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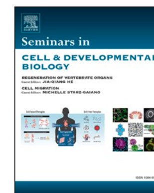

Review

Setting the clock of neural progenitor cells during mammalian corticogenesis

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ABSTRACT

Radial glial cells (RGCs) as primary neural stem cells in the developing mammalian cortex give rise to diverse types of neurons and glial cells according to sophisticated developmental programs with remarkable spatiotemporal precision. Recent studies suggest that regulation of the temporal competence of RGCs is a key mechanism for the highly conserved and predictable development of the cerebral cortex. Various types of epigenetic regulations, such as DNA methylation, histone modifications, and 3D chromatin architecture, play a key role in shaping the gene expression pattern of RGCs. In addition, epitranscriptomic modifications regulate temporal prepatterning of RGCs by affecting the turnover rate and function of cell-type-specific transcripts. In this review, we summarize epigenetic and epitranscriptomic regulatory mechanisms that control the temporal competence of RGCs during mammalian corticogenesis. Furthermore, we discuss various developmental elements that also dynamically regulate the temporal competence of RGCs, including biochemical reaction speed, local environmental changes, and subcellular organelle remodeling. Finally, we discuss the underlying mechanisms that regulate the interspecies developmental tempo contributing to human-specific features of brain development.

1. Introduction

One of the biggest challenges in neuroscience is to understand how developmental programs instruct the generation of enormously diverse cell types, which are assembled into complex neural circuits in the brain with temporal, spatial, and numerical precision. During mammalian embryonic cortical development, neural stem/progenitor cells (NPCs) sequentially give rise to different types of neurons and glia through highly organized processes. In the earliest stages, the cerebral cortex is composed of pseudostratified neuroepithelial cells that mostly divide symmetrically to expand NPC pools. In turn, neuroepithelial cells transform into radial glial cells (RGCs), which serve as the major NPCs in the developing cortex until the early postnatal period [1]. In the developing mouse cortex, most RGCs attach to the ventricular surface with their apical endfeet and thus are named ventricular RGCs (vRGCs). However, the majority of human RGCs are located in the outer subventricular zone (OSVZ), named outer radial glial cells (oRGCs), which retain basal processes without apical attachment and display distinct mitotic behavior [2]. An increased number of oRGCs, which generate the majority of cortical neurons [3], is thought to contribute to the increased complexity and the evolutionary expansion of the human brain compared to other mammals [4].

The temporal competence of RGCs to produce different types of progenies changes over time (Fig. 1). To accomplish the orderly generation of distinct progenies, RGCs go through multi-step transitions of their developmental competence to produce diverse types of daughter cells. These temporal changes of developmental competence are regulated by the stage-specific transcriptome of RGCs controlled by multifactorial gene regulatory networks [5,6]. The timing of the onset/offset and duration of each step are finely controlled by a highly coordinated

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genetic program in a precise and predictable way with some stochastic events [7,8]. Thus, subtle alterations in the timing of these biological processes can lead to individual variability or interspecies differences during development. A remarkable example is the expansion of the human cerebral cortex generated through notably protracted neurogenic processes compared to other primate species [9]. The molecular mechanisms driving the precise temporal coordination of biological processes and ensuring the reproducible generation of neuronal diversity are just starting to be revealed.

Classical and recent studies have shed light on the role of intrinsic and extrinsic factors in determining the temporal competence of NPCs in the various stages of cortical development. Classic heterochronic transplantation experiments in ferrets showed that when NPCs from the young donor cortex were transplanted into an older recipient cortex, the donor NPCs have the capability to generate late-born upper layer (UL) neurons. However, when NPCs from the old donor cortex were transplanted into the younger recipient cortex, the donor NPCs failed to generate early-born deep layer (DL) neurons [10], suggesting the competence of NPCs is gradually restricted and fixed over time. However, it was recently shown that the competence of RGCs is more flexible than previously believed. By rigorously birth-dating vRGCs of the donor cortex, old vRGCs can restore the competence of younger progenitors to generate early-born DL neurons after transplantation into the younger recipient cortex, whereas intermediate progenitor cells (IPCs) cannot, highlighting the progenitor type-specific differences in the fate plasticity [11]. In addition, dynamic Wnt signaling is required for the re-specification of late vRGCs by early cortical environment, suggesting that extrinsic factors and intrinsic receptiveness interplay to modulate the temporal competence of NPCs *in vivo* [8].

The existence of an intrinsic timing program of NPC competence is well supported by *in vitro* experiments. For example, the sequence and timing of the production of diverse cell types were maintained in cultured NPCs from embryonic mouse cortex [12] or differentiated from mouse or human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) [13,14]. However, human NPCs exhibit a longer expansion period and a slower pace of neuronal maturation than chimpanzee NPCs in iPSC-derived 2-dimensional (2D) culture and 3-dimensional (3D) cerebral organoid models [15–17]. Single-cell RNA-seq (scRNA-seq) analysis using cerebral organoids derived from human, chimpanzee and macaque iPSCs revealed that human neural development proceeds at a relatively slower pace than in apes. There was a higher level of expression of neuronal maturation genes and more glial cells in chimpanzee cerebral organoids compared to human cerebral organoids during the same developmental period [18]. Moreover, when cultured human NPCs were transplanted into the mouse neonatal cortex, human NPCs still exhibited a protracted temporal transition of competence and the subsequent neuronal maturation followed the tempo of human neurogenesis in the mouse extrinsic environment *in vivo* [19]. On the other hand, in the co-culture system of human and mouse cells, gene sets associated with neurogenesis, neuronal differentiation, and maturation, and synaptic signaling were upregulated earlier, and peak gene expression profiles were rapidly altered compared to human cell cultures alone [20]. These results suggest that the orchestration of intrinsic and extrinsic pacemakers control the fate specification of RGCs during mammalian corticogenesis. Here we review the recent progress in our understanding of molecular and cellular mechanisms that guide sequential lineage specification of NPCs with a focus mainly on the developing mouse cortex. We also discuss the potential mechanisms that govern the unique protracted neurogenesis of the human brain.

