

REVIEW

# Epigenetic control on cell fate choice in neural stem cells

Xiao-Ling Hu<sup>1</sup>, Yuping Wang<sup>2</sup>, Qin Shen<sup>1</sup> ✉

<sup>1</sup> Center for Stem Cell Biology and Regenerative Medicine, School of Medicine, Tsinghua Center for Life Sciences, Tsinghua University, Beijing 100084, China

<sup>2</sup> Department of Pharmacy, Tianjin Children's Hospital, Tianjin 300074, China

✉ Correspondence: shenqin@mail.tsinghua.edu.cn

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## ABSTRACT

Derived from neural stem cells (NSCs) and progenitor cells originated from the neuroectoderm, the nervous system presents an unprecedented degree of cellular diversity, interwoven to ensure correct connections for propagating information and responding to environmental cues. NSCs and progenitor cells must integrate cell-intrinsic programs and environmental cues to achieve production of appropriate types of neurons and glia at appropriate times and places during development. These developmental dynamics are reflected in changes in gene expression, which is regulated by transcription factors and at the epigenetic level. From early commitment of neural lineage to functional plasticity in terminal differentiated neurons, epigenetic regulation is involved in every step of neural development. Here we focus on the recent advance in our understanding of epigenetic regulation on orderly generation of diverse neural cell types in the mammalian nervous system, an important aspect of neural development and regenerative medicine.

**KEYWORDS** neural stem cells (NSCs), epigenetic regulation, neurogenesis, gliogenesis, radial glial cell, cerebral cortex, subventricular zone (SVZ), DNA methylation, histone modification

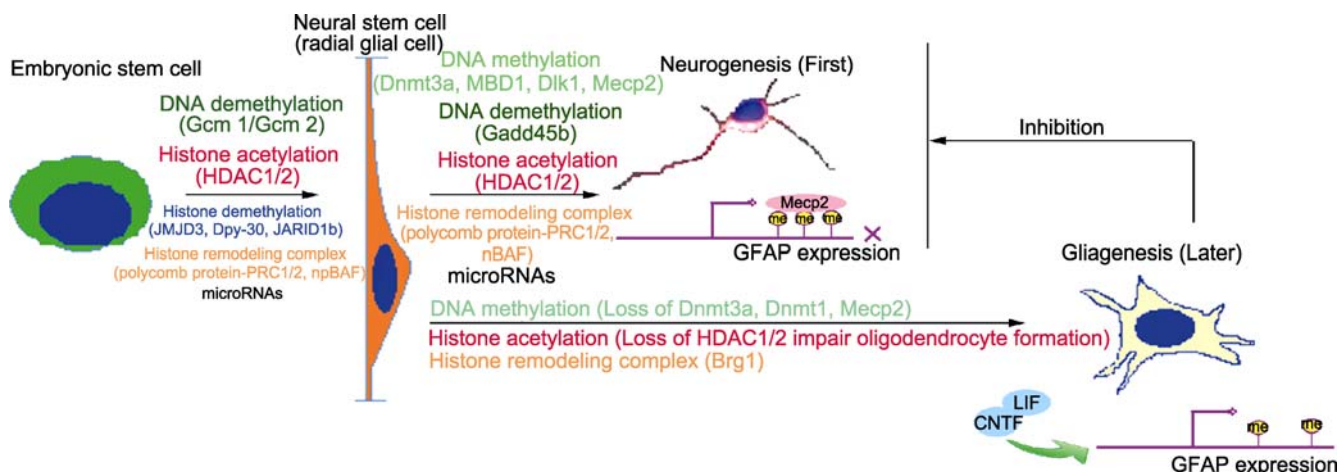
## INTRODUCTION

Neural stem cells (NSCs) in the central nervous system begin as a single layer of columnar neuroepithelial cells in the ventricular zone (VZ) of the neural tube (Temple, 2001). After

initial symmetric divisions to self-expand, NSCs divide asymmetrically to give rise to differentiated progeny and maintain a copy of themselves, demonstrating both self-renewal and differentiation, two defining features of stem cells. Throughout neural development, NSCs undergo changes so as to generate a vast diversity of neural cells: neurons, astrocytes and oligodendrocytes, following a precisely controlled timing program to build up the most complex nervous system.

