression of targeted genes and required for memory formation and maintenance (Halder et al., 2016)
Synaptic activity induced a decrease in *bdnf* promoter I methylation	Increase in *bdnf* expression and decrease in the frequency of mEPSCs (Nelson et al., 2008)
Serotonin-dependent methylation in the promoter of *CREB2*	Decrease in *CREB2* expression and enhance serotonin-dependent memory-related synaptic plasticity (Rajasethupathy et al., 2012)
Synaptic activity increased the cytosine methylation	Decreased the expression of genes encoding glutamate receptors and trafficking proteins and amplitude of mEPSCs (Meadows et al., 2015)

to promote memory consolidation (Gupta et al., 2010). Histone methylation can specifically regulate gene transcription. *Nrxn1* is one of the neurexin family members that encodes presynaptic adhesion molecules and is essential for synapse formation (Südhof, 2008). Neuronal activity triggered binding of Ash1L to the promoter to enrich H3K36me2 at the *nrxn1α* promoter region, leading to the activity-dependent transcriptional repression (Zhu et al., 2016).

Histone phosphorylation represents another form of transcriptional regulation (Banerjee and Chakravarti, 2011). Kainic acid treatment in the mouse hippocampus leads to an increase in H3 phosphorylation at serine 10 (S10), which correlates temporally with *c-fos* induction (Crosio et al., 2003). Nighttime light exposure increases H3S10 phosphorylation, paralleling *c-fos* and *Per1* induction (Crosio et al., 2000). Moreover, contextual fear conditioning increases the global level of histone H3 phosphorylation in area CA1, which is required for memory formation (Chwang et al., 2006) (Fig. 2).

In addition to histone modifications, DNA methylation is another important form of epigenetic regulation. DNA methylation is catalyzed by DNMT3a and DNMT3b via the addition of a methyl group to a cytosine residue; this methylation mark is maintained by DNMT1(Goll and Bestor, 2005). Synchronous neuronal activation modifies the DNA methylome and the chromatin accessibility landscape in the dentate granule neurons of adult mice (Guo et al., 2011; Su et al., 2017). Accordingly, contextual fear conditioning induces changes in DNA methylation in plasticity genes that are required for the formation and maintenance of memory (Halder et al., 2016). Learning also induced exon-specific methylation in the *bdnf* gene, which correlated with increased *bdnf* gene expression and memory consolidation (Lubin et al., 2008). Serotonin-dependent methylation in the promoter of *CREB2* results in a reduction in *CREB2* expression and enhances memory-related synaptic plasticity (Rajasethupathy et al., 2012). Additionally, learning induces persistent DNA methylation of the memory suppressors CaN (Miller et al., 2010) and PP1 (Miller and Sweatt, 2007), resulting in a reduction of target gene expression and facilitates memory consolidation. Active DNA demethylation has also been observed in the regulatory region of *bdnf*, *Npas4*, and *fgf1* (Martinowich et al., 2003; Nelson et al., 2008; Ma et al., 2009; Rudenko et al., 2013). For example, contextual fear conditioning induces demethylation of the synaptic plasticity gene *reelin*, which is correlated with upregulation of *reelin* expression and memory formation (Miller and Sweatt, 2007).

Activity-dependent modification of cytosine hydroxymethylation (5hmC) is widely observed in the brain. This modification is another DNA modification that is carried out via hydroxylation of methylated cytosines (5mC) by members of the ten-11 translocation (TET) protein family (Guo et al., 2011). Neuronal activity regulates *TET1* expression, thus leading to global changes in modified cytosine levels and expression of activity-dependent genes and memory formation (Kaas et al., 2013).

