Published Online: 17 April, 2018 | Supp Info: http://doi.org/10.1083/jcb.201802117

JCB Journal of Cell Biology

REVIEW

Epigenetics and epitranscriptomics in temporal patterning of cortical neural progenitor competence

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During embryonic brain development, neural progenitor/stem cells (NPCs) sequentially give rise to different subtypes of neurons and glia via a highly orchestrated process. To accomplish the ordered generation of distinct progenies, NPCs go through multistep transitions of their developmental competence. The molecular mechanisms driving precise temporal coordination of these transitions remains enigmatic. Epigenetic regulation, including changes in chromatin structures, DNA methylation, and histone modifications, has been extensively investigated in the context of cortical neurogenesis. Recent studies of chemical modifications on RNA, termed epitranscriptomics, have also revealed their critical roles in neural development. In this review, we discuss advances in understanding molecular regulation of the sequential lineage specification of NPCs in the embryonic mammalian brain with a focus on epigenetic and epitranscriptomic mechanisms. In particular, the discovery of lineage-specific gene transcripts undergoing rapid turnover in NPCs suggests that NPC developmental fate competence is determined much earlier, before the final cell division, and is more tightly controlled than previously appreciated. We discuss how multiple regulatory systems work in harmony to coordinate NPC behavior and summarize recent findings in the context of a model of epigenetic and transcriptional prepatterning to explain NPC developmental competence.

Introduction

The central nervous system (CNS) displays an enormous diversity of cell types, which are assembled into neural circuits to serve complex functions such as sensory perception and consciousness. To build the highly ordered cytoarchitecture of the CNS, neurons and glial cells are generated through coordinated production and placement of distinct cellular subtypes. Neural progenitor/stem cells (NPCs) are defined as multipotent cells capable of self-renewal and differentiation into neurons and glial cells such as astrocytes and oligodendrocytes (Gage, 2000). The embryonic cerebral cortex starts from simple pseudostratified neuroepithelial cells, which mostly divide symmetrically to increase NPC pools. Neuroepithelial cells transform into radial glial cells (RGCs), which serve both as primary NPCs and as scaffolds for neuronal migration during corticogenesis (Götz and Huttner, 2005). The developmental competence of RGCs to produce different progeny types changes over time (Fig. 1). RGCs initially directly generate Cajal-Retzius neurons and deep-layer neurons, a process named direct neurogenesis (Guillemot, 2005). This is followed by generation of superficial layer neurons predominantly via intermediate progenitor cells (IPCs) in a process called indirect neurogenesis (Sessa et al., 2008). During later stages, RGCs gradually terminate neuronal production in favor of gliogenesis. This timed program is also maintained in culture for NPCs purified from the embryonic mouse cortex (Qian et al., 1998, 2000; Shen et al., 2006), or differentiated from mouse/human embryonic stem cells (ESCs; Eiraku et al., 2008; Gaspard et al., 2008). The first attempt to understand the nature of this timed transition in NPC competence in vivo used a heterochronic transplantation approach. Young NPCs of donor ferret cortex transplanted into the ventricular zone of older recipients generated later-born superficial layer neurons, but old NPCs transplanted into a younger host failed to generate early-born deep-layer neurons (McConnell and Kaznowski, 1991; Frantz and McConnell, 1996). These pioneering studies led to the concept that both intrinsic programs and extrinsic cues cooperate to regulate the transition of NPC competence, which is gradually restricted over time. Significant progress has been made over the past decade to reveal molecular mechanisms underlying the transition of NPC developmental competence.

A fundamental question in developmental biology is how the same genome in each cell can produce vastly different cell

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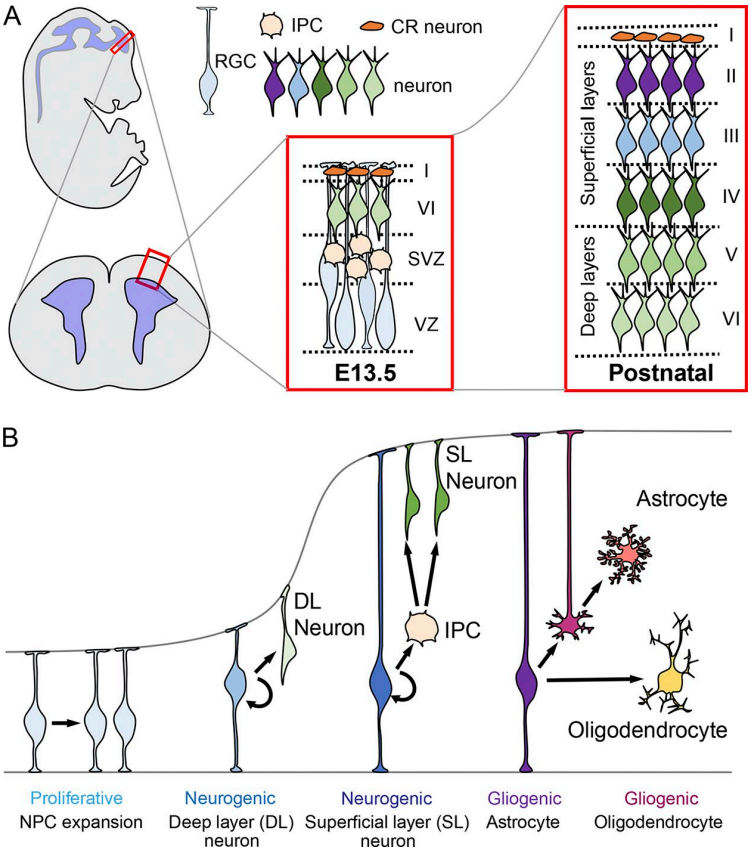

Figure 1. **Temporal transition of NPC developmental competence during mouse cortical development. (A)** Six cortical layers are formed in an inside-out manner during mouse cortical development. Glial cells are omitted for simplification. SVZ, subventricular zone; VZ, ventricular zone. **(B)** During cortical development, multipotent NPCs generate neurons populating the six cortical layers and glial cells such as astrocytes and oligodendrocytes sequentially in a time-dependent manner. During early cortical development, neuroepithelial cells divide symmetrically to increase NPC pools. Neuroepithelial cells transform into RGCs and then typically divide asymmetrically to self-renew and produce either neurons or IPCs. RGCs first produce Cajal-Retzius (CR) neurons (layer I) and deep-layer (DL) neurons (layers VI/V) and subsequently superficial-layer (SL) neurons (layers IV/III/II) mostly though IPCs. In later stages, RGCs transition from neurogenesis to gliogenesis and give rise to astrocytes and oligodendrocytes. Eventually, RGCs are depleted by transforming into astrocyte progenitors in postnatal stages.