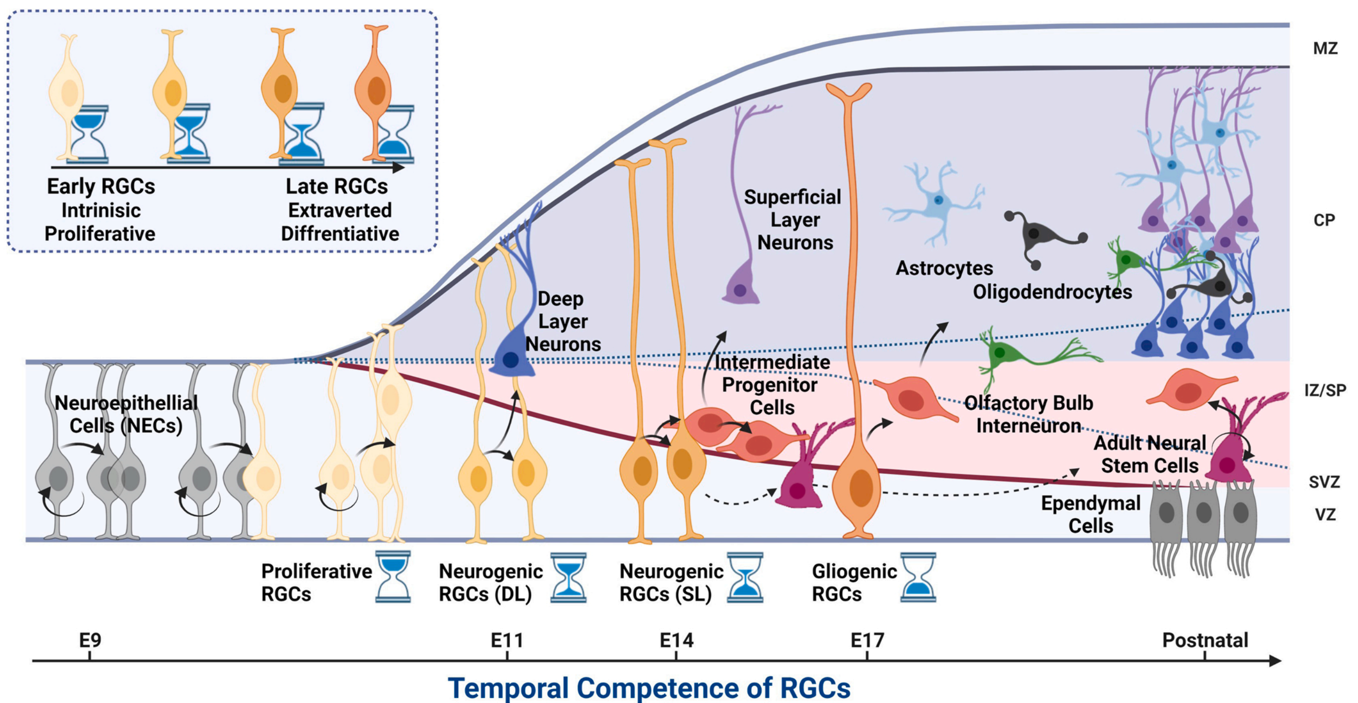

Fig. 1. Overview of the temporal sequence of murine corticogenesis. During cortical development, multipotent NPCs generate neurons in the cortical layers and glial cells, such as astrocytes and oligodendrocytes, sequentially in a time-dependent manner. Corticogenesis begins with the amplification of neuroepithelial cells (NECs) through symmetric divisions. Next, NECs transform into radial glial cells (RGCs), which act as primary neural stem cells. RGCs change their temporal competence during corticogenesis (early RGCs, pale yellow; late RGCs, orange) and sequentially give rise to different neurons and glia cells through asymmetric division. RGCs first produce deep layer neurons (layer VI/V), and subsequently superficial layer neurons (layer IV/III/II) mostly through intermediate progenitor cells. In later stages, RGCs transition from neurogenesis to gliogenesis and give rise to astrocytes, oligodendrocytes, olfactory bulb interneurons, and ependymal cells. In the postnatal stage, most of the RGCs are differentiated, and some of them remain as adult neural stem cells. MZ, the marginal zone. CP, the cortical plate. IZ/SP, the intermediate zone/subplate. SVZ, the subventricular zone. VZ, the ventricular zone.

2. Temporal progression of the stage-specific transcriptome in NPCs

Non-biased scRNA-seq analysis of the embryonic mouse brain revealed characteristic gene expression of spatiotemporally diverse RGCs. A total of 87 subtypes of RGCs can be categorized as early and late RGCs [21]. Early RGCs express a higher level of *Nestin*, *Lin28a*, and *Hes5*, while late RGCs express *Ednrb*, *Neurog2*, and *Pou3f2* [22]. In addition, Fluorescence-activated Cell Sorting (FACS)-isolated RGCs or pulse labeling of isochronic cohorts of cells enabled fine comparison of the temporal transcriptome between early-stage and late-stage RGCs [5,6,23]. RGCs exhibit temporal progression of gene expression from an internally directed "introverted" status to a more exteroceptive "extraverted" status (Fig. 1). Cell cycle-related and chromatin-related processes are prominent in early RGCs, whereas signaling molecules (e.g. Shh) and molecules critical for responding to external stimuli (e.g. membrane receptors and excitability-related proteins) are elevated in late RGCs [6].

Recent scRNA-seq results suggest even more diverse subpopulations of RGCs [24,25]. These subpopulations are categorized by an orchestral combination of spatiotemporal gene sets, such as early RGC marker HMGA2 and late RGC marker CLU. Moreover, mitotic RGCs exhibit not only an RGC-specific transcriptome but also a daughter cell-type-specific transcriptome before their neurogenic division, potentially affecting subsequent asymmetric division and cell fate decisions of daughter cells [26]. For example, neuronal lineage genes, such as *Tbr2* and *Neurod4* mRNAs, are transcriptionally pre-patterned, but those proteins are not expressed in vRGCs [27]. Similarly, UL neuron-specific mRNAs, such as *Cux2* and *Satb2*, or DL neuron-specific mRNAs, such as *Fezf2* and *Otx1*, are also found in a subset of RGCs [28,29]. These results suggest that a subset of RGCs is lineage-biased toward specific neuronal subtypes through transcriptional pre-patterning [30]. Since it is known that mRNAs encoding cell fate determinants are unequally segregated within asymmetrically dividing RGCs [31–33], it will be interesting to investigate whether these pre-patterned transcripts are also regulated during asymmetric division.

In addition, single-cell ATAC-seq revealed dynamic changes of chromatin status during the temporal progression of RGC competence. RGCs and other cell types show a strong connection between transcriptome and chromatin accessibility [34]. This synchronization regulates stage-specific transcription factors, such as DMRTA2 and CUX1. Moreover, the expression of specific transcription factors, such as POU2F2 or NEUROD2, enhances chromatin accessibility and cell fate decisions between corticofugal and callosal neurons during corticogenesis [35].

In summary, single-cell level analyses showed that RGCs are much more heterogeneous than previously thought, and dynamically shape their transcriptome and chromatin status to achieve sequential progression of their temporal competence, which in turn allows for orderly generation of multiple cell types during corticogenesis.