The best example of sequential cell generation by NSCs is demonstrated in corticogenesis, the developmental process of the cerebral cortex. The cerebral cortex is a six-layered structure derived from the anterior neuroectoderm. NSCs in the cerebral cortex first generate neurons, a process called neurogenesis, and then glia. Within cortical neurogenesis, different neuronal subtypes are generated in a precise timing order, aligned into different layers in an “inside-out” manner: early born neurons form the deeper layers while later-born neurons form the upper layers (Jacobson, 1991; Hevner et al., 2003). This timing program is preserved in cultured cortical-derived NSCs (Qian et al., 1998; Qian et al., 2000; Shen et al., 2006; Ravin et al., 2008), and also in NSCs derived from mouse and human pluripotent embryonic stem cells (Eiraku et al., 2008; Gaspard et al., 2008). However, the molecular mechanisms driving the orderly generation of different types of neurons and glia from NSCs remain to be uncovered. Recent studies have begun to reveal the important role of epigenetic mechanisms in timing cell fate choice of NSCs.

Epigenetic regulation leads to inheritable changes in phenotype or gene expression other than changes in the DNA sequence (Morange, 2002; Holliday, 2006; Bernstein et al., 2007; Goldberg et al., 2007; Jamnicky et al., 2010). Epigenetic events are defined as the structural adaptation of chromosomal regions so as to register, signal or perpetuate



**Figure 1.** Major epigenetic regulators involved in the differentiating process from embryonic stem cells into neural stem cells and the timing of cell fate determination of neural stem cells (neurogenesis and gliogenesis).

altered activity states (Bird, 2007), which is accomplished through three highly interconnected pathways: DNA methylation, chromatin modifications including ATP-dependent chromatin remodeling and covalent histone modification, and non-coding RNA expression (Bernstein and Allis, 2005; Goll and Bestor, 2005; Allis et al., 2007; Goldberg et al., 2007). In this review, we provide an overview on epigenetic regulation of neurogenesis through different mechanisms and their interplay and highlight the most recent progresses in the field.

## DNA METHYLATION

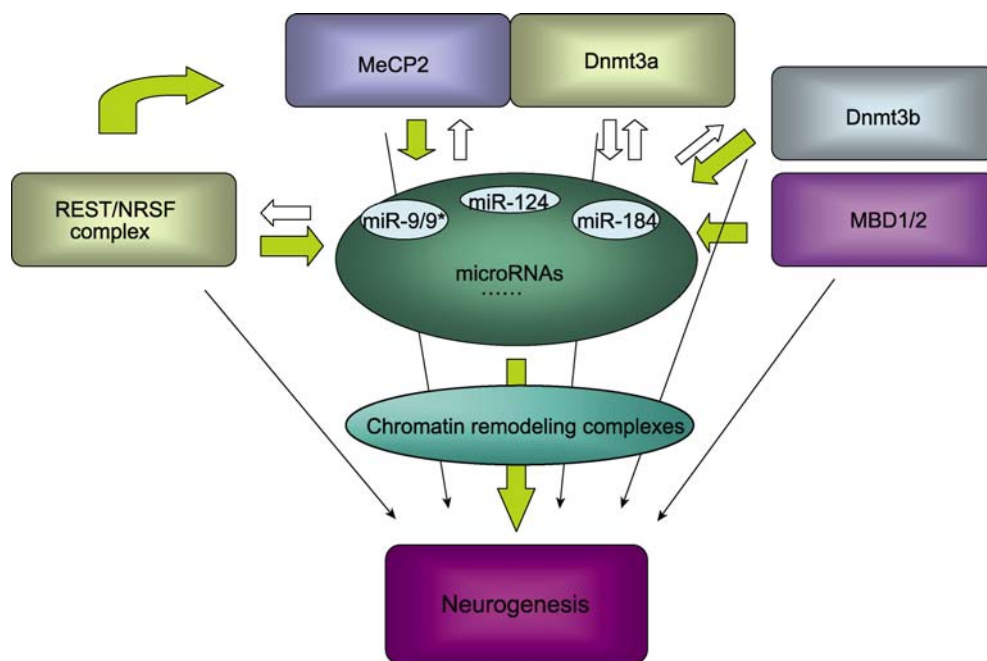
DNA methylation is one of the major epigenetic mechanisms in vertebrate (Groth et al., 2007; Suzuki and Bird, 2008). DNA methylation is required for fundamental processes, including gene imprinting, X chromosome inactivation in females, transcriptional repression of transposons in both germ and somatic cells and the establishment and maintenance of stable cellular identities (Yoder et al., 1997; Walsh and Bestor, 1999; Bird, 2002; Jaenisch and Bird, 2003; Ooi and Bestor, 2008b; De Carvalho et al., 2010; Deaton and Bird, 2011; Goll and Halpern, 2011). A family of DNA methyltransferases (Dnmts), including *de novo* DNA methyltransferases Dnmt3a and Dnmt3b and maintenance methyltransferase Dnmt1, mediates the methylation reaction, which adds a methyl group (-CH<sub>3</sub>) to the 5' position of the pyrimidine ring of cytosine residues and primarily occurs at CpG dinucleotides (Li et al., 1992; Okano et al., 1999; Goll and Bestor, 2005; Surani et al., 2007). DNA cytosine methylation is typically a repressive mark associated with transcriptional silencing. It can directly interfere with the binding of transcription factors to their target gene sequences or indirectly suppress gene expression through a family of methyl-CpG binding domain containing proteins (MBDs) such as MBD1-3 and methyl-CpG binding protein (MeCP2) (Robertson and Wolffe, 2000), which further recruit repressor complexes containing histone deacetylases

(HDAC) (Robertson et al., 2000).

