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REVIEW ARTICLE

Translating neural stem cells to neurons in the mammalian brain

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Abstract

The mammalian neocortex underlies our perception of sensory information, performance of motor activities, and higher-order cognition. During mammalian embryogenesis, radial glial precursor cells sequentially give rise to diverse populations of excitatory cortical neurons, followed by astrocytes and oligodendrocytes. A subpopulation of these embryonic neural precursors persists into adulthood as neural stem cells, which give rise to inhibitory interneurons and glia. Although the intrinsic mechanisms instructing the genesis of these distinct progeny have been well-studied, most work to date has focused on transcriptional, epigenetic, and cell-cycle control. Recent studies, however, have shown that posttranscriptional mechanisms also regulate the cell fate choices of transcriptionally primed neural precursors during cortical development. These mechanisms are mediated primarily by RNA-binding proteins and microRNAs that coordinately regulate mRNA translation, stability, splicing, and localization. Together, these findings point to an extensive network of posttranscriptional control and provide insight into both normal cortical development and disease. They also add another layer of complexity to brain development and raise important biological questions for future investigation.

Facts

- Numerous posttranscriptional regulators including RBPs and miRNAs are expressed in a temporally dynamic and cell-type specific manner during embryonic corticogenesis.
- Posttranscriptional mechanisms control cell fate decisions of embryonic and adult neural precursor cells.
- Environmentally-driven signaling cascades regulate the expression and activity of posttranscriptional machinery.
- Neural precursor cells are transcriptionally primed and posttranscriptional mechanisms selectively repress mRNA translation to regulate self-renewal versus differentiation.

Open questions

- Is transcriptional priming and posttranscriptional control a general cellular strategy employed in developing and adult mammalian stem cell compartments?
- How do individual RBPs and miRNAs fit within the larger network of posttranscriptional control?
- What are the environmental cues that regulate the expression and activity of posttranscriptional machinery?
- How does the posttranscriptional machinery interface with transcriptional and epigenetic mechanisms?
- How do RBPs and miRNAs contribute to neurodevelopmental and neurological disorders?

Introduction

The mammalian neocortex is the most evolutionarily recent structure of the central nervous system and is responsible for processing sensory information, controlling motor output, and mediating higher-order cognitive functions [1]. Excitatory neocortical neurons are generated from neural

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precursor cells (NPCs) between embryonic (E) days 10.5 and E17.5 in mice and gestational week 7–27 in humans, followed by astrocytes and oligodendrocytes [1]. Production of the correct number and subtypes of neurons during this critical developmental window is crucial for the formation of functional neural circuitry, and defects in this process contribute to neurodevelopmental and neurological disorders including microcephaly, autism spectrum disorder, epilepsy, and schizophrenia [2]. In this review, we provide an overview of embryonic and adult ventricular-subventricular zone (V-SVZ) neurogenesis and the emerging role of posttranscriptional control. We also discuss the concept of transcriptional priming in the context of post-transcriptional mechanisms. Finally, we integrate these findings into a model of posttranscriptional control of neurogenesis.

Overview of embryonic cortical neurogenesis

The neocortex develops from the dorsal telencephalon, which begins as a pseudostratified neuroepithelial cell layer consisting of mitotically-active neuroepithelial stem cells (NESCs). This cortical layer, known as the ventricular zone (VZ), forms at E8-9 in mice [3, 4]. NESCs divide symmetrically to expand the precursor pool before transitioning into radial glial precursor cells (RGPs, also known as apical precursors) between E10-12, prior to the onset of cortical neurogenesis (Fig. 1a) [3, 5]. Unlike NESCs, which are limited to symmetric divisions, RGPs primarily divide asymmetrically to give rise to cortical excitatory neurons directly or indirectly by generating intermediate/basal progenitors (IP/BP) with limited cell division capacity that each produce two neurons (Fig. 1a) [3]. IPs populate the space immediately basal to the VZ known as the subventricular zone (SVZ), and provide a means of amplifying the neuronal output per neurogenic division [6]. The SVZ also contains another self-renewing precursor cell called outer/basal radial glia, which are abundant in gyrencephalic animals such as ferrets and primates [7].

The projection neurons that comprise the mature cortex are arranged into six layers and differ with regard to their morphology, axonal connectivity, electrophysiology, and gene expression [4]. These neurons are generated in an inside-out fashion to populate the six layers of the cortex, with earlier-born neurons populating the deepest of the six cortical layers, while later-born neurons populate progressively more superficial layers (Fig. 1a) [4]. While transcriptional profiling of purified populations of projection neurons in various cortical layers have identified important markers [8], these population-based studies do not fully account for the cellular and molecular heterogeneity that is beginning to be elucidated with single-cell RNA sequencing approaches [9].

Models of neurogenesis

In vivo lineage tracing studies indicate that early RGPs are multipotent and sequentially give rise to deep and superficial layer neurons followed by glia [1, 3, 4, 10, 11]. How are these different layer neurons generated from a pool of multipotent RGPs during neurogenesis? Until recently, the prevailing model based on classical transplantation experiments in ferrets was that an initial pool of multipotent progenitors undergoes progressive fate restriction throughout neurogenesis as they sequentially generate deep and superficial layer neurons [12]. Recent work, however has challenged this idea [13]. In this study, a FlashTag approach was used to pulse-label and isolate E15 RGPs that normally only generate later-born superficial neurons. When these tagged RGPs were transplanted into younger E12 embryonic cortices, they reverted to an E12-like RGP state and generated deep-layer neurons, just like the endogenous RGPs [13]. These findings suggest that RGPs do not become fate restricted as they transition from making deep-layer to superficial layer neurons, but that it is the environment that dictates genesis of one neuron type versus another.

Intrinsic regulation of embryonic cortical development

The precise balance between RGP self-renewal and differentiation in the developing neocortex involves the interaction of intrinsic cellular programs with a multitude of environmental cues. Rather than simply generating a homogeneous population of neurons, RGPs must sequentially give rise to diverse neuronal subtypes that populate the different layers of the cortex. How does neuronal subtype specification occur? Gain- and loss-of-function studies have shown that the transcription factors Sox5, Satb2, Fezf2, Tbr1, and Ctip2 comprise a cross-repressive transcriptional circuit that regulates projection neuron specification (Fig. 1b) [1, 4, 10]. Many additional subtype-specific genes have since been identified including the transcription factors Brn1/2 and Rorb that play critical roles in specification [8, 14, 15]. While this transcriptional circuit model has experimental support, the precise molecular controls underlying neuronal subtype specification are likely much more elaborate.

The ability of transcription factors to execute their function requires accessible chromatin sites on DNA, and neural precursors undergo extensive epigenetic changes during corticogenesis, particularly during the neurogenic-to-gliogenic transition [16, 17]. In addition to epigenetic control, regulation of cell-cycle length is another intrinsic regulator of NPC activity. We refer the reader to excellent