types. The identity of each cell type is associated with unique transcriptional profiles, which are shaped by highly ordered gene expression programs. In this review, we define epigenetic changes as chemical and structural modifications on chromatin, DNA, and histones, without the alteration of the DNA sequence (see Epigenetic and epitranscriptomic regulation). These epigenetic mechanisms, in the form of DNA methylation, histone modifications, or chromatin remodeling and looping (Shin et al., 2014), establish a specific chromatin state to specify gene expression patterns associated with cellular memory to maintain a specific cellular identity and responsiveness to stimulation (Ma et al., 2010). Recent evidence suggests that chemical modifications on RNAs can also affect mRNA metabolism, including decay, transport, splicing, and translation (Meyer and Jaffrey, 2017; Zhao et al., 2017a). Similar to the term "epigenome," "epitranscriptome" can be defined as the ensemble of functionally relevant changes to the transcriptome without alteration of the RNA sequence. During development, epitranscriptomic regulation confers additional flexibility to fine-tune spatiotemporal gene expression on top of epigenetic regulation. Thus, epigenetic and epitranscriptomic regulation can form a harmonious system to interpret genetic information in response to intrinsic and extrinsic factors in neurodevelopment. In this review, we discuss recent progress in our understanding of epigenetic and epitranscriptomic mechanisms that guide sequential lineage specification of NPCs with a focus on the developing mouse cortex.

Epigenetic mechanisms regulating the transition of NPC developmental competence

A body of evidence supports critical roles of multiple epigenetic mechanisms in neurogenesis (Hirabayashi and Gotoh, 2010; Sun et al., 2011; Yao et al., 2016). In this review, we focus on roles of DNA methylation, histone modifications, chromatin remodeling, and 3D genome architecture in regulating the transition of NPC competence (Fig. 2). DNA and histone modifications are reversible: they are established by "writers," interpreted by "readers," and removed by "erasers" (see Epigenetic and epitranscriptomic regulation). ncRNAs including lncRNA and microRNA also play important roles in regulating NPC maintenance and differentiation during cortical neurogenesis, which have been reviewed elsewhere (Volvert et al., 2012; Andersen and Lim, 2018).

Progressive alteration of DNA methylome of NPCs during brain development

DNA methylation, especially in gene promoters, is associated with transcriptional repression in the mammalian nervous system (Guo et al., 2011a). Genetic ablation studies using knockout animals have shown that after genomewide eradication of DNA methylation in preimplantation embryos, a de novo DNA methylation pattern is established by DNMT3A and DNMT3B, which is then maintained by DNMT1 (Fig. 2; Li et al., 1992; Okano et al., 1999). DNA methylation is cell type–specific and dynamic during development. Whole-genome profiling of the DNA methylome from isolated NPCs provides initial clues of the sequential changes

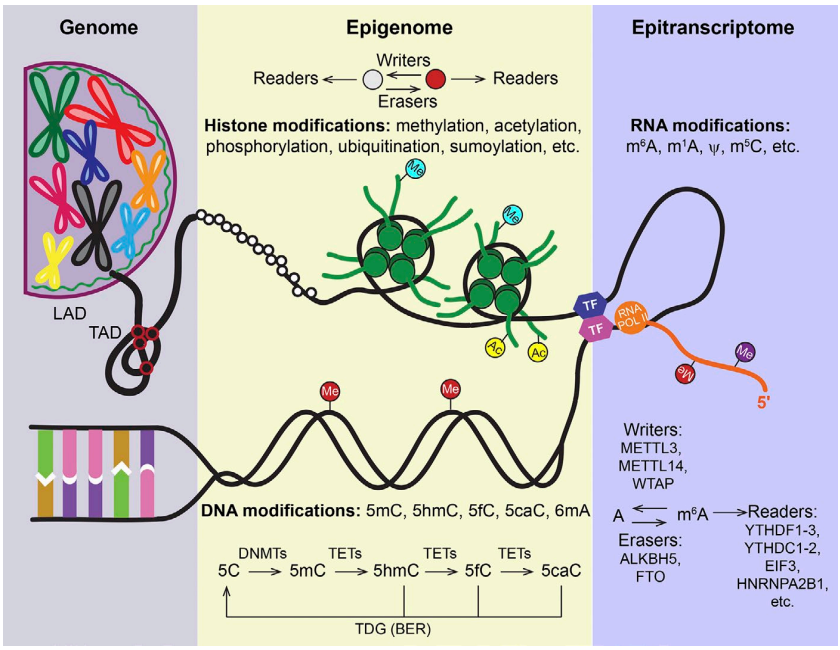

Figure 2. **Multiple layers of gene expression regulation.** Gene regulation occurs across the genome, epigenome, and epitranscriptome. Left: Beyond the DNA sequence, chromosomes are regulated by their locations, or territories, in the nucleus both relative to one another and to the nuclear lamina. Long-range interactions are further regulated by TADs within and across chromosomes. LAD, laminin-associated domain. Middle: At the epigenetic level, gene expression is regulated by reversible histone modifications within nucleosomes including methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. Most DNA methylation occurs in the form of 5mC by DNA methyltransferases (DNMTs), which can be actively removed through an oxidation–DNA repair pathway involving thymine DNA glycosylase (TDG)-dependent base excision repair (BER). DNA methylation could also occur in the form of 6mA. Right: Dynamic chemical modifications on RNA regulate transcript fate through a network of RNA-specific methyltransferases (writers), demethylases (erasers), and reader proteins. Though hundreds of modifications can occur in mRNA, m^6A is the most prevalent.

in the differentiation competence of NPCs at different stages of neurodevelopment. For example, in vivo–purified NPCs at different developmental stages from mouse forebrain showed three steps of global changes in the DNA methylome, including two successive waves of demethylation in early and late neurogenic NPCs and de novo methylation of neuron-specific genes in gliogenic NPCs (Sanosaka et al., 2017). At the neurogenic stage, the promoter regions of many glial-specific genes such as glial fibrillary acidic protein (GFAP) and S100β are hypermethylated, thus limiting responsiveness of NPCs to gliogenic signaling (Takizawa et al., 2001; Fan et al., 2005). Later, at the gliogenic stage, these promoter regions become demethylated to allow glial differentiation in response to gliogenic stimuli such as JAK-STAT signaling (Nakashima et al., 1999; He et al., 2005; Namihira and Nakashima, 2013). Consistently, *Dnmt1* knockout mice showed accelerated demethylation in glial-specific promoters and precocious

Epigenetic and epitranscriptomic regulation

To fully understand epigenetic and epitranscriptomic regulations, it is important to contextualize them in terms of chromatin and RNA structures (Fig. 2). In brief, chromatin is made of units of nucleosomes, which contain double-stranded DNA wrapped around octamers of histone proteins. Nucleosomes are regularly spaced throughout the genome like beads on a string. The chromatin is then further compacted through asymmetric folding of the nucleofilament, which allows for interactions with distant parts of the genome as well as other elements of the nucleus (Woodcock and Horowitz, 1995). Similarly, single-stranded RNA can form complex secondary structures like loops and double-stranded stretches, which mediate which parts of the RNA are available for modification or protein binding (Lewis et al., 2017).