## DNA methylation regulates neural development

Reduction of DNA methylation by ablation of Dnmt1 or Dnmt3b in mice leads to embryonic lethality, with multiple developmental defects including neural tube defects (Li et al., 1992; Okano et al., 1999). While mice lacking Dnmt3a alone are able to live to birth, postnatal neurogenesis is severely affected (Okano et al., 1999; Nguyen et al., 2007; Wu et al., 2010a). The difference in phenotype could be explained by overlapping function of these two genes and the temporal difference in their expression in the nervous system. Dnmt3b is expressed in early neural progenitor cells (NPCs) and decreases as neural development proceeds. In contrast, the Dnmt3a full length variant is barely detectable in E10.5 mouse forebrain but expression significantly increases from E13.5 and persists into adulthood (Feng et al., 2005; Li et al., 2007; Wu et al., 2010a). In the postnatal forebrain, Dnmt3a is expressed in the subventricular zone (SVZ) and the hippocampal dentate gyrus. It mediates methylation at the non-promoter regions in genes related to nervous system development and neurogenesis, but methylates the proximal promoter regions of non-neuronal genes such as GFAP (Wu et al., 2010a). Loss of Dnmt3a in postnatal NSCs leads to down-regulation of neurogenic genes *Dlx2*, *Neurog2* and *Sp8*, but up-regulation of genes involved in astroglial and oligodendroglial differentiation, accounting for the impairment of neurogenesis (Wu et al., 2010a) (Fig. 1).

The MBD protein family members are predominantly expressed in neurons in the central nervous system (Juliandi et al., 2010b), but recently evidence for their involvement in adult neurogenesis begins to emerge. MBD1 is required for postnatal neurogenesis in the SGZ (Zhao et al., 2003). It binds to the promoter of the fibroblast growth factor 2 (*FGF2*) gene, a mitogen for NSCs and progenitor cells. Loss of



**Figure 2. The network of epigenetic regulation in controlling neurogenesis.** Different epigenetic mechanisms can cooperate and constitute a regulation network to regulate cell fate. The color filled arrows indicate experimentally tested regulation and the blank arrows indicate proposed regulation in CNS. REST/NRSF, RE-1 silencing transcription factor or neural restrictive silencer factor; MeCP2, methyl CpG binding protein 2; Dnmt3a/Dnmt3b, DNA (cytosine-5)-methyltransferase 3a or b; MBD1/2, methyl-CpG-binding domain protein 1 or 2.

MBD1 in adult NSCs reduces methylation of the FGF2 promoter region, and increases the level of FGF2, leading to impairment of neuronal differentiation (Li et al., 2008) (Fig. 1). Recently, both MeCP2 and MBD1 have been shown to regulate microRNA expression, suggesting interplay between different epigenetic mechanisms (Liu et al., 2010; Wu et al., 2010b) (Fig. 2).

Interestingly, a recent study shows that postnatal acquisition of methylation at the germline differentially methylated region is associated with specific and selective loss of imprinting of the delta-like homologue 1 (Dlk1) gene, which encodes membrane-bound and secreted isoforms of a NOTCH ligand with the former expressed in NSCs and the latter expressed in niche astrocytes. The membrane-bound Dlk1 in NSCs is required for self-renewal and adult neurogenesis in response to secreted Dlk1 from niche astrocytes (Ferrón et al., 2011) (Fig. 1). These studies demonstrate that DNA methylation could occur at gene- and context-specific level to allow fine tuning of neurogenesis.

DNA methylation is also an important mechanism for timing the neuron/glia fate choice, which has been discussed in excellent reviews by Nakashima's group (Kohyama et al., 2008; Juliandi et al., 2010a, b). A change in DNA methylation of the astrocyte-specific gene promoters (such as GFAP) allows the progenitor cells to generate neurons at early stage, and then switch to adopt glial fate during late stage in re-

sponse to gliogenic signals such as LIF and CNTF (Kohyama et al., 2008; Namihira et al., 2008) (Fig. 1). Conditional deletion of Dnmt1 in Nestin positive neural progenitor cells led to accelerated demethylation in glial differentiation-related genes and precocious astroglial differentiation (Fan et al., 2005). In contrast, ectopic expression of MeCP2, an MBD family gene mutated in Rett syndrome, in NSCs exposed to astrocyte-inducing factors prevents astroglia differentiation but promotes neuronal differentiation; however this is not associated with methylation of the GFAP promoter but the binding of MeCP2 to the hypermethylated exon region of the GFAP gene (Setoguchi et al., 2006; Tsujimura et al., 2009) (Fig. 1). Hence the status of DNA methylation in both promoter and exon regions of cell-specific genes is critical for cell-fate determining.