3. Dynamic epigenetic landscape changes regulating the temporal competence of NPCs

A fundamental question in development is how the same genomic information of stem cells can be interpreted to generate vastly different cell types. Multiple epigenetic regulations, such as DNA methylation and histone modifications, play key roles to shape unique transcriptional profiles to define cell identity [36–38]. Temporal changes in the patterning of various histone modifications in RGCs aid in the transition of these cells through developmentally-regulated competence states during corticogenesis. In particular, stage-specific actions of histone modifiers are critical for precise spatial and temporal gene expression, which determines the competence of NPCs to produce proper cell types at specific time points of development. Although epigenetic mechanisms govern broad aspects of neurodevelopment, which have been comprehensively reviewed elsewhere [38,39], here we focus on recent findings of epigenetic histone modifications in RGCs to determine their temporal competence (Fig. 2).

Epigenome profiling of RGCs at different stages suggested global changes of histone modification during corticogenesis. Chromatin immunoprecipitation sequencing (ChIP-seq) showed that RGCs exhibit dynamic changes in the epigenetic landscape, including active histone marker H3K4me3 and repressive histone marker H3K27me3, during cortical development [40–42]. H3K27me3 on proliferative and cell fate commitment gene sets, including *Tbr2* and *Pou3f2*, rapidly decrease in neurogenic RGCs [43]. H3K9ac also decreases in mouse Tbr2$^+$ IPCs, leading to downregulated *Trnp1* expression, which previously was shown to regulate the tangential expansion of cortical NPCs [44]. Elevated H3K9ac by treatment of an HDAC inhibitor preferentially increases IPC proliferation and *Trnp1* expression, increasing the size and folding of the normally smooth mouse neocortex. In addition, specific epigenome editing on the *Trnp1* locus by a CRISPR-dCas9-based system is sufficient to activate *Trnp1* expression and expand IPC pools [45]. These results show the importance of specific epigenetic programs to regulate key developmental genes that contribute to unique properties of the developing cortex.

General epigenetic machinery, such as polycomb repression complexes (PRCs) or histone acetyltransferases (HATs) are also involved in corticogenesis. For example, ablation of PRC1 component Ring1B increases DL neurons, and the deletion of PRC2 component *Ezh2* extends the duration of the neurogenic period [46,47]. Recent scRNA-seq studies suggested that early RGCs strongly express chromatin organizing factors EZH2 and SUZ12 and a core component of PRC2 named Eed, which delays cell cycle exit [6] (Fig. 2A).

During corticogenesis, RGCs change their epigenetic landscape at the local level by recruiting master regulators with stage-specific factors (Fig. 2C). In the early stage of corticogenesis, extrinsic signaling pathways, including Wnt, Notch, Fgf, and Shh, promote self-renewal of RGCs. Neuronal differentiation is promoted by enhancing intrinsic neurogenic programs and turning down the extrinsic proliferative pathway. BCL6 represses multiple extrinsic signaling pathways, including the Notch, Shh, Fgf and Wnt pathways, by recruiting histone deacetylase SIRT1 to target gene promoters, leading to their transcriptional silencing [48]. Similarly, the Notch signaling pathway inhibits the differentiation of RGCs through the expression of downstream effectors, such as HES1 proteins. HES1 represses proneuronal factors like ASCL1. Neuron-specific transcription factor MYTL1 recruits histone deacetylase component SIN3B to promoter regions of Notch signaling regulators, including HES1, leading to the reduction of Notch signaling and neuronal differentiation [49]. On the other hand, PHF21B recruits both histone deacetylase HDA2 and lysine-specific demethylase LSD1 to the promoters of cell cycle-related genes and mediates the loss of H3K4me1 and H3K27ac, accelerating cell cycle exit and neuronal differentiation [50]. In addition, the number and the proper positioning of cortical neurons is also regulated by temporal epigenetic factors in RGCs. Histone methyltransferase PRDM16 regulates the epigenetic state of transcriptional enhancers in RGCs to instruct the production of IPCs and superficial layer (SL) neurons and neuronal migration [51]. Mechanistically, PRDM16 suppresses target gene expression related to neuronal specification, cell cycle regulators, and neuronal migration by limiting chromatin accessibility of the permissive enhancers [52]. These studies provide examples of how epigenetic regulation shifts the temporal gene expression program of RGCs to achieve neuronal diversity during corticogenesis.

In addition to histone modifications, DNA methylation regulated by the nuclear factor I (NFI) family [53], and noncoding RNAs, including Lnc-Brn1a/b and miR-17–92 [54,55], also epigenetically regulate the properties of RGCs. More details of epigenetic regulation beyond histone modifications have been extensively reviewed elsewhere [38,56,57].

In the near future, more advanced technologies to resolve the connection between the transcriptome and diverse aspects of the