The term "epigenetics" was originally coined by Conrad Waddington to describe dynamic interactions between the environment and the genome that bring the characteristic traits of an organism, defined as the phenotype (Waddington, 1942). Epigenetic alterations are defined as nonpermanent and potentially heritable changes that regulate gene expression without alterations to the DNA sequence. Epigenetic modifications are considered to be dynamic and reversible, established by modification enzymes (named writers), interpreted by modification specific binding proteins (readers), and removed by enzymes (erasers). Traditionally, epigenetic mechanisms that control changes in gene expression levels can be divided into three major groups:

(1) DNA methylation: DNA methylation plays key roles in the regulation of transcription by changing the accessibility of DNA to the transcription machinery. In eukaryotes, DNA methylation mostly occurs at cytosine residues (5-methylcytosine; 5mC) in CpG dinucleotides, but it also occurs at non-CpG sites (CpA, CpT, and CpC), especially in pluripotent stem cells (Lister et al., 2009) and the mature neurons (Guo et al., 2014). In some cases, DNA methylation is found at adenosine as [N^6]methyladenine (6mA; Heyn and Esteller, 2015). During DNA replication, 5mC DNA methylation pattern is established by DNA methyltransferases including DNMT1, DNMT3A, and DNMT3B (writers). Methyl-CpG binding proteins such as MeCP2 recognize 5mC to exert specific functions (readers; Du et al., 2015). There are additional readers that can bind 5mC in a sequence-specific fashion without the methyl-CpG binding domain such as transcription factors (Hu et al., 2013). 5mC DNA methylation can be removed by the action of DNA demethylase such as ten-eleven translocation (TET) proteins (erasers; Guo et al., 2011b; Wu and Zhang, 2014).

(2) Histone and chromatin modifications: Histones can be altered by different processes such as methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, and ADP ribosylation. These posttranscriptional modifications on the 15–30-amino-acid N-terminal histone tails alter chromatin condensation, resulting activation or inactivation of gene expression. For example, diverse residues of histone tails are modified by histone acetyltransferases (HATs) or histone methyltransferases (HMTs; writers) and interpreted by various binding proteins (readers). These modifications can be reversed by histone deacetylases (HDACs) or histone demethylases (erasers).

(3) Noncoding RNAs (ncRNAs): ncRNAs play a crucial role in many regulatory pathways of gene expression. For example, microRNA is a small ncRNA molecule that functions in RNA silencing and posttranscriptional regulation of gene expression.

Over 150 different posttranscriptional modifications are known, including pseudouridine (Ψ), 2′-*O*-methylation, 5-methylcytidine, and [N^6]methyladenosine (m^6A; Gilbert et al., 2016). Many of these modifications can occur on tRNA, ribosomal RNA, long ncRNA (lncRNA), and mRNA (Meyer and Jaffrey, 2017; Zhao et al., 2017a). Studies of these RNA modifications lead to an emerging new field of epitranscriptomics.

astrocyte differentiation of NPCs during the neurogenic stage, suggesting the importance of maintaining DNA methylation patterns from early to midgestational stages (Fan et al., 2005).

DNA methylation can be removed either passively by blocking DNMT1 action on newly synthesized DNA during DNA replication in proliferating cells or actively through the enzymatic actions of the DNA demethylation pathway (Wu and Zhang, 2014). At the neurogenic stage, newborn neurons present the Notch ligands to NPCs to induce expression of nuclear factor IA, which then binds to the promoters of glial-specific genes to prevent DNMT1 action. This leads to passive DNA demethylation, which in turn promotes the neurogenic-to-gliogenic transition of NPC developmental competency (Namihira et al., 2009). Active DNA demethylation involves conversion of 5mC into 5′-hydroxymethylcytosine (5hmC) and then to 5-formylcytosine and 5-carboxylcytosine by the Tet family members, followed by thymine DNA glycosylase–dependent base-excision repair (Fig. 2; Guo et al., 2011b; Wu and Zhang, 2014). During embryonic development, neuronal differentiation is associated with increasing levels of 5hmC, and functional perturbation of Tet2 and Tet3 leads to defects in neuronal differentiation (Hahn et al., 2013). In addition, *Tet1* knockout mouse models show deficits in NPC proliferation in both embryonic and adult neurogenesis (Zhang et al., 2013). 5hmC is elevated during the differentiation of adult neural stem cells in the hippocampus, and Tet2 is primarily responsible for modulating 5hmC dynamics (Li et al., 2017c). Depletion of Tet2 leads to increased adult neural stem cell proliferation and reduced differentiation in vitro and in vivo. Finally, depletion of *Tet3* in *Xenopus laevis* embryos represses expression of many key developmental genes such as *Pax6*, *Ngn2*, and *Sox9* (Xu et al., 2012). These results suggest that both passive and active demethylation processes regulate crucial NPC properties during neurodevelopment and adulthood.

Our understanding of the role of DNA methylation dynamics in cortical neurogenesis is fragmented. For example, it is unknown how the global changes of methylation patterns are achieved with a certain degree of specificity to restrict the developmental competency of NPCs. Considering that DNA-binding factors can mediate turnover of DNA methylation (Feldmann et al., 2013; Marchal and Miotto, 2015), the roles of lineage-specific transcription factors in shaping stage-specific DNA methylation landscapes of NPCs also need to be explored. In addition, DNA 6mA has been shown to participate in transcriptional regulation (Wallecha et al., 2002; Robbins-Manke et al., 2005), DNA repair pathways (Pukkila et al., 1983), and protection against restriction enzymes in bacteria (Arber and Dussoix, 1962). Recently, 6mA has been added to the growing list of potential epigenetic marks in DNA of various eukaryotic species including green algae (Fu et al., 2015), *Caenorhabditis elegans* (Greer et al., 2015), *Drosophila melanogaster* (Zhang et al., 2015), and mouse (Wu et al., 2016; Yao et al., 2017). It is still unclear whether the biological functions of 6mA in eukaryotes are conserved from bacteria or evolved to have unique roles in various tissues. The functional significance of 6mA during mammalian neurodevelopment remains to be investigated.

Histone dynamics in NPCs of the developing brain

The nucleosome is the fundamental subunit of chromatin consisting of an octamer of histone proteins (Fig. 2). The N-terminal tails of histones are highly susceptible to diverse posttranslational modifications such as methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, and ADP ribosylation (Kouzarides, 2007). These reversible modifications define the transcriptional environment by serving as docking stations to attract various epigenetic modifiers and transcription factors for transcriptional activity. For example, promoters of both neurogenic and gliogenic genes undergo various histone modifications to ensure the sequential production of different cell types at proper stages of development (Hirabayashi and Gotoh, 2010).