### DNA demethylation in neural development

DNA methylation can be removed passively through blocking methylation of newly synthesized DNA during DNA replication, or actively through enzymatic reactions that remove the methyl-modifications (Weiss and Cedar, 1997; Kapoor et al., 2005; Niehrs, 2009). Evidence for active demethylation has emerged since the 1980s when it was demonstrated that mammalian cells contain an enzymatic activity, which releases tritium from 5-(3H-methyl) cytosine-labeled DNA

(Gjerset and Martin, 1982) and demethylation occurs in a site-specific manner and independent of DNA synthesis (Wilks et al., 1984). Recent advance in reprogramming differentiated cells to pluripotent state also provides a prominent example of DNA demethylation (Bhutani et al., 2010). The identity of a direct demethylase, an intuitive choice for demethylation, however, has been elusive and controversial (Ooi and Bestor, 2008a; Ma et al., 2009). Interestingly, it has been found that DNMT3a/3b are also capable of deamination that changes a cytosine to thymidine, providing a mechanism for cyclic transition between methylation and demethylation (Métivier et al., 2008). Different groups have identified in the past year or so enzymes that modify the methyl group to indirectly mediate active demethylation in mammalian cells, such as the ten-eleven translocation (TET) family, the AID/APOBEC family, and a family of base excision repair (BER) glycosylases (Rai et al., 2008; Bhutani et al., 2010; Cortellino et al., 2011; Ficz et al., 2011; Guo et al., 2011; He et al., 2011b; Pastor et al., 2011; Song et al., 2011; Wu et al., 2011a, b; Xu et al., 2011). These enzymes first modify the methylated cytosine by hydroxylation, deamination, oxidation, or a combination of these modifications, leading to its replacement by DNA repair. These studies have further supported the notion that active DNA demethylation is an important determinant for the DNA methylation signature of a cell (Bhutani et al., 2011).

The nervous system is perhaps one of the earliest specified tissues during development. It emerges in a process called neurulation which occurs after neural induction of the ectoderm by the underlying mesoderm into the neuroectoderm (Smith and Schoenwolf, 1997). Expression of neural tissue-specific marker genes, such as Nestin and Sox1, first becomes detectable at E7.0–E8.0 in mouse embryos (Wood and Episkopou, 1999; Kawaguchi et al., 2001). NSCs that are responsive to FGF2 to generate floating neurospheres *in vitro* first appear at E8.5 and persist into adulthood (Reynolds and Weiss, 1992; Tropepe et al., 1999). Maintenance of the NSC identity requires activation of Notch signaling pathway (Nakamura et al., 2000; Hitoshi et al., 2002; Hitoshi et al., 2004). However, what mechanism induces early NSC fate has been less clear. A recent study has shown that Hes5, one of the target genes of Notch signaling, is highly methylated in E7.5 embryos but completely demethylated by E9.5 (Hitoshi et al., 2011). Interestingly, two mammalian homologues of the *Drosophila* Gcm gene, Gcm1 and Gcm2, play a critical role in demethylation of the Hes5 promoter, allowing it to respond to the Notch signaling. Single knockout of Gcm1 or Gcm2 partially reduced but double knockout Gcm1 and 2 significantly reduced derivation of definitive NSCs, and the reduction could be rescued by Hes5 expression, suggesting that expression of Hes5 which is enabled by demethylation through Gcms in early embryos is required for generation of NSCs (Hitoshi et al., 2011) (Fig. 1). The demethylation does not involve MBD4, which possesses thymidine glycosylase activ-

ity, so the mechanism of active demethylation by Gcms needs to be further investigated.

DNA demethylation has been shown to be important for activity-dependent modulation of adult neurogenesis in the hippocampus. This is mediated by Gadd45b, an activity-induced immediate early gene, which can act as a sensor in mature neurons for changes in environment. Gadd45b promotes DNA demethylation and relieves repression of genes critical for adult neurogenesis, including brain-derived neurotrophic factor (BDNF) and FGF2, thus providing a bridge between neuronal activity and proliferation and neuron production of adult neural progenitor cells (Ma et al., 2009; Wu and Sun, 2009; Ma et al., 2010) (Fig. 1). Furthermore, the three demethylation enzymatic systems seem to act cooperatively: a TET1/APOBEC-mediated oxidation-deamination mechanism promotes DNA demethylation in the adult brain through a process that requires the BER pathway (Guo et al., 2011), indicating the adult brain possesses a robust, active demethylating machinery.