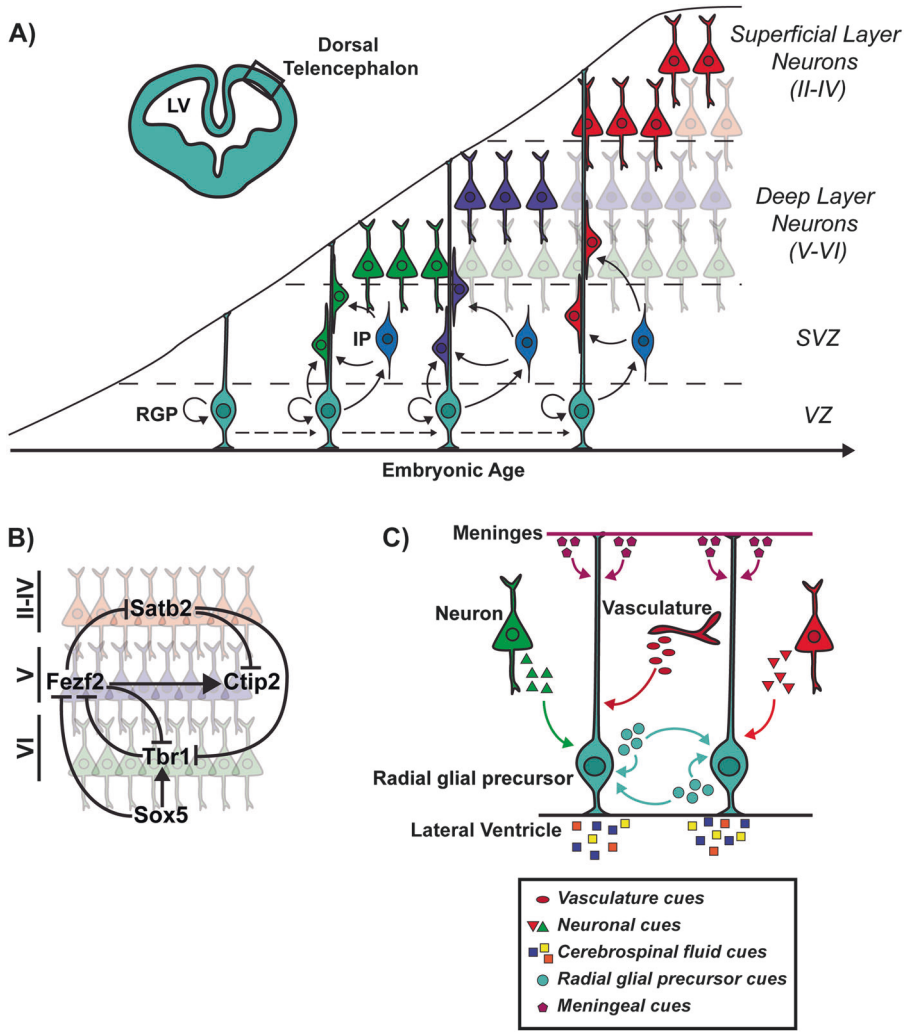

Fig. 1 Embryonic cortical neurogenesis occurs in an inside-out fashion. **a** In the developing dorsal telencephalon, radial glial precursors (RGPs) residing in the ventricular zone (VZ) adjacent to the lateral ventricles (LV) can give rise to a postmitotic neuron directly or indirectly via an intermediate progenitor (IP) cell. IPs populate the space basal to the VZ known as the subventricular zone (SVZ). Cortical neurons are generated in an inside-out fashion to populate the six layers of the cortex. Earlier-born neurons (shown in green and purple) populate the deepest of the six cortical layers (V–VI), while later born neurons (shown in red) populate progressively more superficial layers (II–IV). These layers contain distinct neuronal subtypes that differ based on morphology, electrophysiological activity, axonal connectivity, and gene expression. **b** Illustration of a cross-repressive transcriptional circuit that regulates deep versus superficial layer neuron specification [1, 4]. Tbr1 specifies deep layer VI corticothalamic neurons (shown in green) in part by repressing Fezf2, while Fezf2 acts upstream of Ctip2 to specify deep layer V subcerebral neurons (shown in purple) [1, 4]. Sox5 regulates the timing of deep layer neurogenesis by repressing Fezf2 until the production of layer VI corticothalamic neurons is complete. Satb2 specifies upper layer neurons (shown in red) in part by repressing deep-layer neuronal specifiers Ctip2 and Tbr1 [1, 4]. **c** RGPs integrate autocrine and paracrine factors originating from several sources including the meninges, vasculature, newborn neurons, and cerebrospinal fluid (CSF), many of which regulate RGP cell fate decisions

reviews on transcriptional, epigenetic, and cell-cycle control during neurogenesis [10, 11, 16, 18, 19].

Extrinsic cues regulating embryonic cortical development

The elongated radial morphology of RGPs provides them with access to extrinsic cues originating from the meninges, vasculature, newborn neurons, and cerebrospinal fluid, many of which regulate RGP cell fate decisions (Fig. 1c) [18, 20]. In this regard, combined transcriptome and cell-surface proteomic analysis of NPCs and newborn neurons have revealed a rich growth factor environment in the developing cortex including many previously uncharacterized autocrine and paracrine interactions (Fig. 1c) [20]. In addition to generically controlling NPC proliferation and differentiation, extrinsic cues regulate the specification of particular neuronal

subtypes [21]. We refer the reader to excellent reviews on this topic [18, 21].

Going beyond transcriptional and epigenetic mechanisms: posttranscriptional control of gene expression

Appropriate gene expression requires that proteins are produced at the correct time, amount, and subcellular location. How much do posttranscriptional regulatory mechanisms, for example those controlling translation, regulate this process? Conventionally, mRNA concentration in mammalian cells was assumed to be highly concordant with protein concentration, and mRNA levels were thus commonly used as a proxy for protein levels. However, systems-wide studies have highlighted why this is not always a correct assumption. In this regard, numerous studies have found a moderate to low correlation between protein and mRNA levels, with translation rates contributing to a large percentage of the variance in protein levels [22, 23]. Other studies have challenged this conclusion, showing high correlations between mRNA and protein levels (R^2 ~0.6–0.9), arguing that transcriptional control makes the largest contribution to protein levels [22, 23].

Although transcription is considered the main predictor of protein levels under steady state conditions, posttranscriptional control has been shown to play a dominant role during short-term state transitions such as differentiation [22, 24, 25]. The ability to change mRNA "translation on demand" allows proteins to be rapidly available in response to extrinsic stimuli and cellular changes [22]. Transcription factors are particularly subject to this form of regulation during rapid state transitions [26]. Furthermore, transcription is often spontaneous and stochastic, and the resulting transcriptional noise can be partially buffered by translational mechanisms to avoid aberrant cell fate decisions [22].

Posttranscriptional control is largely mediated by RNA-binding proteins (RBPs) and microRNAs (miRNAs), which assemble on mRNA sequences, often located in 3′ untranslated regions (3′UTRs) [27]. In addition to ~1600 transcription factors, there are over 1500 RBPs and 2600 annotated mature miRNAs encoded by the human genome [28–30]. RBPs are highly ubiquitous *trans*-acting regulators that influence various steps of RNA metabolism including mRNA stability, nuclear export, splicing, localization, and translation (Fig. 2a) [31]. RBPs and miRNAs regulate groups of functionally-related mRNAs along a coordinated pathway of RNA processing, allowing cells to respond with unprecedented efficiency to extrinsic cues, in what has been termed the 'RNA-operon' theory [31].

RBPs regulate multiple aspects of embryonic cortical development

Although most work to date has focused on epigenetic and transcriptional mechanisms, the role of posttranscriptional control in cortical development has only recently been appreciated. Microarray analysis at different timepoints throughout corticogenesis revealed that numerous posttranscriptional regulatory factors involved in mRNA splicing, localization, stability, and translation are dynamically expressed across the neurogenic period, particularly those involved in translational control [32]. A large number of RBPs were dynamically expressed, and single-molecule fluorescence in situ hybridization analyses found that their expression patterns were not only temporally dynamic but cell-type specific in several cases [32, 33]. The combination of ribosomal proteins associated with translating polysomes is also dynamic in both time and space throughout cortical development [34]. Intriguingly, while levels of many mRNAs encoding transcriptional and translational regulators are unaltered over cortical development, they are differentially associated with translating polysomes in a temporally-specific manner, suggesting that the posttranscriptional regulators may themselves be subject to posttranscriptional regulation [34]. Like RBPs, numerous miRNAs are also expressed in a temporally dynamic and cell-type specific manner during mammalian corticogenesis [35–37]. Several miRNAs and RBPs play key roles in multiple aspects of cortical development including NPC maintenance, differentiation, specification, neuronal migration, and survival. We will not focus on miRNA regulation in this review (see Table 2 and reviews [27, 38]). Instead, we will highlight several RBPs with a focus on those that regulate cell fate decisions in the developing cortex (Table 1). RBPs and miRNAs in the developing cortex, their main targets, and their functional roles are summarized in Tables 1 and 2, respectively.

mRNA splicing

Alternative splicing provides one way to amplify the protein diversity of the transcriptome by editing pre-mRNA sequences. In addition to modifying pre-mRNAs to generate unique protein-coding transcripts, alternative splicing modifies the 5′ and 3′ UTRs of mRNAs to impact downstream processing including mRNA translation, stability, and localization by exposing or concealing binding sites for RBPs and miRNAs (Fig. 2a) [39]. In the developing cortex, splicing is regulated in part by RBPs and plays a role in NPC maintenance, differentiation, survival, and neuronal migration (Table 1).