Histone methylation mainly occurs at lysine residues on the N-terminal tails of histones H3 and H4 (Strahl and Allis, 2000). Histone methylation is reversible and regulates transcriptional activity depending on the number and location of methyl groups. Histone H3 methylations at lysine 4 (H3K4), lysine 36 (H3K36), and lysine 79 (H3K79) are associated with transcriptional activation, whereas methylations at H3K9, H3K27, and H4K20 are associated with transcriptional silencing (Vakoc et al., 2006). During neurodevelopment, NPCs acquire different responsiveness to various extracellular signals that regulate the accessibility of transcription factors to promoters of neurogenic or gliogenic genes. For example, H3K9 methylation of the *GFAP* promoter is replaced by H3K4 methylation in response to ciliary neurotrophic factor during the differentiation of cortical NPCs into astrocytes. In this process, fibroblast growth factor 2 facilitates access of the STAT–CBP complex to the GFAP promoter by inducing H3K4 methylation and suppressing H3K9 methylation at the STAT binding site, resulting in the activation of the gliogenic program (Song and Ghosh, 2004; Irmady et al., 2011).

The polycomb group (PcG) complex has been shown to regulate the timing of the transition in generating different neuronal subtypes and glia. The PcG complex catalyzes trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transient transcriptional repression through alteration of local chromatin configuration (Sauvageau and Sauvageau, 2008). The PcG consists of two complexes: polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2). Deletion of Ring1B, a PRC1 component, leads to prolonged expression of Fez transcription factor family member zinc-finger 2 (Fezf2), which drives the expression of downstream target genes for deep-layer neuron identity such as *Ctip2*, resulting in an increased production of deep-layer neurons (Morimoto-Suzki et al., 2014). Enhancer of Zeste homologue 2 (Ezh2), a PRC2 component, is highly expressed in NPCs at the gliogenic stage and inhibits the expression of neurogenic genes such as *Neurogenin 1* (*Neurog1*) by catalyzing H3K27me3 at the promoter region (Hirabayashi et al., 2009). Deletion of Ring1B, or Ezh2, leads to an extended duration of the neurogenic period and a delayed onset of astrogenesis (Hirabayashi et al., 2009; Pereira et al., 2010). Collectively, the PcG complex represses a unique set of genes in a temporally regulated manner, thereby enabling the dynamic transition of RGC competence. The mechanisms of how the PcG complex regulates different target genes in response to intrinsic and extrinsic cues over the course of development need to be further investigated.

Histone acetylation is catalyzed by HATs on the lysine residues of the N terminus of histone tails, which results in removal of positive charge, thereby relaxing chromatin condensation

and enhancing active gene transcription (Kouzarides, 2007). Histone acetylation is broadly involved in both embryonic and adult neurogenesis. For example, the HAT activity of CREB-binding protein (CBP) is important for neural lineage differentiation. NPCs from a heterozygote mutant mouse model of *CBP* showed impaired differentiation into all three neural lineages—neurons, astrocytes, and oligodendrocytes—coincident with decreased CBP binding and histone acetylation at promoters of neuronal and glial genes (Wang et al., 2010). The other well-characterized HAT is KAT6B/querkopf. KAT6B exhibits a dynamic pattern of expression in the embryonic telencephalon, and mutations in *Kat6b* result in reduced numbers of pyramidal neurons and interneurons (Thomas and Voss, 2004).

Histone acetylation is removed by HDACs, causing chromatin condensation and transcriptional repression by preventing binding of transcription factors (Hsieh and Gage, 2004). There are >18 HDACs in the mammalian genome, and they are expressed at different developmental stages and in diverse cell types (de Ruijter et al., 2003). For example, HDAC1 is highly expressed in NPCs and glia, whereas HDAC2 is expressed in neurons but not in most glial cells, suggesting specific gene-silencing programs by various histone deacetylation complexes in a cell type–specific manner (MacDonald and Roskams, 2008). Conditional deletion of *Hdac1*/*Hdac2* in NPCs impairs neuronal differentiation (Montgomery et al., 2009), and inhibition of HDAC activity at the neurogenic stage decreases the production of deep-layer neurons and increases superficial-layer neurons from RGCs by modulating the expression of layer-specific genes (Yuniarti et al., 2013). In addition, conditional deletion of *Hdac1*/*Hdac2* in oligodendrocytes shows severe defects in oligodendrocyte production and maturation (Ye et al., 2009). These studies suggest that histone deacetylation plays important roles at different stages of neurodevelopment.

Frequently, HDACs are recruited by transcription factors and cofactors to exert epigenetic regulatory roles. For example, TLX, a transcription factor that has a crucial role in NSC proliferation and self-renewal, recruits HDACs to suppress downstream target genes including the cyclin-dependent kinase inhibitor P21 and the tumor suppressor PTEN (Sun et al., 2007; Niu et al., 2011). The transcriptional repressor RE1-silencing transcription factor (REST) represses neuronal programs in nonneuronal cells by recruiting histone modifiers such as HDACs, HMTs, and lysine-specific demethylase 1 (LSD1), thereby keeping neuronal genes in a poised state (Shi et al., 2004; Ballas et al., 2005). In another example, HDAC3 is a component of the nuclear receptor corepressor (N-CoR)–silencing mediator of retinoid and thyroid hormone receptor (SMRT) complex, which regulates neuronal differentiation of NPCs in forebrain development (Jepsen et al., 2007; Castelo-Branco et al., 2014).

Collectively, diverse histone marks are dynamically regulated to activate, repress, or poise gene expression throughout neurodevelopment. Stage-specific actions of histone modifiers are critical for the precise control of spatial and temporal gene expression, governing the competence of NPCs to produce proper cell types at specific times of development. How target specificity of histone modifications is achieved in response to intrinsic programs and extrinsic cues in modulating the competence of NPCs remains a major gap in knowledge.

Chromatin remodelers and 3D genome organization

Chromatin remodeling complexes via ATP-dependent changes to histone–DNA interactions provide noncovalent mechanisms to modify chromatin accessibility for transcription factors and chromatin-modifying enzymes (de la Serna et al., 2006; Hargreaves and Crabtree, 2011). The family of ATP-dependent chromatin remodelers is categorized based on similarities of their ATPase domains, including switch/sucrose nonfermenting (SWI–SNF), imitation switch, chromo helicase DNA binding, and inositol auxotroph 80 (Lopez-Ramirez and Nicoli, 2014). These chromatin remodelers play critical roles during multiple steps of development, which have been comprehensively reviewed elsewhere (Ho and Crabtree, 2010; Hota and Bruneau, 2016). Among these, mammalian SWI–SNF complexes, also known as Brg/Brahma-associated factor (BAF) chromatin remodeling complexes, are the most extensively studied remodelers during neurodevelopment.

