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Epigenetic regulation of neurogenesis in the adult mammalian brain

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Abstract

Epigenetic regulation represents a fundamental mechanism to maintain cell-type-specific gene expression during development and serves as an essential mediator to interface the extrinsic environment and the intrinsic genetic programme. Adult neurogenesis occurs in discrete regions of the adult mammalian brain and is known to be tightly regulated by various physiological, pathological and pharmacological stimuli. Emerging evidence suggests that various epigenetic mechanisms play important roles in fine-tuning and coordinating gene expression during adult neurogenesis. Here we review recent progress in our understanding of various epigenetic mechanisms, including DNA methylation, histone modifications and non-coding RNAs, as well as cross-talk among these mechanisms, in regulating different aspects of adult mammalian neurogenesis.

Introduction

Epigenetics can be loosely defined as heritable changes in the function of genetic elements without changes in the actual genetic or underlying DNA sequence (Bird, 2007). There are three predominant mechanisms, namely DNA methylation, histone modifications and non-coding RNAs. There are now numerous studies demonstrating significant roles of epigenetic regulation in biological systems, ranging from modulation of normal embryonic development to plasticity in the adult nervous system. For example, with the same set of genomic DNA, epigenetic regulation allows one zygote to differentiate into hundreds of distinct functional cell types in the body. Aberrant epigenetic regulation has also been implicated in cancer, congenital diseases, neurodegenerative diseases and neuropsychiatric disorders (Jones & Baylin, 2002; Feng & Fan, 2009; Urdinguio *et al.*, 2009).

Adult neurogenesis occurs throughout life in two discrete regions of the adult mammalian brain (Ming & Song, 2005; Lledo *et al.*, 2006; Ma *et al.*, 2009a). In the subventricular zone (SVZ) of the lateral ventricles, neural progenitors proliferate and give rise to neuroblasts, which then migrate through the rostral migratory stream (RMS) and differentiate into granule neurons and periglomerular neurons in the olfactory bulb (Fig. 1A; Alvarez-Buylla & Lim, 2004). In the subgranular zone (SGZ) of the dentate gyrus in the hippocampus, neural progenitors produce immature new neurons that migrate locally into the granule cell layer to become dentate granule cells (Fig. 1B; Zhao *et al.*, 2008). Adult neurogenesis appears to recapitulate the complete process of neuronal development, ranging from neural progenitor activation and fate determination, to differentiation, migration, and axonal and dendritic development of newborn neurons, to synapse formation and functional integration into the existing neural circuitry (Duan *et al.*, 2008). Adult neurogenesis is tightly regulated by their local environment, or 'neurogenic niche' (Doetsch, 2003; Alvarez-Buylla & Lim, 2004). This niche is composed of the extracellular matrix and various cell types, including astroglia, ependymal cells, endothelial cells, immature progeny of adult neural stem cells and mature neurons within the local circuitry (Ma *et al.*, 2005; Jordan *et al.*, 2007). The niche is also a target of many physiological, pathological and pharmacological stimuli that regulate adult neurogenesis. Until recently, the analysis of adult neural stem cells and neurogenesis has largely focused on cellular signalling studies. We have just begun to understand the critical roles of nuclear epigenetic regulation in linking external environmental influence of the niche to the internal transcriptional and post-transcriptional control of gene expression in neural progenitors and their progeny in the adult brain. In this review, we highlight three major epigenetic mechanisms, DNA methylation, histone modifications and non-coding RNAs, in both cell-intrinsic and cell-extrinsic regulation of different aspects of adult neurogenesis in the SVZ/olfactory bulb and SGZ/dentate gyrus. Interested readers are encouraged to read additional reviews on related topics (Ma *et al.*, 2009d, 2010; Covic *et al.*, 2010; Hsieh & Eisch, 2010).