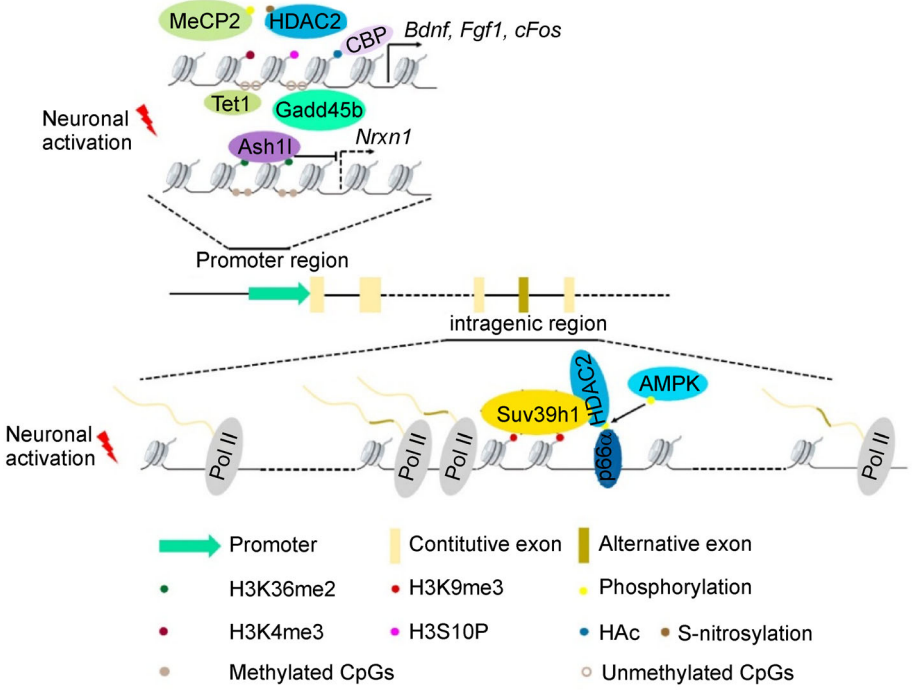

Figure 2 Activity-induced epigenetic mechanisms regulate the transcriptional program. Summary of the activity-dependent epigenetic regulation on gene transcription and alternative splicing

Activity-dependent epigenetic regulation also involves the binding of chromatin regulators. The methyl-CpG binding protein 2 (MeCP2) recognizes and represses methylated genes by recruiting chromatin remodeling factors such as HDACs, REST and CoREST ([59]. Neural activity induces a Ca^{2+}-dependent phosphorylation of MeCP2 that results in its release from the *bdnf* gene promoter IV and increased *bdnf* transcription, correlating with a reduction in DNA methylation at the promoter region (Chen et al., 2003; Martinowich et al., 2003; Zhou et al., 2006).

Activity-dependent regulation of alternative splicing by epigenetic factors

Besides transcriptional regulation, epigenetic regulators also determine the choice between alternative splice isoforms. First, neural activation can regulate splicing by directly recruiting snRNP proteins via epigenetic factors. Chromatin remodelers in SWI/SNF complexes have an effect on alternative splicing that depends on their physical interactions and recruitment of snRNPs U1 and U5 but that is independent of their ATPase remodeling activity (Batsché et al., 2006). Furthermore, the histone acetyltransferase STAGA shows direct interaction with U2 snRNPs (Martinez et al., 2001; Cheng et al., 2007), and the histone arginine methyltransferase CARM1 physically interacts with U1 snRNP proteins (Cheng et al., 2007).

Histone modifications are also associated with alternative splicing. A genome-wide analysis showed that histone marks are non-randomly distributed and several types of histone modifications are enriched in exons compared to the flanking introns (Andersson et al., 2009; Kolasinska-Zwierz et al., 2009; Spies et al., 2009; Schwartz et al., 2009). Specifically, *FGFR2* showed tissue-specific splicing isoforms, and H3K36me3 and H3K4me3 was specifically enriched along the alternatively spliced region according to the respective splicing pattern (Luco et al., 2010). Interestingly, modulation of H3K36me3 or H3K4me3 levels by interfering with the expression of their respective histone methyltransferases causes splice site switching in a predictable fashion(Luco et al., 2010), suggesting that histone modifications are critical for the regulation of alternative splicing. Additionally, treatment of cell culture with the histone deacetylase inhibitor TSA induces skipping of the alternatively spliced *fibronectin* exon 33 and *NCAM* exon 18 (Nogues et al., 2002; Schor et al., 2009).