Several studies have shown dynamic alternative splicing changes in the developing forebrain across different brain regions, cell types, neuronal layers, and developmental stages

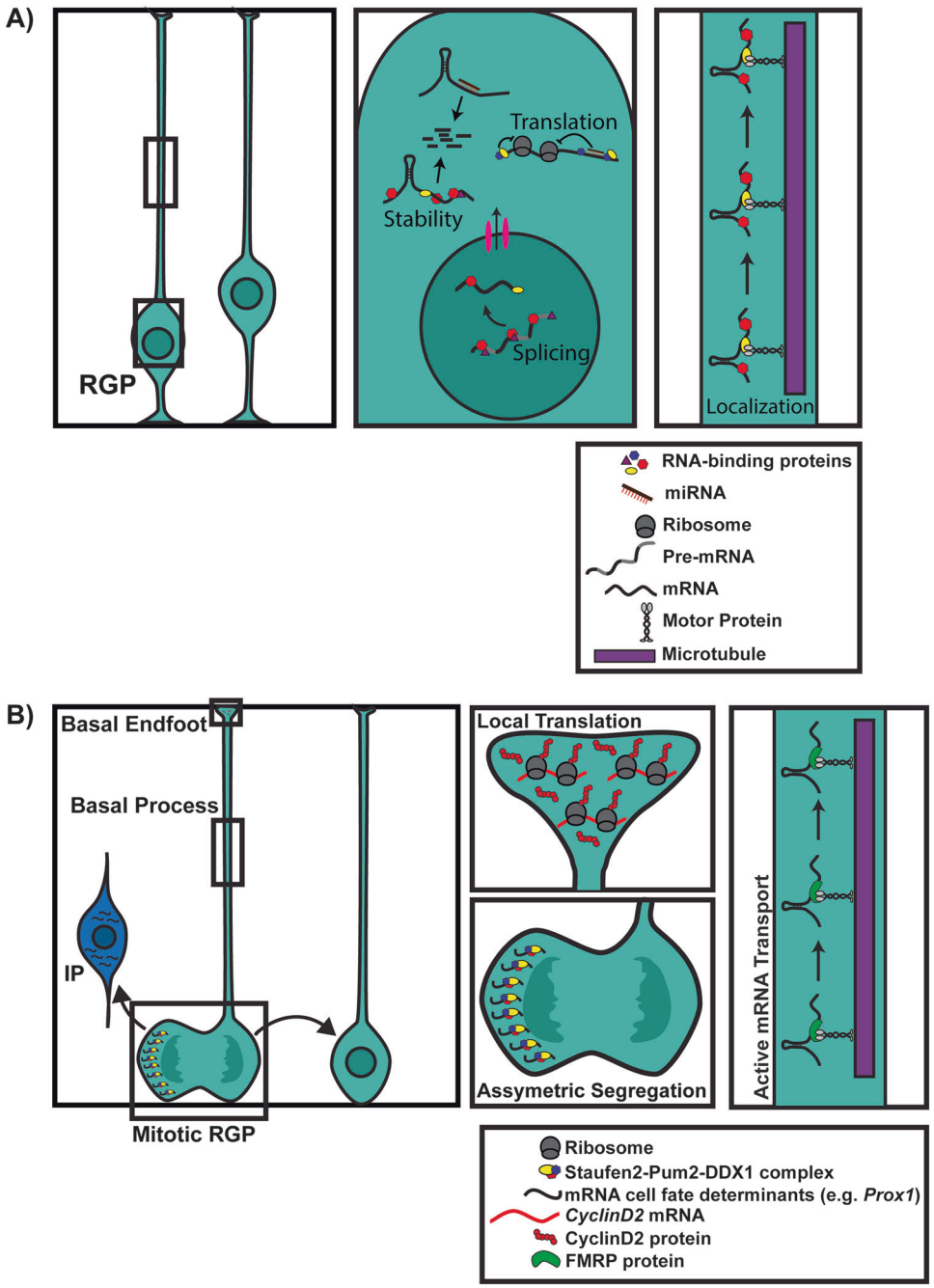

Fig. 2 NPC activity is dynamically regulated by posttranscriptional mechanisms. **a** Radial glial precursors (RGPs, light blue) are dynamically regulated by posttranscriptional mechanisms. The boxed regions of the RGP cell body and basal process are shown at higher magnification at the right. RBPs (shown by colored hexagons, triangles, and ovals) and miRNAs (red/brown lines) are highly ubiquitous and influence various steps of RNA metabolism including mRNA splicing, nuclear export, stability, localization, and translation. In the basal process, mRNAs are actively transported by RBPs (such as FMRP) along microtubules (purple). A figure legend is shown in the lower right panel. **b** mRNA cell fate determinants are asymmetrically segregated and actively transported in RGPs to ensure appropriate cell fate decisions. In RGPs undergoing mitosis, a Staufen2-Pum2-Ddx1 complex asymmetrically segregates cell fate determinants such as *Prox1* mRNA into the daughter cell destined to become an intermediate progenitor (IP). mRNA cell fate determinants are actively transported to basal endfeet by FMRP, where they are locally translated. In RGP basal endfeet, self-renewal factors such as *CyclinD2* mRNA are locally translated, ensuring that the daughter cell inheriting the basal process maintains its self-renewing capacity. A figure legend is shown in the lower right panel

[8, 14, 40–45]. For example, cortical NPCs and neurons transcriptionally profiled using RNA-sequencing showed extensive alternative exon usage during neuronal differentiation, preferentially of genes encoding cytoskeletal proteins [44]. These splicing changes were partially mediated by the RBPs Ptbp1 and Rbfox1/2/3 that antagonistically regulate the inclusion of neuronal exons to promote NPC maintenance and differentiation, respectively. Ptbp1 is expressed in RGPs and downregulated in neurons, and conditional knockdown of *Ptbp1* in RGPs caused loss of adherens junctions, premature neurogenesis, and lethal hydrocephalus postnatally [44, 46, 47]. Ptbp1 maintained RGPs in part by suppressing the inclusion of neuronal exons such as poison exons in Filamin A and Filamin B (exons containing stop codons that result in mRNA decay). *Ptbp1* itself is a transcriptional target of Sox2, a master transcriptional regulator of NPC identity, suggesting that Sox2 acts in part via Ptbp1 regulation [44]. *Ptbp1* is translationally repressed by miR-124, resulting in the inclusion of neuron-specific exons and neuronal differentiation [48]. Together, these findings illustrate how post-transcriptional regulators are themselves regulated by both transcriptional and posttranscriptional mechanisms [27].