## CHROMATIN VARIATIONS: COVALENT HISTONE MODIFICATION AND NONCOVALENT MECHANISMS

The nucleosome is the fundamental repeating subunit of chromatin, consisting of an octamer of histone proteins (Kornberg, 1974). The N-terminal tails of histones are highly subject to a diverse and complex array of posttranslational covalent modifications, including acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP ribosylation, deamination and proline isomerization (Zhang and Reinberg, 2001; Kouzarides, 2007). However, not all these modifications will be on the same histone at the same time. Among these modifications, acetylation and lysine methylation are most studied and can be identified by chromatin immunoprecipitation (ChIP) on ChIP assays using modification-specific antibodies.

### Histone acetylation

Histone acetylation is catalyzed by histone acetyltransferases (HATs) on the lysine residues of the N-terminal histone tails, which destabilizes nucleosome structure or arrangement and allows other nuclear factors, such as transcriptional activators, to gain an access to a genetic locus, leading to gene activation (Roth and Allis, 1996; Wade et al., 1997; Sterner and Berger, 2000). Histone acetylation is a reversible process and can be removed by HDACs, which leads to gene repression (Pazin and Kadonaga, 1997; Kuo and Allis, 1998). For example, HDAC-mediated transcriptional repression is essential for the proliferation and self-renewal of NSCs (Sun et al., 2007; Sun et al., 2011) (Fig. 1). Neural-expressed HDACs interact with TLX, an essential neural stem cell regulator, to suppress TLX target genes, including the cyclin-dependent

kinase inhibitor P21 and the tumor suppressor gene Pten, to promote NSC proliferation (Sun et al., 2007). Inhibition of HDACs by the anti-epileptic drug valproic acid (VPA) or trichostatin A induces neuronal differentiation and inhibits glial cell differentiation of adult NSCs, which is likely mediated through upregulation of neuronal specific genes, such as neurogenic basic helix-loop-helix transcription factors NeuroD, Neurogenin 1 (Ngn1) and Math1 (Hsieh et al., 2004; Yu et al., 2009). Conditional loss of HDAC1 and 2 in neural precursor cells prevented them from differentiating into neurons (Montgomery et al., 2009), while conditional knockout of HDAC1/2 in oligodendrocyte precursor cells disrupts oligodendrocyte formation (Ye et al., 2009), suggesting histone deacetylation plays important roles at different stages of neural development (Fig. 1).

### Histone methylation and demethylation

Compared with HATs and HDACs, which can modify more than one lysine residue, lysine methyltransferases which catalyze histone methylation usually modify one single lysine on a single histone (Bannister and Kouzarides, 2005). Consequently, lysine methylation regulates transcriptional activity depending on the location and number of methyl-groups: histone H3 methylation at lysine 4 (K4), K36 and K79 leads to transcriptional activation (Bannister et al., 2005; Zhao et al., 2005; Cartagena et al., 2008; Edmunds et al., 2008), whereas histone H3 methylation at K9 and K27 as well as histone H4 methylation at K59 leads to transcriptional silencing (Rougeulle et al., 2004; Alvarez-Venegas and Avramova, 2005; Zhao et al., 2005).

Unlike histone acetylation, which seems to be dynamic and reversible, histone methylation had been thought to be stable and could be reversed only by histone replacement. However recent discoveries of histone demethylase indicate that histone methylation could be subject to changes during development. Since the first histone demethylase LSD1 was identified in 2004, many other findings of such enzymes, such as AOF1/KDM1A, JHDM2A, JMJD2/KDM4, GASC1, SMCX/JARID1c, JARID1d, YJR119c/KDM5, JMJD3/UTX/KDM6A, FBXL/KDM2, have been reported (Shi et al., 2004; Cloos et al., 2006; Whetstine et al., 2006; Yamane et al., 2006; Huarte et al., 2007; Iwase et al., 2007; Lan et al., 2007; Lee et al., 2007a, b; Ciccone et al., 2009; Mosammamaparast and Shi, 2010). The selectivity of histone demethylases for mono-, di-, or tri-methylated lysines provides more precise functional control of lysine methylation.

The status of histone methylation is also regulated by growth factors, creating a temporal neuron/glia switch during development. In later stage of cortical culture, FGF2 facilitates the access of transcription factors activated by CNTF to the GFAP promoter by inducing H3K4 methylation and suppressing H3K9 methylation, promoting the astrocyte fate (Song and Ghosh, 2004; Irmady et al., 2011) (Fig. 1).