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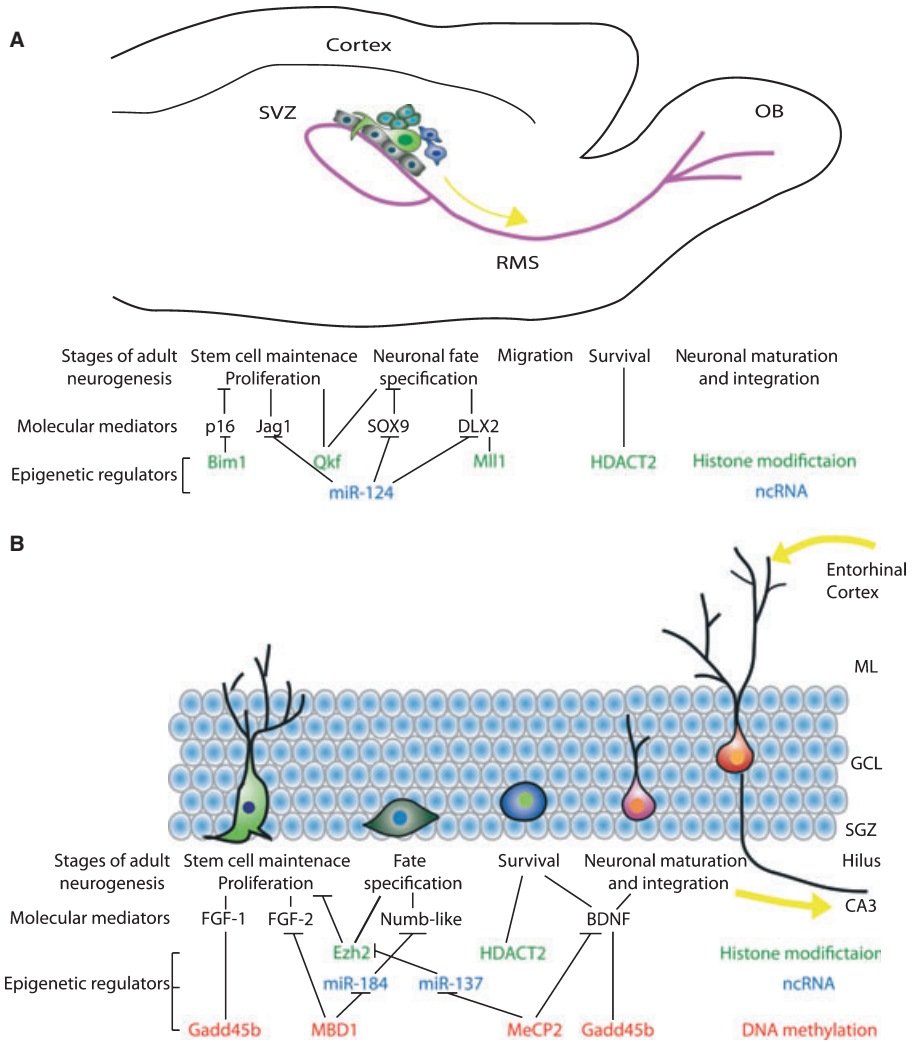

FIG. 1. Epigenetic regulation of neurogenesis in the adult mammalian brain. Shown are schematic diagrams of the neurogenesis process in the adult SVZ/olfactory bulb system (A) and the SGZ/hippocampal system (B). A summary of current knowledge on major epigenetic regulations in regulating gene expression and different aspects of adult neurogenesis is also presented. SVZ, subventricular zone; OB, olfactory bulb; RMS, rostral migratory stream; RGL, radial glia-like cell; TA cell, transient amplifying cell; ncRNA, non-coding RNA; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone.