Table 1 Translational regulators/RBPs involved in embryonic corticogenesis

Translational regulator or RNA binding protein	Known role in mRNA metabolism	Key mRNA targets/pathway	Function during cortical development	References
Apc	Localization	β2B-tubulin, microtubule organization genes	AP polarity; AP proliferation; neuronal migration; lamination; connectivity	Yokota et al. [98]; Preitner et al. [99]
Eif4a3	Localization, translation, stability, splicing	Ribosome, proteasome, and p53 pathway genes	Promote NPC maintenance; NPC/neuron survival; inhibit neurogenesis	Mao et al. [100]
eIF4E1/4E-T	Translation	*Neurog1, Neurog2, Neurod1*, transcription, neurogenesis pathway genes	Promote NPC maintenance; inhibit neurogenesis	Yang et al. [58]
eIF4G	Translation	?	Promote neurogenesis	Yang et al. [58]
FMRP	Translation, localization	*NOS1, Cdh2, Kif26a*, cytoskeletal, signalling, neurogenesis, autism-associated genes	Promote AP maintenance; inhibit AP to IP transition; neuron multipolar to bipolar transition; lamination	Tervonen et al. [57]; La Fata et al. [101]; Saffary and Xie [56]; Kwan et al. [102]; Pilaz et al. [50, 103]
HuR	Translation, stability	*Dll1, Foxp1, Foxp2*, transcription, translation, and layer-specific genes	NPC maintenance/differentiation; neuronal maturation; lamination; corpus callosum formation	Garcia-Dominguez et al. [104]; Kraushar et al. [54]; Popovitchenko et al. [55]
HuD	Translation, stability	?	Inhibit NPC proliferation; promote neurogenesis; neuronal specification and dendritic arborization of deep layer neurons	DeBoer et al. [64]; Akamatsu et al. [105]
Imp1	Localization, translation, stability	*CyclinD1, Hmga2*	Promote NPC maintenance; inhibit neurogenesis and gliogenesis	Nishino et al. [65]
Lin28	Translation, stability	*Hmga2, Igf1r, Igf2*-mTOR signalling genes	Promote NPC proliferation; prevent premature cell-cycle exit; neurite outgrowth; electrophysiogy	Yang et al. [88]; Jang et al. [153]
Marf1	Stability	?	Promote neurogenesis	Kanemitsu et al. [106]
Magoh	Localization, translation, stability, splicing	*Lis1*, ribosome, proteasome, and p53 pathway genes	Promote NPC maintenance; inhibit neurogenesis; NPC/neuron survival; lamination; mitotic spindle orientation; genomic stability	Silver et al. [107]; Pilaz et al. [50, 103]; Mao et al. [100]
Mushashi1/2	Stability, translation	*M-numb, p21*	Promote NPC self-renewal	Sakakibara et al. [108]; Imai et al. [109]; Chavali et al. [110]
Nanos1	Translation	?	Promote neurogenesis	Amadei et al. [60]
Nova2	Splicing	*Dab1*, axonal guidance genes	Late-born neuronal migration; lamination; axonal guidance	Yano et al. [111]; Saito et al. [112]
nSR100/SRRM4	Splicing	*Unc13b*, vescicle transport, axonal guidance, neurogenesis associated genes	Inhibit neurogenesis; neuronal maturation; lamination; axonal guidance	Quesnel-Vallieres et al. [154]
PIWIL1	Translation, stability	*Map1b*, cytoskeletal genes	Neuronal migration; polarity	Zhao et al. [113]
Ptbp1	Splicing	*Psd-95, Ptbp2, Filamin A/B*, cell-cell adhesion, synaptogenesis, neurogenesis genes	INM; promote NPC maintenance; inhibit neurogenesis	Zhang et al. [114]; Shibasaki et al. [46]; Ramos et al. [47]
Ptbp2	Splicing	*Psd-95, Shtn1*, proliferation, cell fate, cytoskeleton, neurogenesis, neurite outgrowth, synaptic, axonogenesis genes	AP polarity; INM; NPC maintenance; inhibit neurogenesis; neuronal maturation; synapse formation; neuronal survival; axonogenesis	Licatalosi et al. [115]; Li et al. [116]; Zheng et al. [117]; Makeyev et al. [48]; Zhang et al. [118]

Table 1 (continued)

Translational regulator or RNA binding protein	Known role in mRNA metabolism	Key mRNA targets/pathway	Function during cortical development	References
Pum2	Translation, localization	*Neurog1, Neurog2, Brn1, Tle4*, adhesion, migration, transcription, neurogenesis, cell fate genes	Promote NPC maintenance; inhibit neurogenesis; neuronal specification; neuronal morphology; synaptogenesis	Vessey et al. [49]; Zahr et al. [62]
Qki5	Splicing, stability	*Nin*, cell-cell adhesion, cadherin-catenin signalling, cytoskeletal genes	AP polarity; promote NPC maintenance; inhibit neurogenesis; neuronal migration	Hayakawa-Yano et al. [119]; [120]
Rbfox1	Splicing, stability, translation	?	Neuronal migration; morphology; electrophysiology; axon extension; dendritic arborization; synapse formation	Zhang et al. [114]; Hamada et al. [121]
Rbfox1/2/3	Splicing, stability, translation	*Nin*	Promote NPC maintenance and neurogenesis	Zhang et al. [114]
Rbm8a	Localization, translation, stability, splicing	Autism, schizophrenia, alzheimer's, growth factor signalling, ribosomal pathway, p53 pathway genes	Promote NPC maintenance; inhibit neurogenesis; neuronal migration; NPC/neuron survival	Mao et al. [122]; Mao et al. [100]; Zou et al. [123]
Sam68	Splicing	*Aldh1a3*, neuron and oligodendrocyte development genes	Promote NPC self-renewal; inhibit premature neuronal and glial differentiation	La Rosa et al. [124]
Smaug2	Translation	*Nanos1*	Promote NPC maintenance; inhibit neurogenesis	Amadei et al. [60]
Stau2	Localization, translation	*Prox1, Bbs2, Trim32*, negative regulation of mitosis, cell cycle, cilium assembly genes	Promote NPC maintenance; inhibit neurogenesis	Kusek et al. [53]; Vessey et al. [49]
Tra2B	Splicing	*Tubd1, Sgol2*	Neuron/NPC survival; NPC proliferation; lamination cortical patterning; axonal outgrowth	Storbeck et al. [125]; Roberts et al. 155
Unkempt	Translation	Protein metabolism, trafficking pathway genes	Neuronal morphology	Murn et al. [126]
Ythdf2	Stability	m^6a modified mRNAs involved in neuronal differentiation and development	NPC proliferation; neurogenesis; neurite outgrowth	Li et al. [61]

NPC neural precursor cell, *AP* apical precursor, *IP* intermediate progenitor, *INM* interkinetic nuclear migration

Table 2 miRNAs involved in embryonic corticogenesis

miRNA	Key mRNA targets/pathway	Function during cortical development	References
miR-9	*Foxp2, Map1b, Meis2, Foxg1, Tlx, Pax6*	Cajal-retzius neuron specification; inhibit NPC proliferation; promote neurogenesis; lamination; layer V neuron specification; neuron migration; axonal outgrowth/branching	Zhao et al. [127]; Shibata et al. [128]; Shibata et al. [129]; Dajas-Bailador et al. [130]; Clovis et al. [131]; Shu et al. [132]
let-7b	*?*	Layer II–IV neuron specification	Shu et al. [132]
let-7d	*Tlx, Imp1*	Inhibit NPC proliferation; promote neurogenesis	Zhao et al. [133]
miR-17–92 cluster	*Pten, p21, Tbr2, Tis21*	Promote NPC proliferation; inhibit AP to IP transition; survival	Bian et al. [134]; Fei et al. [135]; Chen et al. [136]
miR-7	*p21, Ccng1*, p53 pathway genes	Promote neurogenesis (AP to IP transition); NPC survival	Pollock et al. [137]
miR-210	*Cdk7*	Promote premature-cell cycle exit/differentiation	Abdullah et al. [138]
miR-134	*Chrdl-1, Dcx*	Increase NPC proliferation; reduce neuron migration; neuronal survival; neurite outgrowth	Gaughwin et al. [139]
miR-137	*Lsd1*	Inhibit NPC proliferation; promote neurogenesis	Sun et al. [140]
miR-34/449	*Jam-a*	Promote neurogenesis; regulate NPC mitotic spindle orientation,	Fededa et al. [141]
miR-15b	*Tet3*	Inhibit NPC proliferation; promote neurogenesis	Lv et al. [142]
miR-124	*Ptbp1, Rcor1 (coREST), Dcx*	Promote neurogenesis; neuronal migration	Makeyev et al. [48]; Volvert et al., [143]
miR-22	*Rcor1 (coREST)*	Neuron migration	Volvert et al. [143]
miR-128	*Phf6, Pem1*	Inhibit NPC proliferation; promote neurogenesis; layer VI neuron specification; regulate neuronal morphology, migration, excitability	Franzoni et al. [144]; Zhang et al. [114]; Shu et al. [132]
miR-29b	Wnt signalling genes	Cajal-retzius neuron specification; inhibit NPC proliferation	Shin et al. [145]