Recently, bivalent domains which possess both activating and repressive modifications such as H3K4 and H3K27 methylation were discovered in many developmental regulatory gene loci in embryonic stem cells (ESCs) (Azuara et al., 2006; Bernstein et al., 2006; Golebiewska et al., 2009; Jiang et al., 2011). The bivalent marks keep these genes in a "poised" state to maintain the ESC's ability to self-renew but be ready to differentiate upon appropriate signals. Removing the H3K27 methylation ensures them to switch from self-renewing state to differentiation in response to environmental cues (He et al., 2011a). Upon differentiation signals, specific H3K27 demethylases such as JMJD3 resolves the bivalent domain at the nestin promoter, permitting neural lineage commitment (Burgold et al., 2008). Similarly, H3K4me2/3 histone demethylase JARID1b (KDM5b/PLU1) has been found to be essential for ESC differentiation along the neural lineage (Schmitz et al., 2011). Depletion of Dpy-30, a core subunit of the SET1/MLL histone methyltransferase complexes, significantly reduces H3K4 methylation but does not affect ESC self-renewal. Instead, loss of Dpy-30 suppresses the induction of neural specific genes by retinoic acid (Jiang et al., 2011). These results indicate the importance of H3K4 methylation in developmental potential of ESCs into neural lineage (Fig. 1).

### Chromatin remodeling complexes

Chromatin remodeling complexes provide additional noncovalent mechanisms to modify chromatin accessibility by changing histone-DNA interaction in an ATP-dependent manner (Martens and Winston, 2003; Smith and Peterson, 2005; de la Serna et al., 2006; Hargreaves and Crabtree, 2011). These complexes consist of three classes based on the similarities of their ATPase subunits to the Swi2/Snf2, Isw1, and Mi-2 proteins. Mammalian SWI/SNF complexes contain one of two catalytic ATPase subunits: Brm (for Brahma; also called SNF2 $\alpha$ ) and Brg1 (also called SNF2 $\beta$ ). During neural development, the expression of Brg1 is predominantly in neurons, but not in progenitor cells in the embryonic cerebral cortex before E13, then afterwards is induced in progenitor cells in the VZ and SVZ (Randazzo et al., 1994; Matsumoto et al., 2006). Deletion of Brg1 in Nestin-cre mice causes defects in neuronal differentiation and glial generation, suggesting Brg1 is required to maintain gliogenic populations of NSCs (Matsumoto et al., 2006). Interestingly, Brg can function as both repressor and activator independent of its ATPase activity in regulating Shh signaling in the forebrain (Zhan et al., 2011), providing another piece of evidence to reveal the complexity of epigenetic regulation.

The Polycomb group of proteins and recently identified Brahma related gene (Brg)/Brahma (Brm)-associated factor complexes are also important chromatin remodeling factors. In ES cells, lineage-specific genes are repressed by Polycomb-mediated H3K27 trimethylation. The Polycomb group

(PcG) family of proteins was first identified in *Drosophila* because of patterning defects caused in PcG mutant flies (Kenyon, 1995). PcG proteins form two repressor complexes, Polycomb repressive complex 1 (PRC1) and Polycomb repressive complex 2 (PRC2), to serve as enzymes that carry out histone modifications (Ringrose and Paro, 2004; Schmitz et al., 2011). The PRC2 proteins including Eed, Suz12, and Ezh1 or Ezh2 act as methyltransferases to catalyze methylation of lysine 27 of histone H3 (Cao et al., 2002; Nekrasov et al., 2005). The trimethylation marks deposited by PRC2 recruit PRC1, and then members of PRC1 such as Ring1A/B and Bmi1 modify histone H2A, leading to a cascade of actions of gene silencing (Wang et al., 2004). In addition to cooperating on many PcG target genes, PRC2 and PRC1 can also have independent targets (Ku et al., 2008). PcG targeting is highly dynamic during the transition from ESCs to neural progenitor cells, and to fully differentiated neurons (Mohn et al., 2008). ESCs acquire characteristic epigenetic marks during their differentiation to the neural lineage (Meissner et al., 2008; Sato et al., 2010). Ablation of PcG proteins at different developmental stages yields distinct outcomes (Testa, 2011), suggesting the recruitment and targeting of PcG factors is temporally regulated (Fig. 1). How PcG complexes are recruited to different targets at different developmental stages awaits further investigation.

The BAF complexes (npBAFs and nBAFs) exert functions important for self-renewal of NSC or neuronal differentiation depending on the different combinatorial assembly of the complexes (Lessard et al., 2007; Wu et al., 2007; Yoo et al., 2009). For example, differentiation of ES cells into neural progenitor cells is accompanied by activation of Brm and npBAF. While npBAF is assembled specifically in neural progenitor cells to promote self-renewal, nBAF is found only in postmitotic neurons and dedicated to neuron-specific functions, indicating the existence of cell-type specific and developmental stage-specific chromatin remodelers (Lessard et al., 2007; Wu et al., 2007).