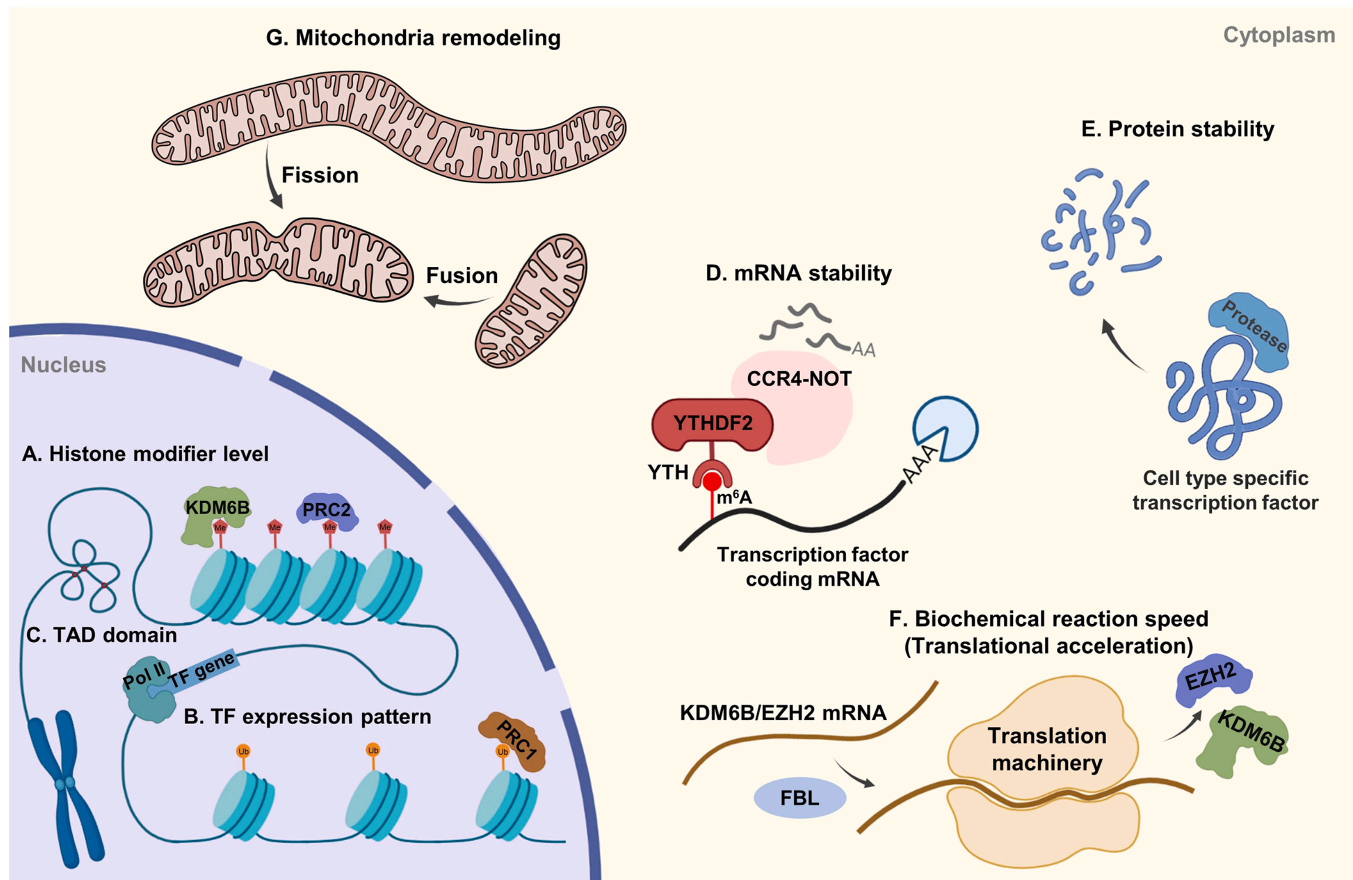

Fig. 2. The regulatory mechanisms for dynamic temporal competence of RGCs during corticogenesis. The temporal competence of RGCs is determined by various intrinsic factors. (A) The expression level of histone modifiers and chromatin remodelers dynamically changes, which affects the stage-specific epigenome profiles of RGCs. (B) The expression pattern of cell type specific transcription factors is a major determinant of RGC fate and differentiation timing. (C) Changes in the topographically associating domain (TAD) boundary of RGCs affect the 3D chromatin architecture and gene expression patterns. (D) The turnover rates of mRNA of cell-type-specific transcription factors can be regulated by epitranscriptomic modifications, which trim the pre-patterned transcriptome of RGCs, enabling the precise timing of corticogenesis. (E) Additionally, species-specific regulation of proteostasis, such as the differential rate of protein degradation, can be an underlying mechanism of interspecies developmental tempo control. (F) The translation efficiency of cell fate regulators, including histone modifiers such as EZH2 and KDM6B, is gradually changed during corticogenesis. This change induces an epigenetic change in RGCs, causing RGCs to differentiate into different types of neurons. **(G)** The cell fates of daughter cells are determined by mitochondria metabolism and dynamics after mitosis of RGCs.

epigenome, such as single-cell multi-omics tools, can reveal precise regulatory mechanisms mediated by epigenome dynamics in stage-specific RGCs. Although the latest research showed that transcriptome profiles and chromatin accessibility changes are highly correlated, detailed epigenetic regulatory mechanisms are not clear [58]. Advanced methods to investigate dynamic epigenomes, such as SNARE-seq [59], scNMT-seq [60], and scMT-seq [61], may expand our understanding of the crosstalk between the transcriptome and epigenome in the developing brain.

4. Posttranscriptional regulations mediated by epitranscriptomic modifications

The transcriptome of NPCs gradually changes according to the developmental stage, which defines the temporal competence of NPCs to generate diverse types of daughter cells. This global alteration in the transcriptome causes proteomic changes in cells and induces a change in cell functions and fates. Therefore, the transcriptomic changes in NPCs can be considered a pre-patterning system to guide the differentiation of NPCs with precise timing [6]. It has been shown that RGCs produce neuronal specification mRNAs prior to differentiation into neurons, suggesting that the neurogenic program is designed to determine the direction of cell differentiation in advance [30,62,63]. However, the molecular mechanisms that shape this pre-patterned transcriptome of RGCs are still not fully understood.

Nascent mRNAs are subject to extensive processing such as 5′ capping, splicing, and poly-A tailing, which alters the final outcome of gene expression. In addition, similar to posttranslational modification of histone proteins, RNA is also subject to various types of post-transcriptional chemical modifications regulating the fate of the RNA transcript, named epitranscriptomic modifications, which play important roles in the nervous system [64]. Over 170 types of RNA modifications that control the fate of transcripts in various mechanisms have been identified [65]. *N*^{6}-methyladenosine (m^{6}A) is the most abundant internal mRNA methylation in eukaryotes, which has recently been investigated as a major regulator of cell fate decisions in various neurodevelopmental contexts [38,66]. m^{6}A is a reversible modification installed by a methyltransferase complex and erased by demethylases and recognized by reader proteins [65,67]. The metabolism of mRNA changes dynamically depending on the site of m^{6}A modification and the type of reader proteins that recognize m^{6}A, directly leading to changes in the transcriptome [68].

m^{6}A methylation is co-transcriptionally installed to pre-mRNA and non-coding RNA by the methyltransferase complex consisting of METTL3 and METTL14 subunits, together with other accessary components, including WTAP, VIRMA and ZC3H13 [65]. Epitranscriptomic regulation via m^{6}A RNA modification is known to influence multiple steps during cortical development [36]. For example, the absence of

m^6A induces the accumulation of m^6A-tagged mRNAs related to temporal and cell-type-specific transcription factors, leading to delayed transitions in developmental competency, including the DL-UL neuron transition and the neurogenic-gliogenic transition [62]. These results suggest that selective rapid degradation of m^6A-tagged mRNAs is essential to maintain the proper temporal progression and transcriptional pre-patterning of RGCs [30]. Interestingly, histone modifications such as H3K27ac, H3K27me3, and H3K4me3 are significantly altered by the loss of m^6A RNA modification, suggesting potential interactions between epigenetic and epitranscriptomic regulation [69]. On the other hand, m^6A methylation is mainly recognized by reader proteins containing a YTH domain, and the YTH domain-containing protein family modulates the fate of RNA by regulating the localization and processing of m^6A-tagged RNA [67]. The YTHDC1/2 reader protein distributed in the nucleus mainly regulates transcription, splicing and nuclear export, whereas the YTHDF1/2/3 reader proteins control m^6A-tagged mRNA metabolism in the cytoplasm [65]. In particular, YTHDF2 promotes the decay of m^6A-tagged mRNA by recruiting the CCR4-NOT complex through direct interaction with the CNOT1 subunit [70] (Fig. 2D). Ablation of *Ythdf2* in the mouse developing brain causes accumulation of YTHDF2 target mRNA and defects in the self-renewal and differentiation capability of RGCs. The loss of the proliferative capacity of RGCs results in a dramatic loss of IPCs, which is the primary cause of impaired neurodevelopment [71]. Fragile X mental retardation protein (FMRP) is another m^6A reader, which promotes nuclear export of m^6A-tagged mRNA targets during cortical neurogenesis [72]. *Fmr1* knockout mice exhibit delayed neural progenitor cell cycle progression and extended maintenance of proliferating neural progenitors into postnatal stages, similar to *Mettl14* knockout mice.