NPC neural precursor cell, *AP* apical precursor, *IP* intermediate progenitor

mRNA localization

RBPs involved in mRNA localization influence many cellular functions in the developing cortex including NPC proliferation, neurogenesis, and neuronal migration (Fig. 2a) (Table 1). During a neurogenic division, mRNAs encoding cell fate determinants are actively segregated within asymmetrically dividing RGPs (Fig. 2b) [49, 50]. For example, mRNA encoding the self-renewal protein CyclinD2 localizes at the basal end feet of RGPs where it is locally translated, a process dependent on transport elements within its 3′UTR [51, 52]. During an asymmetric division, the daughter cell that inherits the basal process and *CyclinD2* maintains its self-renewal capacity, while the other daughter cell begins differentiating (Fig. 2b) [51, 52]. How does mRNA transport occur within RGPs? By live imaging of embryonic organotypic brain slices, mRNAs were shown to be rapidly transported in basal processes toward the basal endfeet of RGPs where they were locally translated (Fig. 2b) [50]. This active transport was mediated by the RBP Fragile X Mental Retardation Protein (FMRP). In RGP basal endfeet, FMRP associates with mRNAs encoding signaling and cytoskeletal factors, many of which are associated with autism and neurogenesis [50].

Staufen2 (Stau2) is another RBP involved in mRNA localization. In RGPs, Stau2 forms a complex with the RBP Pumilio2 (Pum2) and the helicase Ddx1, and this complex asymmetrically segregates cell fate determinants such as *Prox1* into differentiating daughter cells (i.e., intermediate progenitors) during an asymmetric division (Fig. 2b) [49, 53]. Disruption of the complex by shRNA knockdown caused mislocalization and misexpression of *Prox1*, premature differentiation and depletion of RGPs [49, 53]. Collectively, these studies illustrate that regulatory mRNAs are segregated and actively transported in RGPs during asymmetric divisions to ensure appropriate cell fate decisions (Fig. 2b).

mRNA stability and translation

RBPs that regulate mRNA stability and translation play critical roles in NPC cell fate decisions (Fig. 2a) (Table 1). The RBP human antigen R (HuR) that interacts with 3′UTRs to influence mRNA stability and translation [39], controls the association between translating polysomes and functionally-related mRNAs encoding transcriptional, translational, and neuronal layer-specific regulators in a developmental stage-specific manner [54]. HuR also controls the composition of translation initiation factors, elongation factors, and ribosomal proteins within polysomes. These alterations are functionally relevant, as HuR conditional knockout cortices are thinner with defects in neuronal differentiation, lamination, and corpus callosum formation [54]. HuR interacts with common and unique subsets of mRNAs during early and late neurogenesis,

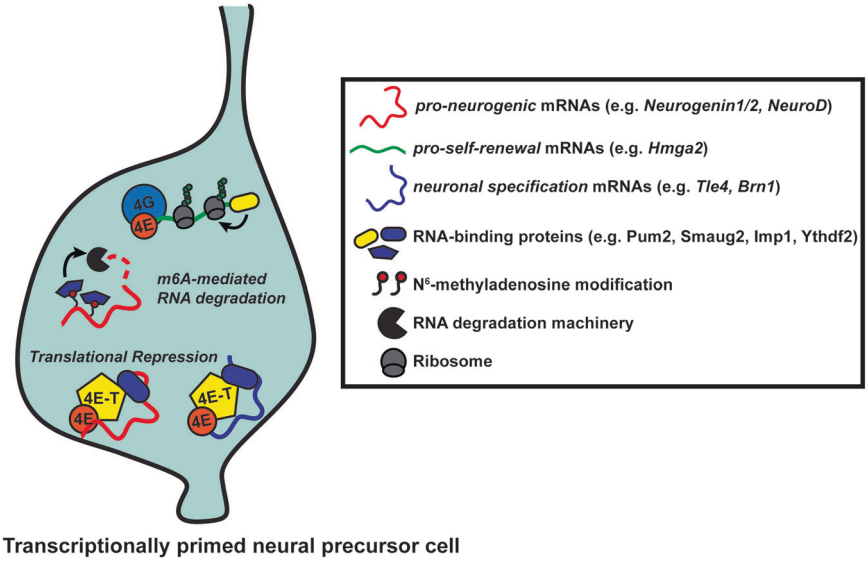

Fig. 3 Transcriptional priming and posttranscriptional control in embryonic neural precursor cells (NPCs). Embryonic NPCs are transcriptionally primed to differentiate into diverse neuronal progeny, but maintained in an undifferentiated state until the appropriate time via posttranscriptional mechanisms. These mechanisms include degradation of m6A-modified mRNAs mediated by RNA-binding proteins (RBPs) such as Ythdf2 and translational repression by a Pum2-4E-T translational repression complex. Silenced mRNAs include proneurogenic mRNAs (e.g., *Neurogenin1/2, NeuroD1*) and neuronal specification mRNAs (e.g., *Brn1, Tle4*). In addition to silencing proneurogenic mRNAs, RBPs (e.g., Imp1) can promote the stability and expression of pro-self-renewal mRNAs (e.g., *Hmga2*) to maintain NPCs in an undifferentiated state

suggesting that the mRNA targets of RBPs evolve as a function of time [55]. Another translational regulator that plays important roles during corticogenesis is FMRP. FMRP maintains RGPs in an undifferentiated state by repressing the RGP to IP transition [56]. This function is mediated in part by regulation of actin cytoskeletal organization at apical endfeet [56, 57].

Transcriptional priming and posttranscriptional control

Paradoxically, during cortical embryonic development, RGPs express mRNAs that maintain stem cell proliferation and self-renewal as well mRNAs that promote neurogenesis. How then do RGPs produce the correct number and subtype of neurons at the appropriate times during development? One mechanism is translational repression of mRNAs mediating neuronal differentiation (Fig. 3). In this regard, a repressive complex consisting of eIF4E and its binding partner 4E-T sequesters and represses proneurogenic mRNAs expressed in RGPs including *Neurogenin1/2* and *NeuroD* basic Helix-Loop-Helix transcription factor mRNAs (Fig. 3) [58]. Disruption of these complexes promoted neurogenesis, arguing that embryonic RGPs are transcriptionally primed (also called transcriptional prepatterning [59]) to generate neurons, with one or more translational repression complexes maintaining the stem cell state by silencing transcription factors that promote differentiation (Fig. 3). Presumably, external proneurogenic cues release this repression by as-yet-undefined mechanisms, enabling translation of mRNAs mediating neurogenesis. Unlike most post-transcriptional regulators, the 4E-T protein does not bind to mRNAs directly and must be recruited to target mRNAs via RBPs. Smaug2 is one RBP that mediates the interaction between 4E-T and target mRNAs such as *Nanos1* to maintain RGPs in an undifferentiated state [60]. Nanos1 is an RBP that reciprocally promotes neurogenesis, likely by repressing self-renewal genes. These findings suggest that appropriate neuronal differentiation involves both the translational derepression of proneurogenic mRNAs as well as the de novo repression of mRNAs required for stem cell maintenance [60].