## NONCODING RNA

Recently, emerging evidence has pointed to an important role of RNAs, particularly non-protein coding RNAs (ncRNA) in controlling multiple epigenetic phenomena such as X-chromosome inactivation, gene imprinting and RNAi-mediated silencing (Bernstein and Allis, 2005; Mattick and Makunin, 2006). The sizes of ncRNAs range from 21 nucleotides (nt), as in the case of mature microRNAs (miRNAs), to more than 100,000 nt, such as the Air (antisense to Igf2r) RNA (Lyle et al., 2000; Storz, 2002; Bartel, 2004; Mattick and Makunin, 2005; Cao et al., 2006). Several distinct classes of ncRNAs, such as small nucleolar RNA (snoRNA), microRNA (miRNA) and long ncRNA (lncRNA), have been found highly expressed in the nervous system (Cao et al., 2006; Mehler and Mattick, 2006, 2007; Mehler,

2008). The involvement of ncRNAs in various cellular and nuclear processes is totally fascinating. The mechanisms by which long non-coding RNAs regulate gene expression await exciting discoveries in the coming years. Here we will focus on the microRNA pathway, which has been extensively studied.

miRNA are a class of small non-coding RNAs of generally 21–25 nucleotides long that alter gene expression by post-transcriptional inhibition or degradation of complementary mRNA sequences (Ambros, 2003; Ambros, 2004; He and Hannon, 2004). The mature miRNA is derived from larger precursors that form imperfect stem-loop structures, and is released from the primary transcript through stepwise processing by two ribonuclease-III (RNase III) enzymes, Drosha and Dicer (Lee et al., 2004; Griffiths-Jones et al., 2008; Moazed, 2009). A miRNA recognizes its target mRNA through a “seed match,” between the seed—a 6 nucleotide stretch at the 5' end of the miRNA—and a matching region at the 3' untranslated region (3'-UTR) of the mRNA (Grimson et al., 2007; Bartel, 2009). Most animal miRNAs form imperfect base-pairs with their targets beyond the “seed region,” allowing a miRNA to regulate many, even hundreds of genes (Cao et al., 2006; Shen and Temple, 2009).

Disruption of miRNA pathway by depleting Dicer expression in zebrafish leads to gross malformation of the brain and defective neuronal differentiation (Giraldez et al., 2005). Conditional knockout Dicer in mouse neocortex results in reduced cortical size, increased neuronal apoptosis and defective cortical layering (De Pietri Tonelli et al., 2008). However neuroepithelial cells and neuronal progenitor cells are spared at early stage until E14 when they undergo apoptosis (De Pietri Tonelli et al., 2008; Kawase-Koga et al., 2010). This could reflect stage-specific requirement of miRNA during cortical development, possibly at the time when neuronal output is at peak. Indeed, several miRNAs including miR9, miR-124, miR-92b and miR-23 are selectively expressed at different stages during neural stem cell and progenitor cell lineage progression (Cao et al., 2006). miR-124, which is the most abundant miRNA in both embryonic and adult CNS, controls the lineage progression from adult SVZ transit-amplifying cells to neuroblasts (Cheng et al., 2009). It promotes neuroblast production by targeting Sox9, a transcriptional factor important for stem cell activity, to suppress its protein expression in neuroblasts (Cheng et al., 2009). miR-9 is also highly enriched in NPCs of many vertebrates, including zebrafish, chickens, mice and humans (Kapsimali et al., 2007; Leucht et al., 2008; Coolen and Bally-Cuif, 2009; Joglekar et al., 2009). Ectopic expression of miR-9 in the developing mouse cortex led to premature neuronal differentiation and disrupted the migration of new neurons in the cortex through targeting Foxg1 (Shibata et al., 2008). In adult neurogenesis, miR-9 inhibits NSC proliferation and promotes neural differentiation by targeting the nuclear receptor TLX, which is an essential regulator of NSC self-renewal (Zhao et

al., 2009). Recently, direct reprogramming of non-neuronal cells into neurons *in vitro* has become possible even from human cells. In addition to a selected set of transcription factors, miR-9/9\* and miR-124 expression in human fibroblasts can also induce their conversion into neurons (Yoo et al., 2011). This process can be facilitated by NEUROD2 and the rate of conversion can be enhanced by transcription factor ASCL1 and MYT1L, suggesting these brain-enriched miRNAs cooperate with neural-specific transcription factors to regulate neural cell fate.