BAF chromatin remodeling complexes are comprised of multiple proteins, including one of the two catalytic ATPase subunits, Brahma and Brg1, and other core subunits named BAFs. ATPase subunits generate energy by hydrolyzing ATP to relax condensed chromatin and increase accessibility of transcription factor binding for activation of gene expression. BAF subunits also contain scaffolding proteins with DNA and histone-binding domains, which enable specific recruitment of transcription factors and histone-modifying proteins (Sokpor et al., 2017). During neural development, cell type–specific BAF complexes, which are formed by combinatorial subunit switching, exert functions important for lineage-specific properties (Ho and Crabtree, 2010). For example, the specialized subunit composition of the ESC–BAF (esBAF) complex is required for ESC maintenance and pluripotency (Ho et al., 2009, 2011; Takebayashi et al., 2013). As ESCs differentiate into neurons, esBAF begins to switch subunits to those unique to neural progenitors (npBAFs), eventually leading to a specific subunit composition in neurons (nBAFs; Staahl and Crabtree, 2013; Bachmann et al., 2016). NPC proliferation requires a BAF complex containing BAF54a and BAF53a subunits (npBAF), and those are replaced by the alternative BAF45b, BAF45c, and BAF53b subunits (nBAFs), when NPCs exit the cell cycle to become post-mitotic neurons (Lessard et al., 2007). Mechanistically, BAF complexes transcriptionally regulate expression of components involved in critical signaling pathways for NPC proliferation and neuronal differentiation, such as Wnt (Vasileiou et al., 2015), Sonic hedgehog (Lessard et al., 2007; Zhan et al., 2011), and Notch pathways (Lessard et al., 2007). BAF complexes have also been shown to regulate various steps of neurodevelopment, including balancing of direct neurogenesis from RGCs and indirect neurogenesis from IPCs (Tuoc et al., 2013a,b), gliogenesis (Matsumoto et al., 2006; Ninkovic et al., 2013; Tuoc et al., 2017), and neuronal dendritic morphogenesis (Wu et al., 2007) with a differential combination of BAF subunits. These studies on BAF chromatin remodeling complexes support the notion that combinatorial assembly of subunits of chromatin regulatory complexes can instruct cell lineage specification by creating specific patterns of chromatin states at different developmental stages.

3D genome architecture is increasingly considered an important epigenetic regulator of gene expression. Mammalian

chromosomes are topologically heterogeneous. Euchromatin comprises open chromatin fibers, whereas heterochromatin is condensed and transcriptionally dormant (Gilbert et al., 2004). The spatial organization of the chromatin in the interphasic nucleus is changing dynamically as the cell differentiates. Although the nuclei of ESCs are relatively homogeneous, heterochromatin foci become more evident in NPCs. Mature neurons show fewer but much larger heterochromatin foci suggesting that heterochromatin regions are actively reorganized during differentiation (Aoto et al., 2006; Williams et al., 2006). In general, the genome is organized into the euchromatic A compartments containing most actively transcribed regions, and the peripheral B compartments corresponding with megabase-sized gene-poor lamina-associated domains (Fig. 2; Guelen et al., 2008). At a more local scale, chromosomes are partitioned into submegabase segments forming topologically associating domains (TADs) that are relatively insulated from neighboring domains (Dixon et al., 2012; Nora et al., 2012). High-resolution analysis of chromatin interactions within TADs reveals the presence of sites of constitutively bound CCCTC-binding factor (CTCF) that facilitate chromatin looping interactions (Dixon et al., 2012; Phillips-Cremins et al., 2013). CTCF-mediated long-range interactions contribute to multiple aspects of 3D genome architecture, including domain insulation and enhancer blocking (Phillips and Corces, 2009). Loss-of-function studies of CTCF reveal its role in cell fate specification and neural differentiation (Hirayama et al., 2012; Watson et al., 2014). Recent advances in chromosome conformation capture technologies such as Hi-C have revealed the dynamic nature of 3D genome architecture during neural differentiation and neuropsychiatric disorders (Dixon et al., 2015; Won et al., 2016; Bonev et al., 2017). How spatial genome architecture is related to gene expression and cell fate specification during neurodevelopment is not well understood. Development of innovative imaging tools to investigate 3D chromatin ultrastructure such as EM-based ChromEMT (Ou et al., 2017), superresolution microscopy (Boettiger et al., 2016), and CRISPR/dCas9-based imaging (Liu et al., 2017; Qin et al., 2017) will synergistically propel our comprehensive understanding of 3D genome remodeling during neurodevelopment.

It is becoming increasingly evident that interactions between different epigenetic modifications play key roles in cell differentiation. In general, chromatin alterations are operated by polyenzymatic complexes that integrate multiple aspects of epigenetic regulation. For example, the transcriptional repressor REST functions as a central hub that recruits an array of epigenetic modifiers including HMT, HDAC, methyl-DNA binding protein, and components of the BAF chromatin remodeling complex (Ballas et al., 2005; Yoo and Crabtree, 2009). Future research into crosstalk among different epigenetic regulators will increase our understanding of molecular mechanisms underlying transition of NPC developmental competence.

Epitranscriptomic regulation of NPCs during neurodevelopment

Although changes in gene expression at the transcriptional level broadly regulate cell fate and behavior, the nascent transcripts are subject to extensive processing that alters the final outcome of protein expression. Just like epigenetic modifications on DNA and histones, RNA is also subject to chemical modifications (Fig. 2). The most abundant internal mRNA modification in eukaryotes is m^{6}A (Desrosiers et al., 1975), which has recently garnered significant interest as a major regulator of stem cell fate.

Early biochemical studies in the 1970s showed the prevalent existence of m^{6}A in mammalian mRNA (Desrosiers et al., 1975), and the importance of m^{6}A as an mRNA modifier was originally shown in 1997 through the knockdown of *Mettl3 (MT-A70)*, a key component of the methyltransferase complex, in HeLa and plant cells (Bokar et al., 1997). The field of epitranscriptomics grew rapidly upon the subsequent discovery of mRNA demethylases, fat-mass and obesity-associated protein (Frayling et al., 2007; Jia et al., 2011), and ALKBH5 (Fig. 2; Zheng et al., 2013), which indicate that m^{6}A is also a dynamic modification with regulatory potential. More recently, the methyltransferase complex has been investigated in depth, leading to discoveries that METTL14 and Wilm's tumor-associated protein (WTAP) work in concert with METTL3 to add m^{6}A methylation onto mRNA (Ping et al., 2014; Wang et al., 2014). WTAP helps recruit the complex to mRNA. METTL14 then binds at the consensus site, and METTL3 uses an *S*-adenosyl methionine molecule to enzymatically transfer a methyl group onto an adenosine nucleoside (Ping et al., 2014).