DNA methylation

DNA methylation was first described in the late 1940s (Hotchkiss, 1948) and early 1950s (Wyatt, 1951) and is probably the most intensively studied type of epigenetic modification. DNA methylation in the mammalian genomes predominantly occurs at the cytosine residue of CpG dinucleotides to generate 5-methylcytosine on the pyrimidine ring (Jaenisch & Bird, 2003; Suzuki & Bird, 2008; Zhu, 2009). Limited non-CpG methylation has been found in embryonic stem cells (Ramsahoye *et al.*, 2000; Lister *et al.*, 2009), but has not yet been characterized in detail in other cell types, such as neural progenitors and their progeny. A family of DNA methyltransferases (Dnmts) is responsible for the catalysis of DNA methylation (Goll & Bestor, 2005; Reik, 2007). Dnmt3a and Dnmt3b act as *de novo* methyltransferases to transfer methyl groups from *S*-adenosyl-L-methionine (SAM) to unmethylated target DNA, whereas Dnmt1 recognizes hemi-methylated DNA after DNA replication and maintains the DNA methylation state in daughter cells. DNA methylation has been traditionally viewed as a very stable epigenetic mark compared with other epigenetic modifications, yet the loss of DNA methylation, or demethylation, has been observed in many biological processes (Wu & Zhang, 2010). The loss of the methyl group from 5-methylcytosine DNA can occur through a passive process during DNA replication in the absence of functional Dnmt1 activity. The mechanism of active demethylation, a process of enzymatic removal of the methyl group from genomic DNA without DNA replication, is under intensive debate (Ooi & Bestor, 2008; Wu & Zhang, 2010). Multiple mechanisms for active DNA demethylation have been proposed for the mammalian system (Ma *et al.*, 2009b; Wu & Zhang, 2010), including DNA excision repair-based mechanisms involving the Growth arrest and DNA damage-inducible protein 45 (Gadd45) family of proteins (Morgan *et al.*, 2004; Rai *et al.*, 2008; Gehring *et al.*, 2009; Ma *et al.*, 2009c) and Radial SAM mechanisms involving the elongator complex (Okada *et al.*, 2010).

The methylation status of DNA, depending on its location and density, has been shown to play critical roles in gene regulation, including tissue-specific gene expression, X chromosome inactivation, gene imprinting and cell reprogramming (Jaenisch & Bird, 2003; Edwards & Ferguson-Smith, 2007; Reik, 2007; Suzuki & Bird, 2008). Deficiencies in Dnmts result in embryonic lethality or other profound developmental defects (Goll & Bestor, 2005; Reik, 2007). Recent

studies have implicated a critical role of DNA methylation in regulating neurogenesis (Meissner *et al.*, 2008; Mohn *et al.*, 2008). During embryonic development, Dnmt1 is critical for the timing of the switch from neurogenesis to gliogenesis; conditional deletion of Dnmt1 in embryonic cortical neural progenitors results in DNA hypomethylation and precocious astrogliogenesis (Fan *et al.*, 2005). Furthermore, proliferating neural progenitors with Dnmt1 deletion exhibit DNA hypomethylation and are rapidly eliminated within 3 weeks of postnatal life (Fan *et al.*, 2001). Thus, the proper DNA methylation status is critical for both maintenance and fate choice of neural progenitors during early development. Whether Dnmts play similar roles in regulating adult neurogenesis remains to be examined.

Methyl-CpG-binding proteins are major mediators of DNA methylation in regulating gene expression. Methyl-CpG-binding domain protein 1 (Mbd1) null mice exhibit defects in neurogenesis in the dentate gyrus of the adult hippocampus (Zhao *et al.*, 2003). Mbd1 directly binds to the promoter region of fibroblast growth factor 2 (Fgf2), a major mitogen for adult neural progenitors *in vitro* and *in vivo* (Ma *et al.*, 2009e), resulting in tight regulation of Fgf2 expression in adult neural progenitors (Fig. 1B; Li *et al.*, 2008a). A recent study has revealed an even more complex picture wherein Mbd1 suppresses several microRNAs (miRNAs) and interaction between two epigenetic mechanisms helps to control the balance between proliferation and differentiation of adult neural progenitors of the hippocampus (Fig. 1B, and see below; Liu *et al.*, 2010).