Furthermore, histone marks affect splicing through the recruitment of splicing regulators via chromatin binding proteins to form chromatin-splicing adaptor systems. High levels of H3K36me3 along the alternatively spliced region attract MRG15 which, in turn, interacts with PTB and recruits it to the nascent RNA and thereby regulating splicing (Luco et al., 2010). H3K4me3 levels affect the pattern of splicing through the bridging of the spliceosome and the alternative spliced region via CHD1(Sims et al., 2007). Another example of chromatin-splicing adaptor systems is that H3K9 trimethylation plays a role in recruiting splicing factors hnRNPs via the chromatin-adaptor protein HP1(Piacentini et al., 2009).

Recent studies showed that epigenetic regulation of alternative splicing can be triggered by neural activity (Ding et al., 2017). Especially in the memory trace neurons, neural activity induced phosphorylation of p66αvia 5′AMP-activated protein kinase (AMPK) to recruit HDAC2 and Suv39h1, thereby establishing repressive epigenetic markers on the *Nrxn1* SS4 site and affecting co-transcriptional *Nrxn1* SS4 splicing. Furthermore, disrupting the build-up of intragenic H3K9me3 by knockout of *Suv39h1* abolished the activity-dependent splicing changes (Ding et al., 2017). This finding suggests that local histone modification is a one of the key regulators of activity-dependent *Nrxn1* SS4 splicing, which supports the idea that alternative splicing is epigenetically regulated through a transcription-kinetic-dependent mechanism (Luco et al., 2011). Thus, neural activity regulates gene transcription and modulates splicing in the central nervous system and thus modifies the epigenetic landscape.

Bi-directional regulation of epigenetic modifications creates stable states of epigenetic landscapes in the cellular genome

DNA methylation and post-translational histone modifications constitute a layer of stable epigenetic information. Many of these markers can be maintained for a long time (Luco et al., 2011; Probst et al., 2009). DNA (cytosine-5)-methyltransferase 3 alpha (DNMT3a)/DNA (cytosine-5)-methyltransferase 3 beta (DNMT3b) in association with a cofactor DNMT3L are essential for the establishment of DNA methylation patterns through de novo methylation (Okano et al., 1999; Jia et al., 2007). *In vitro* methylated DNA templates in cell culture retained methylated-DNA regardless of the DNA sequence, even after many rounds of cell divisions (Pollack et al., 1980; Wigler et al., 1981). Because the DNMT1 enzyme has a high specificity for hemimethylated CpG dinucleotides, unmethylated sites will not be recognized, thus maintaining the precise methylation pattern on the newly synthesized DNA (Gruenbaum et al., 1982). The maintenance of DNA methylation not only depends on the properties of DNMT1 itself (Cheng, 2014), but that the methyl-CpG binding protein, MeCP2, interacts directly with DNMT1 within the hemimethylated sites to perform maintenance methylation in vivo (Kimura and Shiota, 2003). Although DNA methylation can be stably maintained, it can also be erased or re-modified in response to external cues (Reik, 2007).

For the maintenance of post-translational histone modifications, parental histones are used as templates to guide the modification of new histones (Nakatani et al., 2004; Probst et al., 2009). Such a mechanism is widely used in repetitive regions, such as in heterochromatin, in which high density of

H3K9me3 is bound by HP1 proteins. HP1, together with DNA methylation and H3K9me3, contribute to the maintenance of repressed state (Bannister et al., 2001; Lachner et al., 2001). A subset of the histone H3 lysine 9 methyltransferases Suv39h1, G9a, GLP, and SETDB1 also participate in the process of heterochromatin formation as a multimeric complex (Fritsch et al., 2010). With respect to the regions of heterochromatin, the process for maintaining H3K27me3 is carried by PRC2, the enzyme that catalyzes this modification and directly binds to H3K27me3 (Hansen and Helin, 2009; Margueron et al., 2009). Histone deacetylation and DNA methylation often work together to stabilize the epigenetic modifications (Vaute et al., 2002; Scharf et al., 2009). HDACs together with H3K9me3 ensure the maintenance of a deacetylated state of chromatin, while in regions without HDAC targeting, it may be easier to maintain histone acetylation (Vaute et al., 2002). Histone modifications also work in concert with DNA methylation. DNMT1 associates with histone deacetylase (Fuks et al., 2000); additionally, methyl-CpG binding protein 1 (MBD1) interacts with the histone methyltransferase Suv39h1(Fujita et al., 2003), which provides an additional means to perpetuate the exact chromatin states.