A second way that the translation of proneurogenic proteins is maintained at low levels in transcriptionally-primed NPCs is via chemical modifications to mRNAs that trigger their decay (epitranscriptomics) (Fig. 3). Reversible N^6-methyladenosine (m^6A) modifications to mRNAs involved in cell cycle and neurogenesis results in their decay and controls the temporal progression of cortical neurogenesis [59]. These m^6A-modified mRNAs are recognized, in part, by the RBP Ythdf2, which promotes their decay in the developing cortex (Fig. 3) [61]. As predicted if this is an important mechanism, Ythdf2$^{-/-}$ embryos display decreased cortical thickness owing to impaired NPC proliferation, neurogenesis, and neurite outgrowth [61].

Translational control mechanisms and priming not only regulate the timing of neurogenesis but also the types of neurons that are made [62, 63]. RGPs and IPs produce neurons that migrate basally to form the nascent cortical layers, with the earliest-born neurons populating the deepest layers and later-born neurons progressively populating more superficial layers. Subsequent to this neurogenic period, which occurs between E10.5 and E17.5 in the mouse, the same pool of RGPs generates glial cells. How is this timed cell genesis determined when RGPs coincidently express mRNAs encoding transcription factor specifiers for different types of neurons [62]? One mechanism involves selective translational repression of neuronal specifier mRNAs by 4E-T. 4E-T forms a complex with the RBP Pum2 in RGPs, and this complex associates with and silences the neuronal layer specifier mRNAs *Brn1* and *Tle4* (Fig. 3). Disruption of these complexes during the period of superficial layer neurogenesis leads to aberrant translation of deep layer neuronal specifiers and misspecification of cortical neurons. [62] A second RBP involved in neuronal subtype specification is HuD [64]. $Hud^{-/-}$ mice display a selective loss of Tle4-positive deep layer neurons, which the authors speculate may contribute to motor deficits observed in these mice, since corticospinal motor neurons are enriched in deeper layers [64]. A number of additional RBPs show cortical lamination deficits in loss-of-function experiments (Table 1). It is tempting to speculate that, like Pum2 and HuD, these other RBPs control neuronal subtype specification by participating in repression complexes that selectively silence translation of neuronal specifier mRNAs.

Silencing of mRNAs (repression and/or decay) is not the only way that RBPs maintain NPC self-renewal and prevent premature differentiation. This is illustrated by the RBP Imp1 which is important for mRNA stability and translation [65]. Imp1 both translationally inhibits mRNAs associated with differentiation and increases the stability and expression of pro-self-renewal genes such as *Hmga2* (Fig. 3). Consistent with this, cortex-specific Imp1 ablation resulted in reduced NPC self-renewal and accelerated neuronal and glial differentiation. Intriguingly, Imp1 expression is regulated by the miRNA *Let-7*, further highlighting the cross talk between RBP-and miRNA-mediated posttranscriptional control in the developing cortex [65].

These findings add to a growing body of work pointing to transcriptional priming of precursors in vivo, suggesting that RBPs are critical regulators of neuronal differentiation and subtype specification [59, 63]. This type of priming, which also occurs in embryonic and hematopoietic stem cells, makes sense from several perspectives [66, 67]. Transcriptional priming coupled with posttranscriptional control would enable the rapid regulation of neurogenesis and specification by extrinsic cues [58, 60, 62]. This 'priming' model is consistent with a single-cell RNA sequencing study of the developing cortex that showed a surprising degree of transcriptional expression overlap among RGPs, IPs, and neurons at different developmental stages with many cells coexpressing genes associated with two or even three different embryonic cortical cell types [63].

These studies highlight the importance of posttranscriptional control for ensuring the precise and timely genesis of neurons and neuronal subtypes during development (Tables 1 and 2). It should be kept in mind, however, that RBPs such as FMRP and Pum2 regulate multiple aspects of mRNA metabolism and have more than one cellular function during cortical neurogenesis (Table 1). Moreover, several of these RBPs play important roles in postmitotic neurons by regulating neuronal morphology, excitability, axonal growth, and synapse formation, processes that depend on local translation (Table 1) [68].

Postnatal and adult V-SVZ neurogenesis

There are two major regions where neurogenesis occurs in the postnatal and adult brain: the subgranular zone (SGZ) of the hippocampal dentate gyrus and the V-SVZ surrounding the lateral ventricles (Fig. 4a). Here, we will provide a brief overview of V-SVZ neurogenesis before discussing the emerging role of posttranscriptional control. We guide the reader to the following review on SGZ neurogenesis [69].

The V-SVZ niche

Postnatal and adult NSCs (or B1 cells) reside within an epithelium known as the V-SVZ and are largely quiescent or very slowly dividing in vivo (Fig. 4a) [70]. Quiescent and activated (dividing) NSCs coexist in the V-SVZ and can interconvert in vitro [71]. Clonal lineage tracing approaches in vivo indicate that unlike embryonic RGPs, asymmetric divisions of adult NSCs are rare or do not occur [72]. Rather, they divide symmetrically to either self-renew or differentiate, with a greater probability of undergoing symmetric-consuming divisions leading to a decline in NSCs over time [72]. Activated V-SVZ NSCs give rise to transit-amplifying cells (or type C cells), which divide symmetrically three to four times before generating neuroblasts (or type A cells) (Fig. 4a, c) [70, 73]. Neuroblasts migrate along the rostral migratory stream to the olfactory bulb where they differentiate into various subtypes of interneurons [73, 74], integrating into the existing olfactory bulb circuitry, and influencing the plasticity of olfactory-related behaviors [73]. Retroviral fate-mapping of V-SVZ NSCs showed that in both healthy and demyelinating conditions, NSCs can generate oligodendrocytes destined for the corpus callosum where they myelinate axons [75].