Methyl-CpG-binding protein 2 (MeCP2), a gene that is mutated in Rett syndrome, is also a major regulator of gene expression in the nervous system. In the developing brain, MeCP2 functions both cell-autonomously and non-cell-autonomously to regulate maturation and dendritic arborization of cortical pyramidal neurons (Kishi & Macklis, 2010). In the adult dentate gyrus of MeCP2-knockout mice, newborn neurons exhibit pronounced deficits in their neuronal maturation and spine formation (Smrt *et al.*, 2007), suggesting a conserved function of MeCP2 during different developmental stages. One of the best known targets of MeCP2 is brain-derived neurotrophic factor (BDNF), which has been implicated in regulating several aspects of adult hippocampal neurogenesis, including proliferation of neural progenitors (Li *et al.*, 2008b) and development of newborn neurons (Schmidt & Duman, 2007). MeCP2 binds to the BDNF promoter and suppresses its expression. After neuronal activation and membrane depolarization, two potential mechanisms may facilitate the release of MeCP2 from the BDNF promoter to facilitate its transcription. First, in cultured primary neurons, neuronal activity induces DNA demethylation at specific CpG sites in the promoter IV of BDNF, resulting in dissociation of the MeCP2–histone deacetylase–mSin3A complex from the promoter and increased BDNF transcription (Martinowich *et al.*, 2003). Secondly, neuronal activity-induced calcium influx triggers phosphorylation of MeCP2 at serine 421 to facilitate its release from the promoter and subsequent transcription of BDNF (Chen *et al.*, 2003; Zhou *et al.*, 2006). Although MeCP2 was previously believed to regulate neuronal maturation, but not fate choice of neural progenitors (Kishi & Macklis, 2004), a recent study has suggested a novel role for MeCP2 in regulating proliferation and differentiation of adult hippocampal neural progenitors both *in vitro* and *in vivo* through modulating the expression of one miRNA, miR-137 (Fig. 1B, and see below; Szulwach *et al.*, 2010). Similar to the action of Mbd1, MeCP2 represents another example that interaction between two epigenetic mechanisms regulates the balance between proliferation and differentiation of neural progenitors in the adult hippocampus.

Adult neurogenesis is known to be regulated by many stimuli, including neuronal activity and antidepressant treatments. Transient neuronal activation, such as seizures, leads to sustained up-regulation of adult hippocampal neurogenesis over a period of weeks (Parent *et al.*, 1997). Using electroconvulsive stimulation as a paradigm for synchronous neuronal activation of dentate granule cells, Gadd45b was identified as an immediate early gene that requires depolarization-induced calcium influx and CaM kinase activity for its induction (Ma *et al.*, 2009c). A family of Gadd45 proteins has recently been implicated in promoting active DNA demethylation in the vertebrate system, prrobably through its interaction with the DNA excision-repair-based DNA demethylation mechanism (Ma *et al.*, 2009b). Interestingly, Gadd45b-knockout mice exhibit specific defects in neuronal activity-induced proliferation of neural progenitors and dendritic growth of newborn dentate granule cells in the adult hippocampus, by either electroconvulsive stimulation or physical exercise (Ma *et al.*, 2009c). Mechanistically, Gadd45b-knockout mice exhibit defects in neuronal activity-induced CpG demethylation in the brain-specific promoter B of the Fgf1 gene and promoter IX of the BDNF gene, as well as subsequent sustained expression of these specific gene isoforms (Ma *et al.*, 2009c). *In vitro*, FGF-1 exhibits similar potency as FGF-2 in regulating the self-renewal of adult hippocampal neural progenitors. Interestingly, Gadd45b appears to be largely induced in mature neurons, but not in proliferating neuronal progenitors *in vivo*, suggesting a niche-based regulatory mechanism instead of an intrinsic mechanism. Thus, Gadd45b-dependent DNA demethylation may serve as a key mechanism to translate transient environment signalling to epigenetic changes in neurogenic niche cells for sustained regulation of neural progenitors and their neuronal development over the long term.

Histone modifications

The building blocks of chromatin, nucleosome core particles, each consists of approximately 147 bp of DNA wrapped around two copies of four distinct histone proteins: H2A, H2B, H3 and H4 (Luger *et al.*, 1999). The N-terminal tails of histones are subject to at least six distinct post-translational modifications, including acetylation, methylation, ubiquitination, phosphorylation, ribosylation and SUMOylation. These histone tail amino acid-specific modifications, named 'histone codes', regulate the genomic accessibility and provide a platform for binding of other factors to control the activation or repression of associated genes.

Acetylation of histones occurs at lysine residues and is catalysed by histone acetyltransferases (HATs). Histone acetylation is a reversible process and deacetylation is catalysed by histone deacetylases (HDACs). Importantly, HDACs can act on many lysine-acetylated proteins, in addition to their prototype substrate, histones. Thus, any manipulations of HDAC activity might affect acetylation of a wide variety of intracellular targets. Recent studies have implicated HATs and HDACs in regulating adult neurogenesis. Knockout mice for Querkopf (Qkf, Myst4, Morf), an MYST family transcriptional co-activator with HAT activity (Champagne *et al.*, 1999), exhibit reduced proliferation of neural progenitors in the SVZ, and a decreased number of both migrating neuroblasts in the RMS and new interneurons in the olfactory bulb in middle-aged mice (9 months old), but not in young adult mice (3 months old; Merson *et al.*, 2006). Thus, Qkf-dependent epigenetic mechanisms may help to maintain the neurogenic capacity of neural progenitors in the adult brain (Fig. 1A). In support of this view, neurospheres derived from Qkf-knockout mice exhibit a decreased capacity for neuronal differentiation, whereas overexpression of Qkf increases neuronal production from both wild-type and Qkf mutant neurospheres *in vitro* (Merson *et al.*, 2006). In a rodent model of human temporal lobe epilepsy, kainic acid-induced seizures lead to increased