Epigenetic regulators in neural differentiation

Epigenetic regulators play essential roles in neural differentiation. The central nervous system consists of many cell types, including neurons, astrocytes, and oligodendrocytes, all of which are differentiated from the same neural stem cells (NSCs) (Dietrich et al., 2006). The migration and differentiation of neural cells must be strictly regulated during development by extracellular cues and intracellular gene expression programs, which are, in part, regulated by epigenetic mechanisms(Mizutani et al., 2007; Namihira et al., 2008). Epigenetic mechanisms are key regulators for both pluripotency maintenance and cell fate specification (Hirabayashi and Gotoh, 2010).

The promoter region of genes such as sodium channel type II, BDNF or calbindin are highly methylated to prevent differentiation into neurons during the early stage (Lunyak et al., 2002; Ballas et al., 2005). Neuronal specification of NSCs requires the de-repression of neuronal genes such as *Sox2* via DNA demethylation in the promoter region (Sikorska et al., 2008). Astrocytic gene loci are also silenced by DNA methylation during neuronal commitment, and this silencing is attenuated by demethylation of the genes coding for the astrocytic markers such as *GFAP* (Sun et al., 2001; Takizawa et al., 2001; Namihira et al., 2004; Fan et al., 2005). The proper DNA methylation pattern during each stage of development is coordinated with a tight regulation of the DNA methyltransferases, DNMT1, DNMT3a, and DNMT3b. *DNMT1* is highly expressed in NSCs (Brooks et al., 1996), and studies in *DNMT1*-deficient NSCs showed enhanced astrogliogenesis (Fan et al., 2005). Furthermore, depletion of *DNMT3a* and *DNMT3b* lead to precocious glial differentiation (Wu et al., 2012) and failed neuronal differentiation in vitro (Bai et al., 2005).

In addition to DNA methylation, histone modifications are also regulated during development, both spatially and temporally. Histone deacetylation represses the expression of *Mash1*, an important regulator of cell fate decision in NSCs; however, upon neural differentiation, *Mash1* is actively expressed via histone acetylation (Williams et al., 2006). Other neural genes such as *NeuroD* and *Cdkn1c* are also activated via histone acetylation during neuronal fate commitment (Sun et al., 2001; Attia et al., 2007).

Epigenetic regulation of the neural circuit assembly

Epigenetic regulators also play an essential role in the formation of functional neural circuit assemblies in the mature brain. Failure to assemble proper neural circuits is associated with neurodevelopmental disorders including intellectual disability and autism spectrum disorders (Geschwind and Levitt, 2007; Gogolla et al., 2009; Wood and Shepherd, 2010). In addition to transcription factors, epigenetic mechanisms are critical for regulation of gene expression during the development of the neural assembly (Ho and Crabtree, 2010; Ronan et al., 2013). In the cerebellum, as well as in the hippocampus, granule neurons form ample dendrites and then prune them. Presynaptic boutons were formed along axons of granule neurons during maturation and integration of the circuits (Yamada et al., 2014; Yang et al., 2016). Conditional knockout of the NuRD component or *Suv39h1* in granule neurons disrupts the formation of presynaptic boutons and dendrite elimination. Conditional knockout of *Chd4*, a chromatin helicase in the NuRD complex, impairs synaptic neurotransmission between granule neurons and its downstream target in Purkinje cells responding to sensorimotor stimuli in the cerebellum.

Epigenetic regulation of learning and memory

Activity-dependent synaptic dynamics are crucial for learning and memory formation (Fortin et al., 2012). Early research on learning and memory formation emphasized the role of transcription factors (Chen et al., 2012); however, epigenetic mechanisms have recently emerged as a key player in the regulation of synaptic plasticity and memory formation (Gräff et al., 2012). Histone deacetylases such as HDAC2, HDAC3, and HDAC6, has been shown to regulate the critical genes related to regulation of plasticity and synapse formation, thereby modulating memory formation and consolidation (Levenson et al., 2004; Chwang et al., 2006; Gupta et al.,