Within the nucleus, a recent study showed that m^6A signaling regulates alternative splicing in cortical NPCs [73]. In addition, m^6A also regulates transcription and chromatin status [74]. Co-transcriptionally installed m^6A on mRNAs recruits histone-modifying enzymes, such as KDM3B histone demethylase, to local chromatin locations and causes chromatin remodeling [75]. m^6A also labels non-coding RNA species, including chromosome-associated regulatory RNA (carRNA), such as enhancer RNA (eRNA) and promoter-associated RNA (paRNA), which affects their stability [76]. In *Mettl3* KO mESCs, the abundance of m^6A-tagged carRNAs is significantly increased compared to that of non-m^6A carRNAs, suggesting m^6A methylation destabilizes the m^6A-tagged carRNAs to regulate transcription levels. On the other hand, eRNA can induce promoter-enhancer interactions by DNA loop formation and eRNA increases the localization of transcription coactivators, such as CREB-binding protein (CBP), to target gene alleles [77]. A recent study suggested that m^6A-eRNA has a broad role in enhancer activation and transcriptional control by recruiting YTHDC1 to form a transcriptional condensate through phase separation [78]. By altering the profile of the epigenome and transcriptome, epitranscriptomic modification may directly contribute to the transcriptional regulation of NPCs, which will be an important topic for future investigation.

Other RNA modifications have been also examined for their roles in neurodevelopment [64,79]. m^5C occurs in a variety of RNA species, including tRNA, rRNA, and mRNA, and is a critical regulator of RNA function and fate in different contexts [80]. mRNA m^5C labeled by NSUN methyltransferase is mainly present in the 5′UTR and 3′UTR, and it selectively induces mRNA export and regulates the translation process to control the biochemical reaction speed of mRNA [81]. An m^5C methyltransferase NSUN2 mutation is associated with neurodevelopmental disorders in humans [82]. NSUN2 depletion also causes neurodevelopmental defects in mice, such as delayed neuronal differentiation and synapse formation [83]. Changes in the distribution of m^5C methylation are thought to be a key component in determining cell identity and function during the developmental progression from ESCs to the brain [84]. These results suggest that epitranscriptomic modifications are actively involved in the regulation of cellular functions and cell fate decisions. It will be exciting to explore roles and mechanisms of various epitranscriptomic modifications in regulating NPC competence and neurogenesis in the future.

5. Timing mechanisms among different species: biochemical reaction speed

Diversification of various cell types with the same genomic information is enabled by the temporal-spatial regulation of the expression of cell-type-specific transcription factors. The composition of the key regulatory networks including cell-type-specific transcription factors in RGCs becomes a temporal measure to define cell identity and differentiation capacity [85]. Therefore, biochemical reaction speeds, such as the synthesis and degradation kinetics of key proteins, are a critical factor to determine cell identity and developmental timing.

In the developmental process of various species of mammals, events of embryonic development are processed through a precisely predictable sequence [86]. Although a highly conserved program, the developmental tempo of cellular differentiation is different for each species during corticogenesis [87]. A recent study on neurodevelopment in humans and mice suggested that developmental tempo regulation is related to the stability of cell-type-specific transcription factors [88] (Fig. 2E). The turnover of cell-type-specific transcription factors was slower in human neural tube development compared to mice. When mouse and human ESCs were differentiated toward motor neurons *in vitro*, the differentiation tempo of human cells was 2.5 times slower than that of the mouse cells, and this difference was correlated to the difference in stability of cell-type-specific transcription factors, such OLIG2 and SOX2 [88]. Furthermore, a recent study showed that the segmentation clock is determined by the rate of degradation and expression of HES7, a key protein of the segmentation clock. This result suggests that the difference in the oscillation period of segmentation is caused by species-specific intracellular biochemical reaction speeds [89]. Together, these findings suggest that the differential speed of the biochemical reaction, including protein stability, can have a role in regulating the developmental tempo of the mammalian brain, and global differences in the key metabolic processes might be the pivotal mechanism to understand the interspecies differences in developmental processes.

Protein synthesis metabolism has recently been proposed as an important regulatory factor for the temporal progression of RGCs in brain development [63,90]. During the temporal progression from early RGCs to late RGCs, the rRNA methyltransferase FBL accelerates the translation efficiency of mRNA, which is poly U-enriched at the 5′UTR [90,91]. Protein species with increased translation efficiency include epigenetic regulators, such as KDM6B and EZH2 (Fig. 2 F). The global pattern of H3K27me3 was modified by these histone modifiers, inducing changes in the chromatin status and gene expression within RGCs subtypes. Collectively, it is suggested that time-specific translational acceleration causes epigenetic modifications and transcriptome pre-patterning in RGCs, influencing the timing of cell fate decisions and differentiation.

6. Mitochondrial dynamics and membrane potential of RGCs

Whether vRGCs differentiate into neurons or glial cells or have the ability to continuously divide can be determined by the asymmetric inheritance of the cellular structure and organelles [92]. For example, mitochondrial dynamics regulate stem cell identity, self-renewal, and fate decisions by orchestrating a transcriptional program [93] (Fig. 2 G). Stem cells can delay the accumulation of damage in a way that avoids transferring damaged subcellular components to daughter cells. Human stem-like cells (SLCs) maintain daughter cell identity by differentially apportioning senescent mitochondria when they undergo asymmetric division. Daughter cells harboring fewer old mitochondria tend to maintain stemness properties after asymmetric division [94]. In addition, a recent study investigated the relationship between mitochondria

structure and daughter cell type during asymmetric division of RGCs using photoconvertible mitochondria sensors [95]. A high level of mitochondria fission after mitosis causes daughter cells to differentiate into neurons, whereas mitochondria fusion redirects daughter cells toward self-renewal. When mitochondrial fusion was chemically promoted, the proportion of daughter RGCs/IPCs over neurons was significantly increased after mitosis. These results suggest that alteration of mitochondria dynamics determines daughter cell fates after asymmetric division.