proliferation of neural progenitors, defective migration, and aberrant axonal and dendritic development of newborn dentate granule cells in the adult hippocampus (Jessberger *et al.*, 2005, 2007a,b). Interestingly, treatment with the HDAC inhibitor valproic acid blocks seizure-induced proliferation of neural progenitors in the adult dentate gyrus and protects animals from seizure-induced cognitive impairment in a hippocampus-dependent learning task (Jessberger *et al.*, 2007a). In a separate study, treatment with sodium butyrate, another HDAC inhibitor, immediately after cerebral ischaemia promotes proliferation of neural progenitors in both SVZ and SGZ (Kim *et al.*, 2009). Given the non-specificity of these drugs, studies using conditional knockout mice of different HATs and HDACs will provide more insight into the direct role of histone acetylation in regulating specific aspects of adult neurogenesis and the potential molecular mechanisms. Indeed, a recent study with inducible deletion of HDAC2 in neural progenitors using GLAST-CreER^{T2} mice shows abnormal maturation of newborn neurons in both the SGZ/hippocampus and the SVZ/olfactory bulb system, leading to increased cell death in both neurogenic regions (Jawerka *et al.*, 2010). Further characterization suggests that HDAC2 plays an cell autonomous role during the immature neuronal stage only in adult neurogenesis, but not embryonic neurogenesis (Jawerka *et al.*, 2010). One potential mechanism underlying HDAC2-dependent regulation is the silencing of Sox2 expression after neuronal differentiation of neural progenitors (Jawerka *et al.*, 2010).

Histone methylation represents another important epigenetic mechanism for gene expression. The polycomb and trithorax group (PcG and TrxG) proteins are antagonistic chromatin complexes: members of the PcG complex catalyse trimethylation of lysine 27 of histone 3 (H3K27me3) that leads to transient transcriptional repression through local heterochromatin formation, whereas the TrxG complex is recruited by RNA polymerase II and catalyzes H3K4 trimethylation (H3K4me3) of promoter proximal nucleosomes to activate their target loci (Ringrose & Paro, 2007; Ng & Gurdon, 2008). The PcG and TrxG complexes have also been implicated in regulating specific aspects of adult neurogenesis. For example, in knockout mice for Bmi-1, a member of the PcG complex, neural progenitors, but not transient amplifying cells, are depleted in the SVZ (Molofsky *et al.*, 2003). The effect of Bmi1 appears to be mediated by the cell cycle inhibitor p16 protein, as Bmi1 and p16 double knockouts have largely restored numbers of adult neural progenitors. Furthermore, Bmi1 overexpression *in vitro* significantly expands the number of adult SVZ neural progenitors and maintains their developmental potential to generate neuronal lineages (Fasano *et al.*, 2007, 2009). In another example, mixed-lineage leukaemia 1 (Mll1), a TrxG member that encodes an H3K4 methyltransferase, is specifically required for neuronal differentiation, but not glial differentiation, from SVZ neural progenitors (Lim *et al.*, 2009). Dlx2 was identified as a direct target of Mll1 and is crucial for SVZ neurogenesis.

Our understanding of the roles of histone modifications in adult neurogenesis is just beginning to be developed. Rapid progress in the field has led to the identification of many histone methylatransferases and demethylases (Klose & Zhang, 2007). With an increasing number of animal models available to determine roles of specific histone modifications in different stages of adult neurogenesis, we expect to uncover an expanded role of such epigenetic mechanisms in regulating adult neurogenesis as well as underlying molecular mechanisms.