2010; Gräff et al., 2012; Gupta-Agarwal et al., 2012; Ding et al., 2017). The histone variant H2A.Z is altered in response to fear conditioning in the hippocampus and the cortex, inhibiting memory formation through downstream effects on gene expression(Zovkic et al., 2014). Moreover, a significant increase in the incorporation of H3.3 into the chromatin of active genes was observed in hippocampal neurons, while blocking the turnover of H3.3 impairs hippocampus-based learning (Maze et al., 2015). Genome-wide analyses of the hippocampal DNA methylation status after learning show that DNA methylation is dynamically regulated, including both de novo methylation and demethylation (Martinowich et al., 2003; Miller and Sweatt, 2007; Lubin et al., 2008; Miller et al., 2010; Halder et al., 2016). Both pharmacological inhibition and conditional knockout of DNA methyltransferases resulted in an impairment in synaptic plasticity and long-term memory formation and maintenance (Levenson et al., 2006; Miller and Sweatt, 2007; Lubin et al., 2008; Miller et al., 2010; Morris et al., 2014; Mitchnick et al., 2015). Therefore, epigenetic regulation encompasses different mechanisms, including histone modification, histone variants (Kamakaka and Biggins, 2005; Zovkic et al., 2014), and DNA methylation, all of which help regulate gene expression for memory formation and consolidation.

Recent progress showed that Suv39h1, a histone methyltransferase for H3K9me3, regulates *Nrxn1* SS4 inclusion in response to learning engaged neural activity, that is essential for memory preservation probably through constraining their connection specificities as well as their plasticity in the memory circuit (Ding et al., 2017). Knockout of HDAC2 or inhibition of HDAC2 with HDACi converts stable memory into an alterable state (Gräff et al., 2014).

Transgenerational Inheritance

Many psychiatric and neurological disorders have strong genetic heritable components (Kendler, 2001; Millan et al., 2012); however, the genome-wide association studies performed to date have failed to identify the causal genetic basis of these disorders (Gibson, 2012), and the key factors of their heritability are still unknown (Eichler et al., 2010; Gershon et al., 2011; So et al., 2011). It has recently been recognized that, in addition to genetically inherited information, non-genetic components, such as epigenetics, may also contribute to disease heritability (Danchin et al., 2011; Bohacek and Mansuy, 2013). Previously, epigenetic modifications were considered to be completely erased between generations; however, several studies have confirmed that epigenetic information can be transmitted to subsequent generations through the germline, a process termed transgenerational epigenetic inheritance (Horsthemke, 2007; Daxinger and Whitelaw, 2010).

DNA methylation is well known to be involved in one form of epigenetic inheritance: genomic imprinting, a process governed by DNA methylation that allows the selective expression of only one parental allele (maternal or paternal) (Paoloni-Giacobino and Chaillet, 2006; Sha, 2008). Sex-specific DNA hypermethylated imprints are essential for silencing of the inactive allele and are protected from global demethylation activity during the following fertilization (Feng et al., 2010; Bartolomei and Ferguson-Smith, 2011). In addition to genomic imprinting, DNA methylation in germ cells that is altered by environmental stresses at specific gene loci can be transmitted between generations (Franklin et al., 2010).

Histone modifications modify chromatin structure and play an essential role in gene expression in somatic tissues, while their function in sperm cells is less clear. Histones are mainly replaced by protamines (up to 98% in mice and 85% in human) in sperm cells (Hammoud et al., 2009; Johnson et al., 2011); however, the remaining histones are specifically retained at genetic loci that are essential for embryogenesis (Puri et al., 2010). H3K4me2 and H3K27me3 are present at functional genes in spermatogenesis and developmental regulation and maintain genes in either an activated or repressed state (Hammoud et al., 2009; Brykczynska et al., 2010). Interestingly, genes repressed by H3K27me3 in sperm cells are maintained in a repressed state in the early embryo (Brykczynska et al., 2010), suggesting that H3K27me3 in sperm can be inherited across generations.

Epigenetic dysregulation in neurological diseases

Environmentally induced epigenetic modifications in neurological disorders

The environment exerts some of its effects on disease progression through epigenetics. Genetically identical individuals in monozygotic twins can show discordancy for neurological diseases such as autism (Hallmayer et al., 2011), schizophrenia (Cannon et al., 1998), and Alzheimer's disease (Gatz et al., 1997), suggesting a contribution from the environment to the disease through alterations of the epigenome of the individual. Studies have demonstrated the existence of epigenetic differences in monozygotic twins (Fraga et al., 2005).