Differences in extracellular ROS distribution also affect the cell fate decisions of RGCs [96]. Previous studies have found that endogenous ROS levels are critical for sustaining the proliferation of RGCs, suggesting that ROS is a key factor that controls cell fate [97]. As mouse corticogenesis progresses, the oxidative stress of RGCs gradually increases in a time-dependent manner. Furthermore, each RGC subtype has a different level of ROS-related gene expression, raising the possibility that oxidative stress can be a key indicator of developmental timing [96]. Conditional deletion of ROS regulator PRDM16 during early corticogenesis causes developmental defects, such as acceleration of RGC proliferation and mis-positioning of DL/UL neurons [51,96]. These results support that cell fate specification of RGCs can be controlled non-autonomously by environmental factors in the developing cortex [11].

Bioelectrical processes also regulate the properties of RGCs. For example, calcium waves propagate among vRGCs by extracellular ATP as cortical development proceeds, which promote vRGC proliferation [98]. The membrane potential of RGCs is progressively changing as cortical development proceeds, which affects the intracellular signaling pathways of RGCs [99]. vRGCs become more hyperpolarized as they generate successive subtypes of neurons (Fig. 3). When a membrane channel Kir2.1 was overexpressed to induce artificial hyperpolarization of the vRGC membrane, the daughter cell fate of vRGCs was altered *in vivo* [100]. This finding showed that the daughter cell fate can be determined by differences in membrane potential of RGCs, which affects differential sensitivity to the extracellular stimuli, such as Wnt signaling [100,101]. It is consistent with previous findings that late RGCs have a higher sensitivity to an external signal, demonstrating that extracellular and intracellular factors act together to regulate the competence of RGCs [6,102].

7. Feedback mechanisms controlling the speed of neurogenesis

As a factor to influence the competence and the cell fate specification of RGCs [6,11], the extracellular environment in the developing cortex changes depending on a variety of factors, including the local cell population, distribution of growth factors, and composition of the

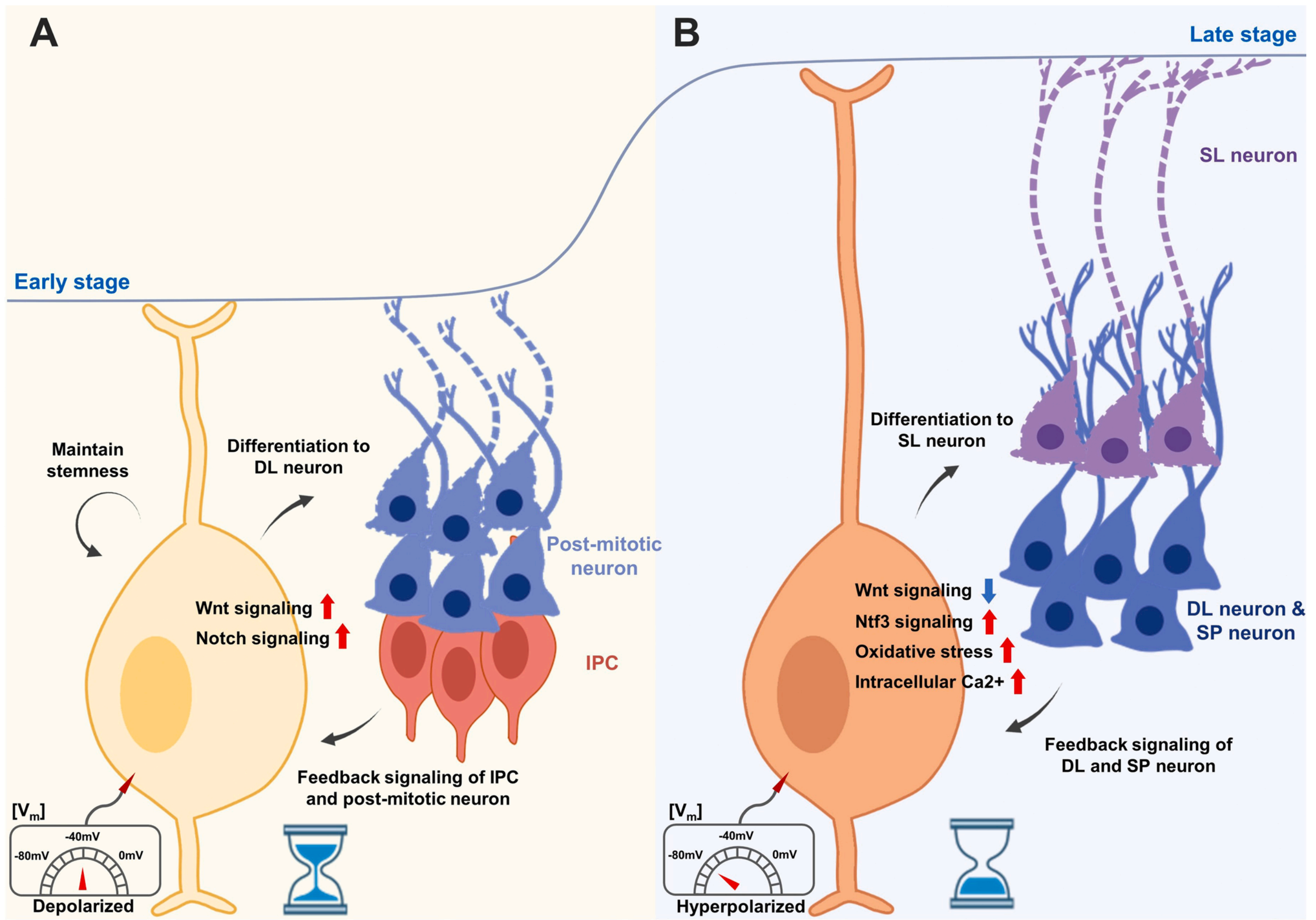

Fig. 3. Effects of the extrinsic environment and feedback signaling on the temporal competence of RGCs. The environmental factors surrounding RGCs change as cortical development proceeds. (A) Early-stage IPCs and postmitotic neurons contribute to the maintenance of the RGCs stemness by activating Notch signaling of local RGCs. The enhanced Wnt signal by the local cell population affects the temporal competence of RGCs to stimulate differentiation into DL neurons. (B) Late-stage DL neurons promote the neurogenesis of RGCs into SL neurons by producing and secreting neurotrophin-3 (NTF3) to the local environment. The calcium wave of RGCs displays a robust increase during temporal progression and sensitivity to the external environment which is also increased in late-stage RGCs. These feedback mechanisms contribute to the formation of a superficial layer at the late stage of cortical development. As development progresses, oxidative stress in the VZ gradually increases and alters the competence of the RGCs.