Non-coding RNAs

Recent large-scale genome sequencing projects have revealed that only a very small percentage of the mammalian genome encode mRNAs that translate into proteins. Non-coding RNAs, which are transcribed from non-protein-coding regions, have emerged as an important class of epigenetic regulators that interact with chromatin modifiers and transcription factors to regulate gene expression (Hobert, 2008; Morris, 2009; Iorio *et al.*, 2010). There are both long and small non-coding RNAs, which include small nucleolar RNAs (snoRNAs), miRNAs, small interfering RNAs (siRNAs) and PIWI-interacting RNAs (piRNAs). This list continues to grow with the recent identification of promoter-associated small RNAs (PASRs), transcription initiation RNAs (tiRNAs), microRNA-offset RNAs (moRNAs), MSY2-associated RNAs (MSY-RNAs), telomere small RNAs (tel-sRNAs) and centrosome-associated RNAs (crasiRNAs; Taft *et al.*, 2010). The non-coding RNAs regulate gene expression largely by modulating chromatin modifications, DNA transcription, RNA modifications, splicing, mRNA translation and RNA stability. Recent evidence has revealed multiple members of the small RNA family that regulate adult neurogenesis.

One major class of non-coding RNAs is miRNAs, which inhibit gene expression through post-transcriptional mechanisms (Makeyev & Maniatis, 2008). A brain-specific miRNA, miR-124, although not detectable in neural progenitors, is up-regulated during the transition from transient amplifying cells to proliferating neuroblasts in the adult SVZ and is further up-regulated in immature neurons in the RMS and olfactory bulb (Cheng *et al.*, 2009). Gain- and loss-of-function analysis suggests that miR-124 functions in transient amplifying cells to promote their differentiation into neuroblasts, and specifically regulates the timing of lineage progression, instead of fate specification *per se* (Fig. 1A). Mechanistically, miR-124 has three direct targets in the SVZ lineage: Dlx2, Jag1 and Sox9 (Cheng *et al.*, 2009). Dlx2 is a transcription factor involved in interneuron formation (Doetsch *et al.*, 2002), whereas Jag1 is a Notch ligand that is important for self-renewal of neural progenitors in the postnatal SVZ (Nyfeler *et al.*, 2005). By contrast, Sox9 promotes the generation of GFAP^{+} cells while suppressing neuronal production. Importantly, miR-124 appears to eliminate Sox9 and Jag1 expression while only reducing Dlx2 expression in SVZ neuroblasts. Thus, a single miR-124 can fine-tune both the amount and the timing of neurogenesis from transient amplifying cells to interneurons during postnatal SVZ neurogenesis (Fig. 1A).

Two miRNAs have so far been implicated in regulating adult hippocampal neurogenesis. First, miR-184 is a direct target of Mbd1 in adult hippocampal neural progenitors (Liu *et al.*, 2010). High levels of miR-184 promote proliferation and inhibit differentiation of adult hippocampal neural progenitors both *in vitro* and *in vivo*. Mechanistically, miR-184 acts through post-transcriptional repression of Numb-like, a known regulator of neuronal differentiation during development. Second, miR-137 has been identified as a direct target of Sox2 and MeCP2 in adult SGZ neural progenitors (Szulwach *et al.*, 2010). Similar to miR-184, overexpression of miR-137 promotes the proliferation of adult hippocampal neural progenitors whereas a reduction of miR-137 enhances both neuronal and astrocyte differentiation from these progenitors *in vitro*. One major function of miR-137 appears to repress the translation of Ezh2, an H3K27 methyltransferase and PcG complex protein, leading to a global reduction of H3K27 methylation in adult SGZ neural progenitors. These interesting studies demonstrate a complex signalling network involving multiple epigenetic mechanisms to exquisitely regulate the fine balance between proliferation and differentiation of adult neural progenitors.