Exposure to early life stress (ELS) has been thought to alter gene expression programs and enhance the risk of psychopathologies such as schizophrenia, bipolar disorder, depression, and PTSD (Gershon et al., 2013). Epigenetic modifications have the ability to modulate gene expression in response to external factors, and provide a potential mechanism for such programming. ELS pups show DNA hypermethylation and reduction of H3K9ac in promoter region of *Grm1* and *Gad1*, correlating with decreased expression of targeted genes (Zhang et al., 2010; Bagot et

al., 2012). Additionally, maltreated pups show an increase in DNA methylation at the *bdnf* promoter and a corresponding decrease in *bdnf* expression in the adult prefrontal cortex (Roth et al., 2009), which has been found in schizophrenia patients (Hashimoto et al., 2005).

Monogenetic neurological diseases associated with epigenetic defects

Notably, many neurological disorders are linked to mutations of epigenetic regulators, including DNA methyltransferase and histone modifying enzymes (Table 2). Those mutations indicate the essential role of epigenetic regulation in these diseases. Interestingly, the list includes not only embryonic defects, but also neurological disorders with symptom onset in childhood and in adults, suggesting the epigenetic regulation is essential both for the development of the nerve system and for the physiologic function in matured brain.

Disordered chromatin in neurological disease

Many neurological diseases showed correlation to the activity-dependent epigenetic regulations. Interestingly, reports showed that treatment with sodium butyrate, the histone deacetylase inhibitor, ameliorated the neurodegenerative phenotype in Huntington's disease mice (Steffan et al., 2001; Ferrante et al., 2003), suggesting the epigenetic regulators might also serve as the drug targets to treat neurological diseases.

Autism spectrum disorder

A significant number of genetic syndromes of ASD are associated with mutations in epigenetic regulators (Crawford et al., 2001; Beyer et al., 2002; Richards et al., 2015). For example, mutations of CHD8, which encodes the chromatin modifier, show strong association ($>87\%$) with the ASD phenotype (Bernier et al., 2014; Merner et al., 2016). Interestingly, mutations in CHD7 also showed a significant risk (40%) for ASD (Smith et al., 2005; Johansson et al., 2006). Furthermore, abnormal DNA methylation is also detected in ASD patients, including the dysregulation of DNA methylation in the 3′ untranslated region of PRRT1, TSPAN32 and C11orf21(Ladd-Acosta et al., 2014; Nardone et al., 2014) and in promoters of GAD65, OXTR, SHANK3, reelin, UBE3A and MECP2 (Jiang et al., 2004; Nagarajan et al., 2006; Gregory et al., 2009; Zhu et al., 2014; Elagoz Yuksel et al., 2016). For histone modifications, excess expansion of H3K4me3 and H3K27Ac from the transcription start sites into downstream gene bodies and upstream promoters have been identified in ASD patients (Shulha et al., 2012; Sun et al., 2016).

Alzheimer disease

Alteration of the epigenome has been understood in the aging process and in age-related neurodegenerative diseases (Hernandez et al., 2011; Lu et al., 2013). Recent findings implicate the dysregulation of REST and REST-dependent epigenetic remodelling is associated with cognitive impairment and Alzheimer disease (Lu et al., 2014). Epigenome-