extracellular matrix. As cortical neurogenesis proceeds, basally-located differentiating cells, such as IPCs or newborn neurons, exert feedback regulation to apically-located RGCs by providing extrinsic paracrine signaling or cell-to-cell interactions (Fig. 3). For example, feedback signals from DL neurons are essential to switch the competence of RGCs to generate UL neurons. Genetic ablation of DL neurons prolongs the production period of DL neurons from RGCs, suggesting that the onset of UL neurons generation is controlled by the termination of DL competence promoted by signaling from postmitotic DL neurons [103]. Such feedback signaling mechanisms are mediated by secretory factors, such as neurotrophin-3 or fibroblast growth factor 9 from postmitotic neurons, which control the timing of the cell fate switch of RGCs [104,105]. In the developing neocortex, Wnt expression levels and Wnt signaling activity also decrease during corticogenesis progression [11]. Wnt-related differentiation pathways regulating the generation of CTIP2-expressing DL neurons are re-induced when late-stage RGCs are stimulated by chemical-based Wnt activation, or co-cultured with early-stage cortical dissociates, leading to the restoration of the competence of early RGCs [11,106]. Another feedback mechanism is Notch ligand expression in migrating neurons or IPCs to stimulate Notch signaling in RGCs. The stemness of RGCs is preserved during symmetric and asymmetric division by Notch signaling, which is activated locally by IPCs and post-mitotic neurons, allowing RGCs to maintain their stemness for an extended period [107,108]. In addition, NMDAR-mediated synaptic transmission from subplate neurons to multipolar neurons promotes migration and multipolar-to-bipolar transition [109]. Also, the final identity of migrating neurons can still be influenced in postmitotic stages by extrinsic signals [106,110]. These findings suggest that the identity and differentiation timing of RGCs in the local population are influenced by signals provided from previously generated daughter cells.

8. Human-specific developmental programs to regulate the competence of RGCs

Although humans have a common developmental program with other mammalian species in general, our brain exhibits distinct and unique structural features, including vastly expanded surface area and an overwhelming number of neurons relative to body size compared to other species. Recent studies with human and primate organoid models have provided insights into human-specific developmental processes [17,111,112]. In addition, advanced next generation sequencing technologies have revealed human-specific genetic features, a transcriptome, and signaling pathways during human brain development

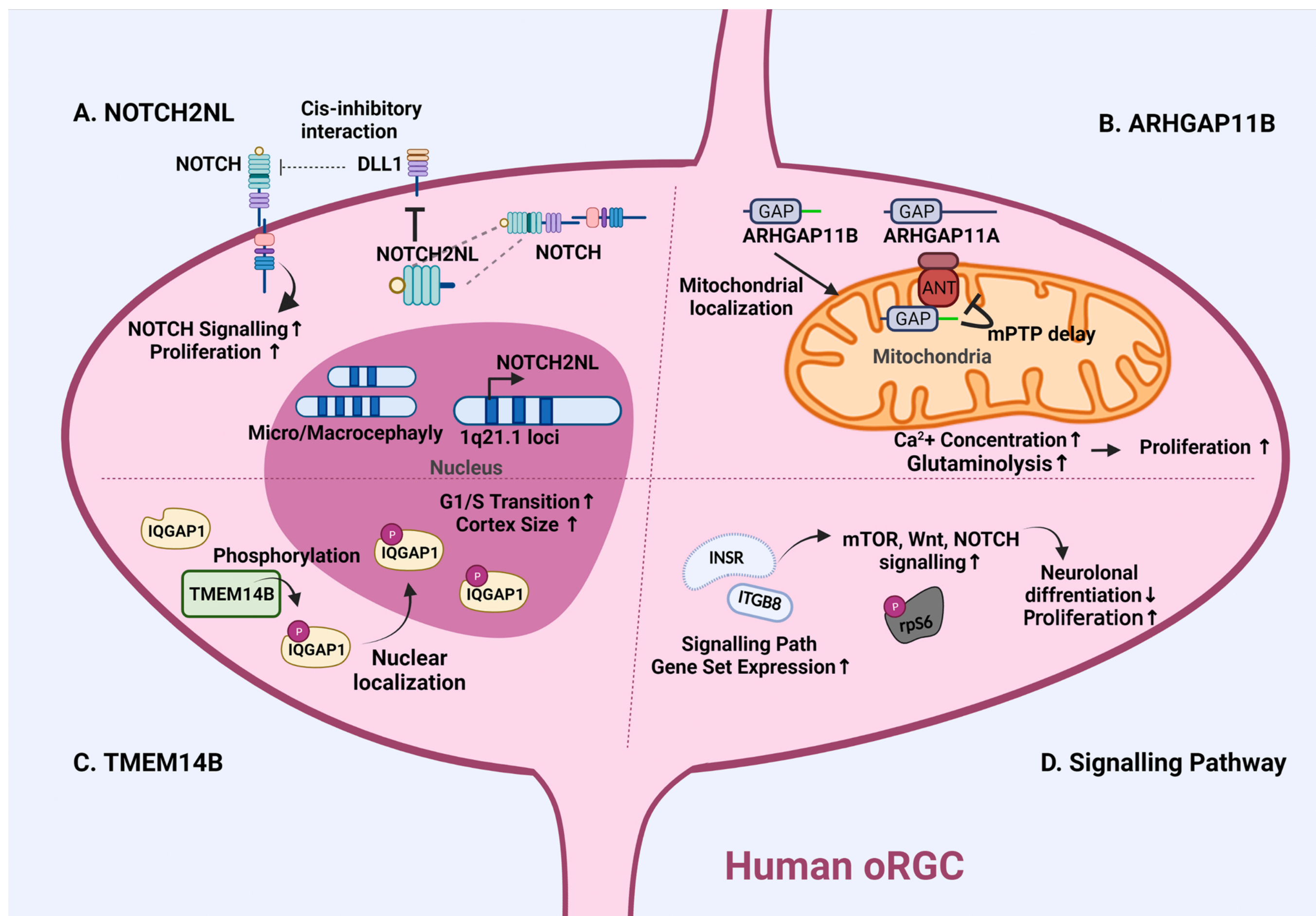

Fig. 4. Human-specific mechanisms for protracted neurogenesis and the expansion of the neocortical area in the human brain. Compared to other mammals and primates, humans have a large size and surface area of the neocortex promoted by human-specific genetic features and signaling pathways. (A) NOTCH2NL on 1q21.1 loci is a human-specific gene, enhancing the proliferation of oRGCs by increasing Notch signaling through cis-inhibition of Delta/Notch interactions. (B) ARHGAP11B is a human-specific gene containing a unique C-terminal mutated from ARHGAP11A. ARHGAP11B localizes to the mitochondria and inhibits the mPTP complex component ANT. As a result, increased glutaminolysis and calcium concentration enhance the proliferation of oRGCs. (C) TMEM14B is a primate-specific gene that phosphorylates IQGAP1. Activated IQGAP1 localizes to the nucleus and increases RGC proliferation and eventually cortex size. (D) Human oRGCs express the gene sets for multiple signaling pathways, including mTOR, WNT, and NOTCH-related genes, such as INSR and ITGB8. As a result, signaling effectors like rpS6 are activated to increase RGC proliferation.