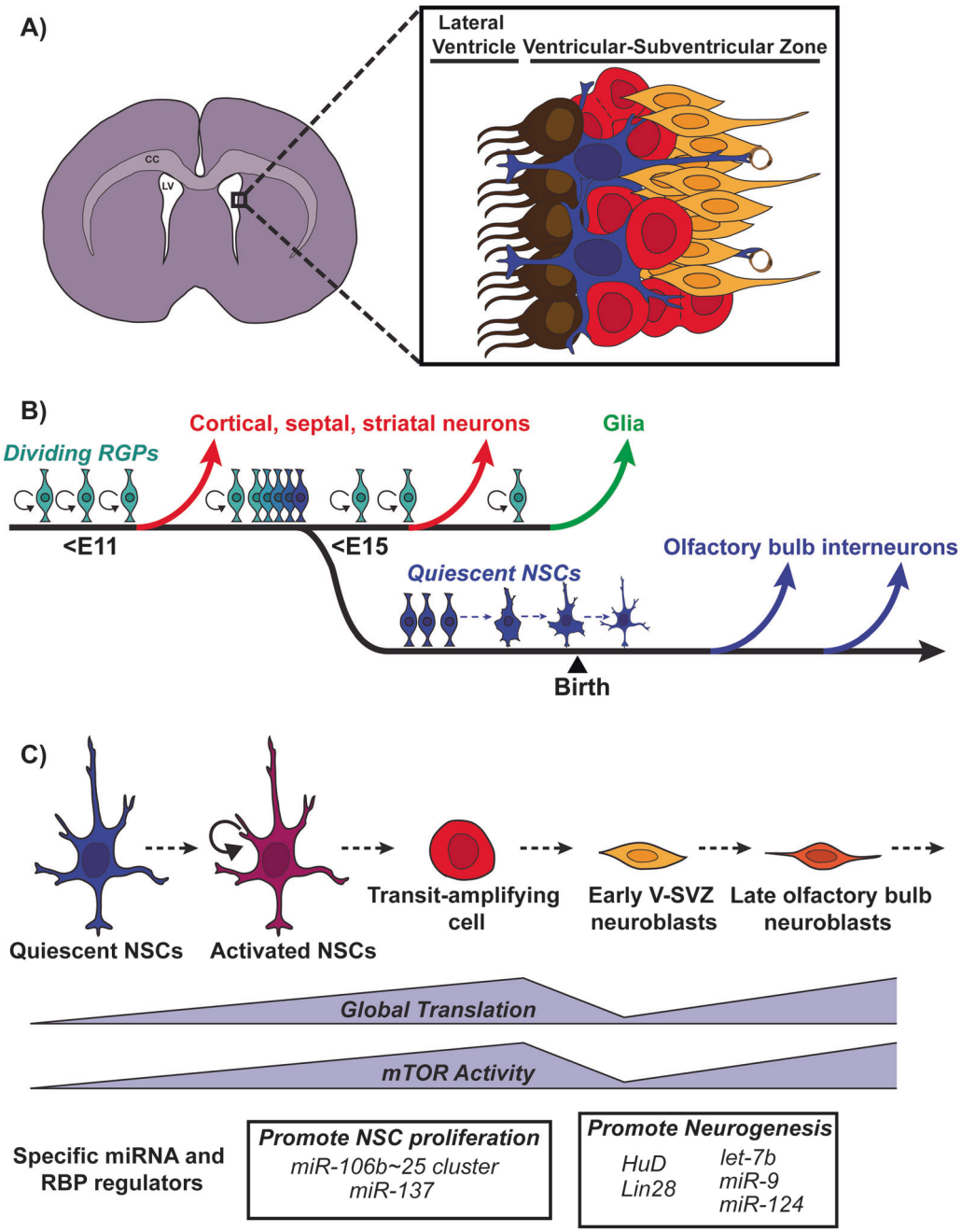

Fig. 4 The postnatal/adult ventricular-subventricular zone (V-SVZ) niche. **a** Coronal section of the postnatal/adult brain. Lining the lateral ventricles of the postnatal/adult brain is a cell dense area known as the V-SVZ. The V-SVZ contains several cell types: ependymal cells (brown), neural stem cells (blue), transit amplifying cells (red), and early neuroblasts (orange). CC corpus callosum, LV lateral ventricle. **b** A subpopulation of radial glial precursors (RGPs) that produce cortical, septal, striatal neurons, and glia embryonically, becomes quiescent between ~E13 and E15. These cells remain quiescent until they are activated during adulthood and generate olfactory bulb interneurons [77]. The transition to quiescence is indicated in the schematic by the shift in the color of RGPs from light to dark blue. **c** In the V-SVZ, quiescent NSCs (blue) become activated (purple) and give rise to transit amplifying cells (red) before generating early V-SVZ neuroblasts (yellow), which migrate toward the olfactory bulb. In the olfactory bulb, these late neuroblasts (orange) complete their differentiation into various subtypes of interneurons. Global protein translation and mTOR activity increase as quiescent NSCs become activated and generate transit amplifying cells, but then drops in early neuroblasts before increasing again as early neuroblasts mature into late OB neuroblasts [82]. miRNAs and RBPs regulate the translation of specific mRNAs to either promote V-SVZ NSC proliferation or promote neurogenesis

V-SVZ NSCs also generate astrocytes following a photothrombotic ischemic cortical injury [76].

Intrinsic and extrinsic regulation of postnatal/adult V-SVZ neurogenesis

Adult V-SVZ NSCs, which generate inhibitory interneurons and glia, are derived from three embryonic sources. The majority derive from the ganglionic eminence, and the remainder from the embryonic cortex and septum (Fig. 4b). Lineage tracing has shown that embryonic RGPs from these three origins give rise to distinct postnatal V-SVZ NSC compartments, and ultimately generate different subtypes of olfactory bulb interneurons depending on their location along the anterior–posterior and dorsal-ventral axes of the V-SVZ [70, 73, 77]. In addition to generating interneuron subtypes, there is emerging evidence that at least some of the cortical RGPs that produce excitatory neurons during embryogenesis switch to generating inhibitory interneurons postnatally (Fig. 4b), even though they maintain their transcriptional core identity as they make this switch [63, 77]. Thus, one of the major questions in the field is how the same population of adult NSCs is regulated to generate these diverse populations of neurons. V-SVZ NSCs reside in a specialized niche rich in extracellular cues, including factors that originate from the NSCs themselves, surrounding niche cell types such as ependymal cells, vascular cells, astrocytes, microglia, the more committed progeny of NSCs, and the CSF and circulation. These factors likely regulate the activity of transcription and epigenetic factors important for the regulation of NSC maintenance, differentiation, and cell fate determination. For reviews on intrinsic and extrinsic regulation of V-SVZ neurogenesis, we guide the reader to several reviews [70, 73, 74].

Going beyond transcriptional and epigenetic control in the postnatal/adult V-SVZ

Global control of protein translation

Low protein synthesis is a general feature of the stem cell state in embryonic, hematopoietic, hair follicle, muscle, and neural stem cells [25]. In these cells, inhibition of protein synthesis tends to increase self-renewal while activation of protein synthesis promotes the onset of differentiation [25]. Consistent with this, ribosomal genes are transcriptionally upregulated and protein synthesis is increased as adult NSCs transition from a quiescent to activated (dividing) state, and mTORC1, an inducer of global protein synthesis, is activated when NSCs transition to transit-amplifying cells (Fig. 4c) [78–80]. Moreover, hyperactivating mTORC1 in neonatal V-SVZ NSCs results in depletion of NSCs (i.e., reduced self-renewal) and increased differentiation into transit-amplifying cells and neuroblasts, while reducing mTORC1 activity in NSCs prevents their differentiation and decreases neuroblast formation [81]. This phenotype was recapitulated in young adult mice in a follow-up study; elevating mTORC1 activity in slowly-dividing NSCs robustly increased transit-amplifying cells and neuroblasts [80].

How does mTORC1 activity control the NSC to neuron transition? Using a RiboTag approach to profile the transcriptome (total mRNA) and translatome (ribosome-bound mRNA) in quiescent NSCs, activated NSCs, early neuroblasts (isolated from SVZ), and late neuroblasts (isolated from the olfactory bulb), Baser et al. captured the overall state of transcription and translation as stem cells transitioned to newly-born neurons [82]. Global translation increased from the NSC to transit amplifying cell stage, but then dropped in early neuroblasts before increasing again as early neuroblasts matured to late olfactory bulb neuroblasts (Fig. 4c). The decrease in translation in early neuroblasts was attributable to a decrease in mTORC1-mediated translational activity (Fig. 4c). The translation of the stem cell maintenance factor *Sox2* was repressed at this stage, suggesting that appropriate progression along the differentiation pathway involves the repression of stem cell maintenance factors at the early neuroblast stage [82]. One interpretation of these data is that translational repression mechanisms keep quiescent NSCs in an undifferentiated state, and that derepression needs to occur to trigger the switch to activation and early differentiation. However, as described above, once cells are on a differentiation trajectory, additional selective translational repression of stemness genes regulated for example by RBPs and miRNAs are required to ensure that they differentiate at the right time and place (Fig. 4c).