Table 2 Neurological disorders caused by mutation in epigenetic regulator genes

Gene	Function	Syndromes
DNA methylation		
DNMT3b	DNA methyltransferase	ICF1 syndrome (Jin et al., 2008)
DNMT1	DNA methyltransferase	Parkinson's disease (Jowaed et al., 2010); ADCA-DN (Winkelmann et al., 2012)
DNMT3a	DNA methyl transferase	Amyotrophic lateral sclerosis (Chestnut et al., 2011)
MeCP2	Methyl-CpG–binding protein	Rett syndrome (Amir et al., 1999; Chen et al., 2001; Guy et al., 2001; Collins et al., 2004; Mnatzakanian et al., 2004); Autism (Carney et al., 2003)
Histone modification		
EHMT1	Histone methyltransferase	Kleefstra syndrome (Kleefstra et al., 2009); Schizophrenia (Kirov et al., 2012)
EP300	Histone acetyltransferase	Rubinstein-Taybi syndrome (Roelfsema and Peters, 2017)
KANSL1	Histone acetyltransferase	Seizures (Zollino et al., 2012)
KDM5C	Histone demethylase	X-linked mental retardation (Michelson et al., 2011); Autism (Adegbola et al., 2008)
NSD1	Histone methyltransferase	Sotos syndrome (Berdasco et al., 2009)
PHF8	Histone demethylase	X-linked mental retardation (Kleine-Kohlbrecher et al., 2010)
RPS6KA3	Histone phosphorylation	Coffin-Lowry syndrome (Pereira et al., 2010)
EZH2	Histone methyltransferase	Weaver syndrome (Gibson et al., 2012)
MLL	Histone methyltransferase	Wiedemann-Steiner syndrome (Jones et al., 2012)
MLL2	Histone methyltransferase	Kabuki syndrome (Ng et al., 2010)
KAT6B	Histone acetyltransferase	Genitopatellar syndrome (Campeau et al., 2012)
KDM6A	Histone demethylase	Kabuki syndrome (Lederer et al., 2012)
HDAC4	Histone deacetylase	Brachydactyly mental retardation syndrome (Williams et al., 2010)
ASH1L	Histone methyltransferase	Autism (De Rubeis et al., 2014; Stessman et al., 2017)
KMT5B	Histone methyltransferase	Autism (Iossifov et al., 2012; Stessman et al., 2017)
MLL3	Histone methyltransferase	Autism (De Rubeis et al., 2014)

wide association studies assessed the methylation state of the brain's DNA in relation to Alzheimer's disease (De Jager et al., 2014; Lunnon et al., 2014). Differentially methylated regions are found at four loci: ANK1, CDH23, RHBDF2 and RPL13, inducing a corresponding RNA expression alteration. Moreover, alterations in global levels of DNA methylation and hydroxymethylation were found in monozygotic twins discordant for AD (Mastroeni et al., 2009; Chouliaras et al., 2013). Additionally, DNA hypo- and hyper-methylation of genes that are implicated in AD pathology have been found in AD brains, such as TMEM59 and PSEN1 (Wang et al., 2008; Bakulski et al., 2012). Considering the later onset of these diseases, the defects of activity-dependent epigenetic regulation might contribute to its pathology.

Huntington disease

The interaction of mutant huntingtin with the transcriptional machinery and miRNA-mediated gene silencing complexes results in transcriptional silencing, which is central to the pathophysiology of Huntington disease (Savas et al., 2008). The dysregulation of REST and REST-dependent epigenetic remodelling described above was associated with Huntington disease through regulating gene silencing (Buckley et al., 2010). Huntingtin binds to REST, thus inhibiting its translocation to the nucleus to regulate neuronal survival (Zuccato et al., 2003). The CAG repeats in mutant huntingtin disrupts the binding of huntingtin to REST, resulting in reduced transcription of REST target genes (Zuccato et al., 2003, 2007). Furthermore, polycomb proteins have also been implicated in Huntington disease. Loss of PRC2 induces the upregulation of genes involved in Huntington disease (von Schimmelmann et al., 2016). Lastly, genome-wide association studies have shown a deficiency in 5-hydroxymethylcytosine in a mouse model of Huntington disease. The aberrant methylation and silencing of genes are involved in neurogenesis, neuronal function and survival in HD brain (Wang et al., 2013).

Conclusion and remarks

Although epigenetic changes are observed in many diseases, further research is required to better understand the learning induced epigenetic modifications in the genome of functional neural circuits. The various states of the transcriptional program, which are determined by epigenetic regulators, need to be further characterized. Furthermore, there is still a lack of studies dissecting the signaling pathways that transduce the external signals to the epigenetic modifications.

Nonetheless, accumulating evidence has shown the critical role of epigenetics in regulating transcription and disease conditions. Drugs targeting epigenetic factors show efficiency in treating multiple brain disorders, including AD and depression. To develop more potent and selective epigenetic treatments against brain disorders, a better understanding of the epigenetic machinery in disease pathogenesis is required.

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Compliance with ethics guidelines

Ji-Song Guan declares that he has no conclict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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