[113,114].

Human-specific genetic features produce the unique characteristics of NPCs during corticogenesis. In particular, the 1q21.1 locus associated with neurological symptoms, including microcephaly and macrocephaly, is one of the human-specific genetic elements. Human-specific *NOTCH2* derived genes, *NOTCH2NLA*, *NOTCH2NLB*, *NOTCH2NLC*, and *NOTCH2NLR*, at the 1q21.1 locus are active in RGCs (Fig. 4A) [115]. Ectopic expression of NOTCH2NL in the mouse cortex increases oRGC and IPC proliferation, and delays mouse cortical neuron differentiation [115,116]. NOTCH2NL encodes the six epidermal growth factor (EGF) repeats, which directly interact with the NOTCH ligand Delta-like 1 (DLL1), and promotes the Notch pathway through *cis*-inhibition of Delta/Notch interactions [117]. As result, *NOTCH2NL* enhances NPC expansion by increasing NOTCH signaling.

Another human-specific gene *ARHGAP11B* is a hominin RGC-specific gene both expressed on aRGCs and oRGCs [116] (Fig. 4B). *ARHGAP11B* is duplicated from Rho guanosine triphosphatase activating protein ARHGAP11A, however, it loses its RhoGAP activity and has 47 unique C-terminal amino acids resulting from a frameshift mutation. Ectopic expression of ARHGAP11B in several model organisms results in increased basal progenitor proliferation in the OSVZ, increased production of UL neurons, and overall expansion of the cortex size with gyrification [116,118,119]. A recent study suggests that the N-terminal of ARHGAP11B targets the protein to mitochondria and interacts with the inner mitochondrial membrane protein ANT through the GAP domain (Fig. 4B). Human-specific C-terminal amino acids modulate the mitochondrial permeability transition pore mPTP and increase the calcium concentration and glutaminolysis, leading to increased proliferation of oRGCs [120]. Human-specific flexible memories and high intelligence are thought to be involved with ARHGAP11B-dependent corticogenesis [121]. In addition, human RGCs have a much longer fate plasticity period for mitochondrial remodeling, which potentially contributes to the increased self-renewal capacities of RGCs [95]. These results suggest that the unique properties of mitochondria metabolism and dynamics may confer human-specific features of neocortex expansion.

TMEM14B is a primate-specific gene that is specifically expressed in oRGCs. TMEM14B expression in mouse progenitor cells results in increased neural progenitor cells and cortical gyrification [122] (Fig. 4C). TMEM14B interacts with Ras GTPase activating-like protein IQGAP1. TMEM14B phosphorylates IQGAP1 and induces nuclear localization (Fig. 4). As a result, phosphorylation of IQGAP1 promotes G1/S transition of RGCs enabling cortical expansion. Human-specific cis-regulatory elements also contribute to the unique features of human brain development. For example, human *G protein-coupled receptor 56* (*GPR56*) has 15 promoters that enhance NPC proliferation in the human cortex [113]. Even short base-pair mutations of this noncoding region change the *GPR56* expression pattern on the cortex and selectively disrupt the Sylvian fissure bilaterally and the primary language area.

Human cortical development is regulated by a characteristic signaling pattern, including the Notch, Jak-Stat, and Shh pathway in RGCs (Fig. 4D). scRNA-seq results of the human fetal cortex and cerebral organoids showed higher expression of PI3K/AKT/mTOR pathway genes such as *INSR* and *ITGB8* specifically in oRGCs [23,112,123]. As result, phosphorylation of the mTOR effector ribosomal protein S6 (rpS6) increased, which enhances the proliferation of oRGCs. The Shh signaling pathway, which promotes proliferation of IPCs and oRGCs to induce cortical folding, is also strongly activated in human oRGCs compared to that of mice [124]. In addition, Notch signaling drives indirect neurogenesis through the expansion of IPC pools, contributing to the expansion and complexity of the human brain [125]. Human Notch signaling is also precisely regulated by human-specific genes including the aforementioned NOTCH2NL and human-specific expression of Notch target genes, such as *FOS* or *EGR1* to enhance the proliferation of RGCs [115,126].

In summary, human-specific genetic features, gene expression patterns, and signaling pathways maintain self-renewal of RGCs and protracted neurogenesis, which orchestrate the expansion and the gyrification of the human cortex.

9. Conclusion

Recent progress has suggested multiple regulatory mechanisms to accurately control the developmental competency of RGCs in a time-dependent manner. Advanced sequencing techniques are opening a new avenue for comprehensive understanding of the transcriptome, epigenome, and epitranscriptome during corticogenesis. For example, scRNA-seq [21,22,25] and ATAC-seq [34] analysis using the human fetal brain samples showed heterogeneity and pre-patterning of RGC subtypes. Moreover, scRNA-seq from the mouse cortex [6] suggested this heterogeneity is the result of orchestral regulation at multiple levels, including transcriptional and epigenetic mechanisms. Time-dependent gene expression of RGCs can be regulated by global and local epigenetic changes [6,43,48] with reorganization of cell-type-specific 3D chromatin architectures [127,128]. Posttranscriptional processes including epitranscriptomic RNA modification and protein stability also modulate the temporal competence of NPCs and developmental timing [36]. Furthermore, external factors such as mitochondrial ROS, membrane potential, and feedback signaling from postmitotic neurons regulate the temporal transition of the RGC status [96,100,103,106,109].

Beyond coordinating temporal events within an individual, the differences in the relative timing of developmental events contribute to species-specific features of brain development. Recent large-scale human fetal cortex [25,26] and brain organoid [18,112] studies have pointed out the differential temporal transcriptome in the brain of humans compared to that of other mammalian species. Likewise, understanding the human-specific regulatory mechanism of the epigenome and epitranscriptome bring out the hidden secrets that construct the complex human brain architecture and cause neurodevelopmental diseases. One example is m^6A RNA modification, which is known to be highly associated with neurodevelopmental genes and shows a distinct pattern in the human brain [62,129]. Although the human-specific contribution of m^6A on the temporal regulation of NPCs is not yet clear, advanced m^6A mapping tools with high sensitivity [130,131] and single-cell resolution [132] may provide a comprehensive understanding of the temporal-spatial dynamics of m^6A RNA modification in the developing brain.

In conclusion, our understanding of the temporal progression in NPC competence has advanced through studies of unique temporal codes in the epigenome, transcriptome, and epitranscriptome regulating multiple aspects of NPC behaviors. Future investigations to decipher these codes and manipulate them in animal models and brain organoids will provide mechanistic insights into the principles of temporal organization of the complex cytoarchitecture in the developing brain, and contribute to therapeutic treatments to overcome neurodevelopmental disorders.

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Competing interests

The authors declare no competing interests.

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