Recent research in cell lines has suggested that m^{6}A mRNA modifications can affect various aspects of mRNA metabolism, including decay, transport, splicing, and translation, and represent a critical regulatory mechanism in the transition of cell identities during development (Zhao et al., 2017a). *Mettl3* knockdown in naive mouse ESCs impairs differentiation and promotes self-renewal by altering the decay rates of mRNA transcripts that are m^{6}A tagged (Batista et al., 2014; Geula et al., 2015). m^{6}A also regulates maternal-to-zygotic transition in zebrafish, stem cell self-renewal and differentiation in the mouse blood system, and progression of various types of human cancer cells (Cui et al., 2017; Li et al., 2017b; Zhao et al., 2017b). Although m^{6}A seemingly regulates all cell types, the abundance of m^{6}A on mRNA is highest in the brain (Dominissini et al., 2012). During embryonic cortical development, m^{6}A controls both proliferation and differentiation of NPCs (Yoon et al., 2017; Wang et al., 2018). Transcripts related to mitosis, stem cell maintenance, and neural differentiation are broadly tagged with m^{6}A in mouse forebrain, human fetal cortex, and human forebrain organoid derived from induced pluripotent stem cells (iPSCs; Yoon et al., 2017). Loss of m^{6}A in *Mettl14* conditional knockout (cKO) specifically in the developing brain causes a prolonged persistence of RGCs into postnatal stages (Yoon et al., 2017). Moreover, cKO RGCs displayed delayed transitions in developmental competency, including the deep layer/superficial layer neuron transition and the neurogenic/gliogenic transition (Fig. 3 A). In RGCs, mRNA transcripts tagged with m^{6}A are fated for rapid degradation. When m^{6}A is lost in a cKO or knockdown of *Mettl14* in mouse and human NPCs, m^{6}A-tagged transcripts exhibit an extended half-life (Yoon et al., 2017). For example, loss of m^{6}A on stem cell genes such as *Sox1 and Emx2* causes up-regulation of these genes and persistence of the stem cell phenotype. However, loss of m^{6}A on neuronal genes such as *Tbr2* and *Neurod1* causes their up-regulation in NPCs, which seemingly conflicts with the expression of stem cell genes. Indeed, *Mettl14*

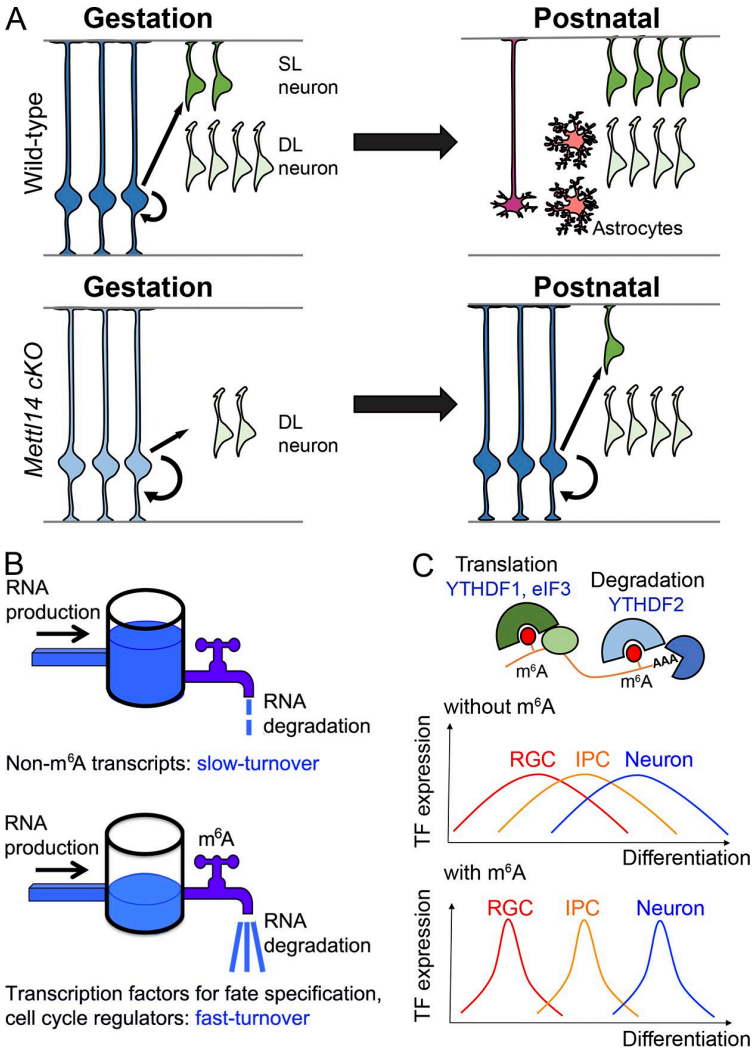

Figure 3. **Epitranscriptomic regulation in NPCs during neurodevelopment. (A)** Delayed temporal progression of corticogenesis with the depletion of m^{6}A RNA modification. Embryonic cortices of *Mettl14* cKO mice, which have diminished m^{6}A modification on mRNAs, display reduced production of deep-layer (DL) neurons and impaired production of superficial-layer (SL) neurons. During the postnatal period, *Mettl14* cKO mice catch up and produce adequate numbers of deep-layer neurons but still produce fewer superficial-layer neurons. In addition, the postnatal cortices of *Mettl14* cKO mice retain a residual population of RGCs similar to embryonic cortices, whereas the WT RGCs are depleted and differentiated into astrocytes after birth. These phenotypes suggest that m^{6}A methylation plays a critical role in developmental fate transition of NPCs. **(B)** Selective facilitation of mRNA degradation by m^{6}A tagging regulates mRNA turnover. Steady-state mRNA levels are determined by the rate of mRNA production and the rate of mRNA degradation. In the embryonic cortex, mRNAs without m^{6}A tags including most transcripts of housekeeping genes have relatively slow turnover rates compared with m^{6}A-tagged mRNAs. Meanwhile, m^{6}A-tagged mRNAs, which are enriched with transcription factors (TFs) for fate-specification and cell-cycle regulators, have a faster turnover rate because of active RNA degradation. **(C)** A model of epitranscriptomic regulation on protein expression of transcription factors for fate specification. m^{6}A mRNA modification positively regulates protein translation (by YTHDF1 and eIF3) and negatively regulates RNA stability (by YTHDF2). This dual regulation potentially enables coordinated translation and clearance of mRNA, resulting in sharp and nonoverlapping expression domains of fate-specification factors during the stepwise transition of NPCs during differentiation.

cKO NPCs show coexpression of neuronal and stem cell–promoting genes. Further analysis of nascent mRNAs showed that neuronal lineage genes are already expressed in normal RGCs. These results lead to the model that NPCs are prepatterned for differentiation by actively transcribing neuronal genes, which are rapidly degraded through m^{6}A-mediated mRNA degradation (Fig. 3 B; Yoon et al., 2017). Recent studies have also shown that m^{6}A promotes translation efficiency of tagged mRNAs (Li et al., 2017a; Shi et al., 2017; Weng et al., 2018). These results raise the possibility that the m^{6}A-depedent enhancement of mRNA decay and translation allows a transient and high-level expression of tagged transcripts for timed fate transition during development (Fig. 3 C).

m^{6}A is a highly conserved regulatory mechanism in many species (Roundtree et al., 2017). In a recent study comparing mouse and human neural development, both unique and conserved aspects of m^{6}A regulation have been found (Yoon et al., 2017). When comparing E13.5 mouse forebrain and post-conception week 11 human brain, m^{6}A was found to tag transcripts crucial for neural development in both species. However, m^{6}A was much more prevalent in humans than in mice, tagging 31.4% of detected transcripts compared with only 19.3% in mice. Interestingly, the transcripts uniquely tagged in humans are strongly enriched with a disease ontology of mental disorders including autism spectrum disorder and schizophrenia. Another study found that the stress-mediated regulation of m^{6}A is impaired in human patients of major depressive disorder, implying dysregulation of m^{6}A epitranscriptome might be associated with development of human mental disorders (Engel et al., 2017).