In addition to miRNAs, a novel small non-coding double stranded (ds) RNA containing the NRSE sequence, NRSE dsRNA, was suggested to be a key regulator of neuronal differentiation of adult hippocampal neural progenitors *in vitro* (Kuwabara *et al.*, 2004). The

NRSE sequence is a 21- to 23-bp conserved DNA response element recognized by neuronal restricted silencing factor/RE-1 silencing transcription factor (NRSF/REST) (Schoenherr *et al.*, 1996; Chen *et al.*, 1998; Huang *et al.*, 1999). NRSF/REST is a key transcriptional repressor for neuron-specific genes in non-neuronal cells and it mediates transcriptional repression through the association of the N-terminal repressor domain with the mSin3/histone deacetylase-1/2 (HDAC1/2) complex and through the association of C-terminal repressor domain with the CoREST complex (Huang *et al.*, 1999; Naruse *et al.*, 1999; Lunyak *et al.*, 2002). One of the known REST/NRSF targets is miR-124, which regulates adult SVZ neurogenesis (Fig. 1A; Yoo *et al.*, 2009; Juliandi *et al.*, 2010). Surprisingly, NRSE dsRNA appears to convert NRSF/REST from a transcriptional repressor to an activator in adult neural progenitors to promote neuronal differentiation (Kuwabara *et al.*, 2004). *In vitro* analysis suggests that NRSE dsRNA is both sufficient and necessary for neuronal differentiation of adult neural progenitors. It remains to be determined whether this mechanism plays a critical role in regulating adult SGZ and SVZ neurogenesis *in vivo*.

Conclusions

Adult neurogenesis not only exemplifies the tremendous plasticity of the adult mammalian brain, but also provides a unique experimental model system to explore both intrinsic and extrinsic mechanisms regulating stem cell maintenance, activation and development. Although the field of epigenetic analysis of adult neurogenesis is still in its nascent stage, significant progress has been made in the past few years and a number of basic principles have started to emerge. (i) Each stage of the adult neurogenesis process, ranging from maintenance and activation of neural progenitors, their fate specification, to maturation and development of neuronal progeny, is fine-tuned by multiple mechanisms involving various epigenetic regulators. In most cases, this regulation involves a complex interaction among different epigenetic mechanisms. (ii) Each epigenetic regulator appears to have multiple targets and affects multiple processes of adult neurogenesis, especially at the transition stages. (iii) Epigenetic mechanisms regulate both intrinsic developmental stage-specific signalling and environmental niche signalling during adult neurogenesis. (iv) Certain epigenetic mechanisms regulating adult neurogenesis exhibit some unique features that are not present during embryonic and early postnatal neurogenesis.

Given the tremendous technical advances in recent years, we expect to see an explosion of studies of epigenetics in the field of adult neurogenesis. First, we need to understand the profile of epigenetic status during different stages of adult neurogenesis. Such studies present a unique technical challenge as each diploid cell has only two such gene-specific modifications. A number of technologies are being developed to enrich specific cell types based on immunophenotyping (Rietze *et al.*, 2001; Capela & Temple, 2002; Nagato *et al.*, 2005; Corti *et al.*, 2007; Pastrana *et al.*, 2009) or transgenic reporter animals (Encinas & Enikolopov, 2008; Kanki *et al.*, 2010). Emerging sequencing technologies also have made it possible for more sensitive, precise and genome-scale measurements of epigenetic DNA and histone modifications, and for profiling of mRNAs and various non-coding RNAs. Second, we need to gain knowledge of specific roles of different epigenetic regulators at distinct stages of adult neurogenesis *in vivo*. A number of Cre-ER^{T2}-based driver mice are now available for inducible deletion or overexpression of many epigenetic regulators. Progress in the past decades has delineated the sequential steps during functional adult neurogenesis and such a detailed blueprint to adult neurogenesis will guide future analyses. These new endeavours will significantly enrich our knowledge regarding the basic mechanisms of adult neurogenesis and its regulation. Given the wealth of evidence implicating both epigenetics and adult neurogenesis in epileptogenesis, neuronal injury, degeneration and psychiatric disorders, futures studies may also lead to novel therapeutic targets and treatment strategies.

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Abbreviations

BDNF, brain-derived neurotrophic factor; Dnmts, DNA methyltransferases; dsRNA, double-stranded RNA; Gadd45, growth arrest and DNA damage-inducible protein 45; HATs, histone acetyltransferases; HDACs, histone deacetylases; Mbd1, methyl-CpG-binding domain protein 1; MeCP2, methyl-CpG-binding protein 2; miRNAs, microRNAs; NRSF/REST, neuronal restricted silencing factor/RE-1 silencing transcription factor; PcG, polycomb group; RMS, rostral migratory stream; SGZ, subgranular zone; SVZ, subventricular zone; TrxG, trithorax group.

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