## NETWORK OF EPIGENETIC REGULATION IN CONTROLLING NEUROGENESIS

Epigenetic state of a gene involves a complex chromatin signature, but not just any single epigenetic mechanism. These different epigenetic mechanisms can cooperate and constitute a regulation network to regulate cell fate. For example, DNA methylation/demethylation is often found to be coupled with histone modification during neural development. Using ChIP, it has been shown that unmethylated DNA is largely assembled with acetylated histone and methyl groups on identical DNA sequences correlated with non-acetylated histones (Eden et al., 1998; Hashimshony et al., 2003). This effect might be partially mediated by methylcytosine-binding proteins MeCP2 and MBD1, which recruit histone deacetylases to the methylated regions. On the other hand, histone modification complex can also affect DNA methylation. The PcG protein Ezh2, which catalyses trimethylation of H3K27 on surrounding nucleosomes, directly interacts with DNMTs (Viré et al., 2006). Dnmt3a is generally excluded from H3K4me3-high, CpG-rich proximal promoters, but is enriched in inter- and intragenic regions flanking CpG islands, possibly because of the inhibitory effect of H3K4 methylation on Dnmt3a binding to chromatin. Inhibition of DNMT induced cell cycle arrest and decreased multipotency, and these effects might be mediated by an increase in miRNAs expression to suppress PcG proteins, which are targets of miRNAs (So et al., 2011). On the other hand, miRNA expression can be modulated by promoter methylation or histone acetylation. For example, genome-wide sequencing of miRNA in WT and MeCP2-KO mouse cerebella has shown that MeCP2 directly controls miRNA expression (Wu et al., 2010b). MBD1 has been shown to suppress miR-184 and posttranscriptionally regulate *Numbl* expression, which is known as a regulator of brain development (Liu et al., 2010). The interaction between miRNA and other epigenetic machinery suggests that there is a highly controlled feedback mechanism (Gatto et al., 2010; Iorio et al., 2010).

Remarkably, in this epigenetic regulation network, REST/NRSF, a transcription repressor, seems to be able to link the different mechanisms together. By binding DNA and co-repressor Co-REST, N-CoR, mSin3A, REST/NRSF can recruit histone deacetylases, histone methyltransferases and

LSD1-containing complexes to facilitate nonneuronal lineage restriction (Lunyak and Rosenfeld, 2005). Interestingly, comparative sequencing has revealed that REST/NRSF also targets multiple brain-related miRNA including miR-9/9\* and miR-124 (Conaco et al., 2006; Wu and Xie, 2006). MiR-9 and miR-124 can mediate the switch from npBAF to nBAF during neuronal differentiation from neural progenitor cells, adding another level of regulatory complexity to the neural fate transition (Yoo et al., 2009) (Fig. 2).

## CONCLUDING REMARKS

Neural development, a life-long process beginning from neural induction, involves regional patterning and temporal specification, neurogenesis and gliogenesis, and synaptic connection and plasticity. The delicate balance between gene activation and repression in different neural cell types, undoubtedly requires multiple levels of regulation in addition to transcriptional regulation, including those imposed by epigenetic mechanisms that involve neural cell specialized chromatin states, so the cells know where, when, what to be, and how to interact and respond. Environmental factors such as morphogens and niche molecules that specify neural progenitor fate and that enable the switch from neuronal to glial cell generation must also impinge on the epigenetic system. It is quite likely that fundamental progenitor programs, such as those seen during cortical development, are encoded at the epigenetic level. Moreover, alterations on the epigenomic machinery cause aberrant DNA methylation and histone acetylation triggering alterations on the transcriptional level of genes involved in the pathogenesis of neural degenerative diseases such as Alzheimer's disease, Parkinson's disease (Balazs et al., 2011; Habibi et al., 2011; Mastroeni et al., 2011). It remains to be investigated how epigenetic regulation of neurogenesis plays a role in the etiology and progression of neurodegenerative diseases. While epigenetic mechanisms control neurogenesis can be as universal as an open hand, we must bear in mind for generating such a sophisticated scheme as the nervous system, epigenetic regulation must also be as individual as a fingerprint. With the tremendous technical advances in our ability to analyze gene expression, decode deep sequences, and uncover complex structures, we can imagine the day for deciphering epigenetic fingerprints of specific neural cell types will soon be coming.

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## ABBREVIATIONS

BER, base excision repair; ChIP, chromatin immunoprecipitation;

DLK1, delta-like homologue 1; ESCs, embryonic stem cells; FGF2, fibroblast growth factor 2; HATs, histone acetyltransferases; HDAC, histone deacetylases; lncRNA, long ncRNA; MBDs, methyl-CpG binding domain containing proteins; ncRNA, non-protein coding RNA; NSCs, neural stem cells; PRC1, polycomb repressive complex 1; snoRNA, small nucleolar RNA; SVZ, subventricular zone; VZ, ventricular zone

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