The role of other RNA modifications in neurodevelopment has also been explored. Loss-of-function mutations in the 5-methylcytidine RNA methyltransferase *NSUN2* cause neurodevelopmental disorders in humans (Abbasi-Moheb et al., 2012; Martinez et al., 2012). Ablation of *Nsun2* in the mouse developing brain leads to impaired differentiation of superficial layer neurons because of the reduced sensitivity of NPCs to growth factors (Flores et al., 2017). In *Drosophila*, there is a minimal amount of 5mC DNA methylation (Delatte et al., 2016). Demethylase Tet enzyme appears to target RNA instead, and 5hmC preferentially marks mRNAs that show high translation efficiency. A

loss-of-function mutant of *Drosophila* Tet leads to reduced and disorganized NPCs and resultant brain malformation, suggesting that the mRNA demethylation pathway through 5hmC is critical for brain development (Delatte et al., 2016).

In the future, single-cell RNA-sequencing analysis (scRNA-seq) will provide a more in-depth understanding of when exactly NPCs begin to transcribe neuronal genes and how this poises them for the switch from stem cell maintenance and renewal to different phases of neurogenesis and gliogenesis. In addition, the roles of other posttranscriptional regulatory functions of m^{6}A in brain development, including controlling protein translation, alternative splicing, and nuclear export, will require further examination. Future studies are also needed to understand how epitranscriptomic mechanisms including other mRNA modifications interplay with various epigenetic mechanisms to temporally coordinate changes of transcriptomes during neurodevelopment and how dysregulation of epitranscriptomic mechanisms may contribute to brain disorders.

Prepatterning of neural progenitor competence

A precise and predictable developmental schedule requires rapid, tightly controlled changes in gene expression. During embryonic cortical development, RGCs sequentially produce distinct progenies with remarkable precision according to the developmental timeline. These progenies are also required to rapidly differentiate as they migrate to the proper place. Emerging evidence suggests that robust spatiotemporal gene expression programs could be preestablished in precursor cells before cell fate specification.

First, research in other somatic stem cells such as liver and pancreatic lineages has shown that in undifferentiated precursor cells, some lineage-specific genes are transcriptionally silent but are marked with specific histone modifications and regulatory proteins at their regulatory elements that poise them for activation, a phenomenon referred to as epigenetic prepatterning (Xu and Zaret, 2012). Recent research suggests that this epigenetic prepatterning might be a widespread mechanism in cell fate specification of multipotent progenitor cells (Chen and Dent, 2014). Some neuron-specific genes are also in a "poised" state in NPCs, repressed but primed for expression upon neuronal differentiation (Mohn et al., 2008). Future studies are needed to identify regulatory elements that are prepatterned for production of distinct cell types such as deep-layer and superficial-layer neurons as well as astrocytes from RGCs at different developmental stages.

Second, transcriptome analyses have provided evidence that some neuronal lineage genes are expressed at low levels in a subset of RGCs, suggesting the presence of lineage-restricted RGCs that are transcriptionally prepatterned. For example, mRNAs of *Cux2* and *Satb2* are expressed specifically in superficial neurons of the mature cortex but also in a subset of IPCs and RGCs during embryonic development, suggesting that superficial-layer versus deep-layer neuronal fate is likely determined before neuronal differentiation (Nieto et al., 2004; Franco et al., 2012). Likewise, mRNAs of deeper-layer neuron markers such as *Fezf2* and *Otx1* are also found in a subset of RGCs (Frantz et al., 1994; Molyneaux et al., 2005). Studies with scRNA-seq analysis further confirm that RGCs express mRNAs of specification factors for different types of cortical neurons (Telley et al., 2016; Zahr et al., 2018). This transcriptional prepatterning may be beneficial for the rapid progress of differentiation and restriction of RGC competence by allowing active transcription of specification factors (Fig. 4). However, precocious activation of the neuronal differentiation program may perturb self-renewal or multipotency of RGCs. To maintain actively transcribed mRNAs of neuronal specification factors at a very low level, RGCs use an m^{6}A modification–specific RNA degradation pathway via the CCR4–NOT complex, a major mRNA deadenylase for cytoplasmic mRNA decay (Yoon et al., 2017). However, a recent study suggested that protein expression of neuronal specification factors is further translationally repressed (Zahr et al., 2018). The RNA binding proteins Pum2 and 4E-T form a complex in RGCs and inhibit protein translation of target mRNAs that regulate the timing and specificity of neurogenesis (Yang et al., 2014; Zahr et al., 2018). Thus, neuronal specification factors, which are transcriptionally prepatterned in undifferentiated RGCs, are subjected to multiple layers of posttranscriptional regulation, providing readiness and flexibility for specification of diverse neuronal subtypes. Considering that many layer-specific genes including *Satb2* and *Otx1* are m^{6}A methylated (Yoon et al., 2017), the role of m^{6}A-mediated RNA degradation in fate-restricted RGCs for specific cortical layer formation will be an interesting topic for future research. It will also be interesting to investigate whether transcriptional prepatterning and posttranscriptional regulations represent a general mechanism of fate specification of stem cells in other somatic tissues.

Collectively, both epigenetic and transcriptional prepatterning could contribute to the efficient competence transition of RGCs. Although epigenetic prepatterning confers a permissive status to respond to developmental cues, transcriptional prepatterning allows NPCs to rapidly and accurately change cellular identity. Furthermore, targeted mRNA degradation and translational repression provide gate-keeping systems to prevent premature activation of the differentiation program (Fig. 4). These prepatterning mechanisms also suggest that the transition of NPC developmental competence is primed much earlier than previously recognized because of the focus on actual protein expression of fate-specification factors in previous studies. Future studies are needed to address how the initiation of epigenetic and transcriptional prepatterning in NPCs is triggered.