In addition to the global regulation of translation, several specific miRNAs and RBPs control V-SVZ NSC self-renewal and neurogenesis (Fig. 4c; Table 3). For example, miR-124 promotes neuronal differentiation by repressing *Sox9* mRNA, which promotes NSC self-renewal in neuroblasts [83]. miR-137, in contrast, inhibits differentiation and promotes NSC proliferation by repressing the histone methyltransferase *Ezh2*, highlighting the interplay between posttranscriptional control and epigenetic mechanisms (Fig. 4c) [84]. miRNA-mediated repression also controls the dorsal-ventral regionalization of V-SVZ NSCs and consequently, interneuron subtype specification [85]. In this regard, Pax6 protein expression is restricted to the dorsal V-SVZ, while *Pax6* mRNA is expressed all along the dorsal-ventral axis. This restricted expression pattern is due to miR-7a-mediated translational repression of *Pax6* mRNA in the ventral V-SVZ [85]. Inhibition of miR-7a results in translation of *Pax6* mRNA in ventral regions and increased production of dopaminergic neurons in the olfactory bulb [85]. Together, these findings

Table 3 miRNAs and RBPs involved in postnatal/adult V-SVZ Neurogenesis

miRNA	Key mRNA targets/ pathway	Function in postnatal/adult V-SVZ	References
let-7b	*Hmga2, Tlx, CyclinD1*	Promote neurogenesis; inhibit NSC proliferation	Nishino et al. [146]; Zhao et al. [147]
miR-7a	*Pax6*	Dopaminergic neuron subtype specification	De Chevigny et al. [85]
miR-9	*Foxo1 (predicted)*	Promote neurogenesis	Kim et al. [148]
miR-19	*Rabgef2*	Neuronal migration	Han et al. [149]
miR-124	*Sox9*	Promote neurogenesis; inhibit gligogenesis (astrocytes)	Cheng et al. [83]
miR-137	*Ezh2*	Promote NSC proliferation; inhibit neurogenesis	Szulwach et al. [84]
miR-25 (miR-106b~25) cluster	*Foxo3 (predicted)*	Promote NSC proliferation	Brett et al. [150]
RNA-binding protein			
HuD	*Satb1*	Inhibit NSC proliferation;promote neurogenesis	Akamatsu et al. [105]; Wang et al. [151]
Lin28	*Let-7*	Promote neuroblast formation (long term depletion of OB neurons and astrocytes)	Romer-Seibert et al. [152]
Hnrnpab	*Eps8*	SVZ cell migration	Lampasona et al. [156]

NSC neural stem cell, *OB* olfactory bulb

argue that miRNAs play important roles in NSC self-renewal, differentiation, regionalization, and specification of particular interneuron subtypes.

A recent single-cell RNA sequencing study of adult V-SVZ NSCs identified a subset of activated NSCs that express GABAergic neuronal differentiation genes such as *Dlx1* and *Dlx2*, suggesting that a subpopulation of NSCs may be primed for GABAergic differentiation [58, 86]. This raises the intriguing possibility that posttranscriptional mechanisms control the onset of differentiation in an analogous fashion to embryonic RGPs [58, 60, 62]. This avenue of research, still at an early stage, should identify the RBPs, miRNAs, translational regulators, and their functional roles at various stages of postnatal V-SVZ neurogenesis (Table 3) [25].

An integrated network of posttranscriptional control

How do these RBPs, miRNAs, and other translational regulators fit within the larger landscape of global post-transcriptional control? It is now clear that many of these factors are expressed in a temporally dynamic and cell-type specific manner throughout corticogenesis [32, 35–37]. Moreover, evidence from RNA immunoprecipitation (RIP) and transcriptome analyses suggest that these regulators share partially overlapping mRNA targets. For instance, HuR and FMRP share target mRNAs in the developing cortex, and Pum1/2 share targets with FMRP in the brain [55, 87]. 4E-T interacts with and shares mRNA targets with the RBPs Pum2 and Smaug2 [58, 60, 62]. Interestingly, the RBP Lin28a promotes NPC proliferation in a manner dependent on its interaction with Imp1, suggesting that there are also important functional interactions between RBPs [88]. Together, these findings point to an extensive network of posttranscriptional control, in which RBPs, miRNAs, and other translational regulators coordinately control the expression of partially overlapping, functionally important mRNAs [89]. This partial redundancy makes the system robust and ensures that perturbations in any one component would not necessarily lead to massive, irreversible alterations in gene expression [89]. Similar networks exist in the model organisms *S. cerevisiae* and *D. melanogaster*, and in the developing cortex these networks are now being validated by mining RIP datasets for overlapping mRNA targets of individual RBPs [31]. Moreover, as described previously, posttranscriptional regulators are themselves the target of posttranscriptional control. Thus, as others have argued, this network with overlapping targets and multiple feedback loops provides a "self-limiting" and "self-sustaining" balance of RBPs, lending further resilience to posttranscriptional control networks [31].

Upstream regulation of the posttranscriptional machinery

As discussed above, NPC niches are rich in extrinsic cues that regulate their proliferation, differentiation, and cell fate specification, and it is therefore likely that environmentally-driven signaling pathways regulate RBP expression and/or interactions with target mRNAs [20]. For example, Wnt1 signaling, which enhances embryonic NPC maintenance and proliferation, promotes Imp1 expression during

cortical development [65]. As a second example, timed Wnt3 secretion from thalamocortical axons around mid-neurogenesis regulates both the composition of ribosomal proteins and the subset of mRNAs that are associated with polysomes [34]. Wnt3 promoted *Foxp2* mRNA association with and translation in polysomes via regulation of its 3′UTR, and conditional ablation of thalamic Wnt3 impaired the specification of Foxp2-positive deep layer neurons [34]. How then might these extrinsic cues feed onto the posttranscriptional machinery? Many RBPs contain multiple consensus phosphorylation sites, suggesting that they can be regulated by phosphorylation [90]. In this regard, HuR phosphorylation is important for regulating its translational control of the autism-associated mRNAs *Foxp1* and *Foxp2* in the developing cortex [55]. Moreover, RBP interactions with target mRNAs are regulated by phosphorylation in response to growth factor stimulation in other contexts [91]. Thus, receptor-mediated phosphorylation of RBPs likely provides one mechanism for rapidly and reversibly altering the translation of subsets of mRNAs that regulate NPC biology.

Concluding remarks

The ability to rapidly modulate protein expression levels is crucial for neural stem cells, which must integrate a multitude of cues to ensure the genesis of the right cells at the right time, while at the same time maintaining the requisite levels of self-renewal. These decisions require both the fast induction of particular lineage programs and the rapid turning off of programs that specify alternative fates. Furthermore, differentiation involves extensive rearrangements in morphology and increased metabolic requirements, further highlighting the need for rapid control of protein synthesis [78, 92]. Post-transcriptional regulation plays multiple roles along these differentiation trajectories, regulating the onset of differentiation, stem cell maintenance, and consolidation of the differentiated phenotype [58, 60, 62, 82, 83].

Given the emerging importance of posttranscriptional control in rodents, could analogous mechanisms be operating in the developing human cortex and partially underlie its increased expansion and complexity? In support of this idea, numerous miRNAs are expressed in the developing macaque but not mouse cortex, and are differentially expressed in the VZ and outer SVZ where they regulate cell cycle and neurogenic genes [93]. Moreover, extensive changes in 3′ and 5′-UTR-mediated translation occur as human ES cells differentiate into cortical neurons [94]. Furthermore, all of the RBPs mentioned in this review have human and nonhuman primate orthologs, and these RBPs are highly expressed during the human neurogenic period [95]. RBPs involved in alternative splicing have likely contributed to the increased complexity of the human brain by amplifying the protein diversity of the transcriptome. In support of this idea, the human brain expresses more alternatively spliced mRNAs than any other tissue [40].

Several RBPs and miRNAs have been causally implicated in the pathogenesis of human neurodevelopmental and neurodegenerative disorders including Fragile-X-syndrome, autism spectrum disorder, spinal muscular atrophy, amyotrophic lateral sclerosis, and frontotemporal dementia [96]. Dysregulated activity and expression of RBPs and miRNAs are also causally associated with glioblastoma and medulloblastoma [97]. Therefore, as future work elucidates their roles during rodent and ultimately human cortical development, this should provide valuable insights into both normal and pathological brain function [27, 96, 97].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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