Future perspectives

Remarkable progress has been made over the last decade to understand gene-regulatory mechanisms controlling cell-fate specification of NPCs during embryonic brain development. In particular, rapid advances in next-generation sequencing technology allow us to identify genomewide transcriptomic and epigenomic changes at each stage of CNS development (Shin et al., 2014). Although heterogeneity and the constantly changing nature of the developing brain have posed major challenges, newly developed single-cell sequencing methods including scRNA-seq (Pollen et al., 2014; Johnson et al., 2015; Shin et al., 2015; Nowakowski et al., 2017), assay for transposase-accessible chromatin using sequencing (ATAC-seq; Cusanovich et al., 2015), chromatin immunoprecipitation followed by sequencing

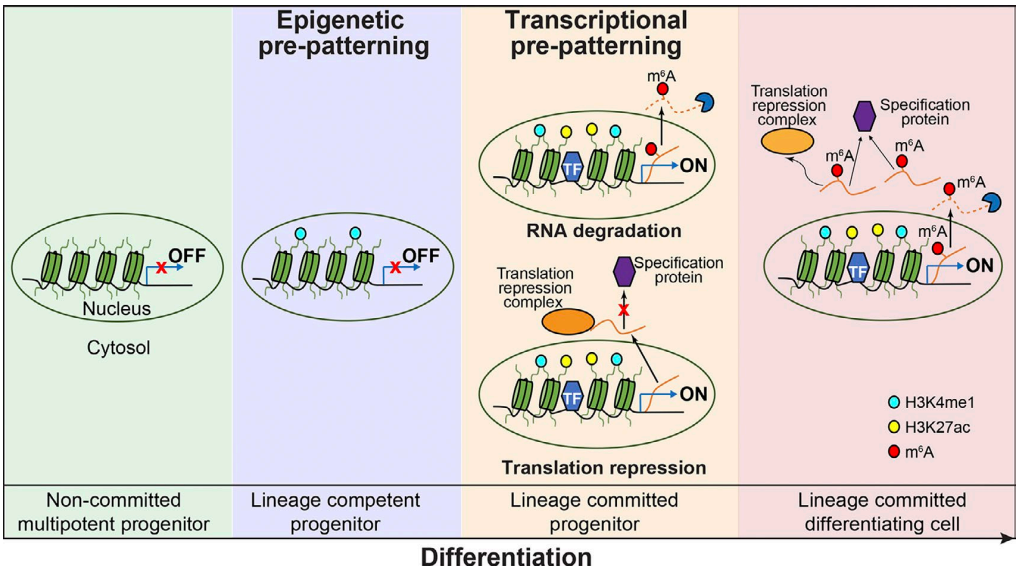

Figure 4. **Prepatterning of NPC developmental competence.** During the fate-specification process, regulatory elements of lineage specification genes in multipotent NPCs are prepatterned with distinct chromatin marks. This epigenetic prepatterning primes the lineage competence of NPCs. Upon stimulation by developmental cues, these lineage-primed NPCs readily initiate transcription programs that are transcriptionally prepatterned, but protein expression of lineage specification genes is suppressed by two mechanisms. RNA degradation by m^{6}A mRNA modification and translational repression by Pum2–4E-T complex provide gate-keeping systems to prevent the precocious activation of the lineage specification program. This transcriptional prepatterning potentially contributes a rapidly induced and fine-tuned cell fate specification process from multipotent progenitors in different tissues.

(Rotem et al., 2015), and single-cell DNA methylome sequencing (Smallwood et al., 2014; Luo et al., 2017) make it feasible to investigate transcriptome and epigenome signatures at single-cell resolution. Recently developed methods such as single-cell methylome and transcriptome sequencing (scMT-seq; Hu et al., 2016) and single-cell genome, DNA methylome and transcriptome sequencing (scTrio-seq; Hou et al., 2016) have further enabled us to simultaneously analyze the DNA methylome and transcriptome in a single cell. In the future, various single-cell multiomic approaches (Macaulay et al., 2017) will enable a new way to understand the complex interplay of genomic, epigenomic, and transcriptomic information during neural cell lineage specification. Considering dynamic and cell type–specific changes of the epitranscriptome during neural development (Meyer et al., 2012; Basanta-Sanchez et al., 2016; Yoon et al., 2017), single-cell sequencing technology for RNA modifications will be largely advantageous for in-depth appreciation of epitranscriptomic regulation. In addition to profiling different specific cellular states as a "snapshot," bioinformatics tools such as Monocle (Trapnell et al., 2014) and Waterfall (Shin et al., 2015) can use population single-cell omics data to generate a continuous video for understanding the temporal progression of the developmental process.

Studies using the mouse as a model have revealed many basic principles in brain development, yet we still have limited knowledge of human brain development, which exhibits unique features. Human brains expand in size with increased complexity of the cerebral cortex, and much of this expansion can be attributed to the increased number of NPCs during development, especially outer RGCs (oRGCs; Dehay et al., 2015). Single-cell transcriptomic studies reveal unique transcriptional profiles of distinct human NPC populations including oRGCs (Johnson et al., 2015; Pollen et al., 2015; Nowakowski et al., 2017; Zhong et al., 2018), but epigenetic and epitranscriptomic regulatory mechanisms governing NPC fate specification for diverse populations of NPCs are not well understood. A recent study examined regulatory elements involved in human cortical neurogenesis using ATAC-seq and Hi-C and revealed that human-gained enhancers preferentially regulate oRGC-specific genes (de la Torre-Ubieta et al., 2018). Analysis of m^{6}A epitranscriptomes in mouse and human fetal cortex at comparable developmental stages also unveiled more prominent m^{6}A tagging in humans (Yoon et al., 2017). Notably, many genes associated with genetic risk for mental disorders are only m^{6}A tagged in humans, not in mice (Yoon et al., 2017). Development of iPSC technology has brought us unprecedented opportunities to study human brain development and disorders (Wen et al., 2016). Furthermore, rapid advances in generating 3D organoid models provide easily accessible, genetically modifiable, and well-controllable platforms to study early human brain development in a dish (Lancaster et al., 2013; Qian et al., 2016; Sloan et al., 2017). Finally, to better understand the role of different RNA modifications in neural development and function, development of new chemical sequencing techniques will be key. Current methods depend on antibody recognition of individual modifications, which are less specific and sensitive than chemical methods like bisulfite sequencing. Additionally, multiple RNA modifications on a single transcript may be read in a code similar to the histone code. Development of chemical-based sequencing techniques could enable studies on how multiple mRNA modifications affect functionality. Understanding epigenetic and epitranscriptomic gene regulation specifically used by unique human NPCs such as oRGCs could provide insights into

molecular mechanisms underlying human cognitive capabilities and their dysregulation in neurodevelopmental disorders. Together with studies in other model systems such as worms, flies, fish, rodents, and primates, we expect that additional basic principles on molecular determinants of the sequential lineage specification of NPCs in the developing brain will be revealed in the near future.

Acknowledgments

We thank K.M. Christian for comments.

The research in the authors' laboratories was supported by grants from National Institutes of Health (R37NS047344, U19MH106434, P01NS097206, and R01AG057497 to H. Song and R01MH105128, R35NS097370, and U19AI131130 to G-l. Ming), Simons Foundation (to H. Song and G-l. Ming), and The Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (to G-l. Ming). K-J. Yoon was partially supported by a Young Investigator Award from the Brain and Behavior Research Foundation, and C. Vissers was partially supported by a National Science Foundation predoctoral fellowship and National Institutes of Health grant T32GM007445.

The authors declare no competing financial interests.

Submitted: 20 February 2018
Revised: 5 April 2018
Accepted: 6 April 2018

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