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Epigenetic regulation of neural stem cell fate during corticogenesis

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ABSTRACT

The cerebral cortex comprises over three quarters of the brain, and serves as structural basis for the sophisticated perceptual and cognitive functions. It develops from common multipotent neural stem cells (NSCs) that line the neural tube. Development of the NSCs encompasses sequential phases of progenitor expansion, neurogenesis, and gliogenesis along with the progression of developmental stages. Interestingly, NSCs steadfastly march through all of these phases and give rise to specific neural cell types in a temporally defined and highly predictable manner. Herein, we delineate the intrinsic and extrinsic factors that dictate the progression and tempo of NSC differentiation during cerebral cortex development, and how epigenetic modifications contribute to the dynamic properties of NSCs.

1. Introduction

The cerebral cortex is composed of two main populations of neurons: projection (or pyramidal) neurons which are glutamatergic and excitatory, and interneurons which are GABAergic and inhibitory. In rodents, the projection neurons originate from neural stem cells (NSCs) in the cortical ventricular zone (VZ), and in contrast, almost all interneurons originate from NSCs located outside the cortex (Gorski et al., 2002; Martin and Rubenstein, 2001). It has been well established that the cerebral cortex is organized in layers that are defined by the densities and morphologies of these neurons.

During mammalian cerebral cortex development, distinct cell types are generated successively in a strictly regulated temporal order. Neurons are first generated followed by glial cells: astrocytes and then oligodendrocytes. Strikingly, sequential shift is also observed in neurogenesis *per se* whereby cortical neurons of different layers are sequentially generated in an 'inside-first outside-last' manner (Molyneaux et al., 2007). The first neurons to exit cell cycle and migrate out of the VZ occupy the preplate, which is subsequently split into two zones by the intercalation of later neurons. The upper zone of the splitted preplate (also known as marginal zone/MZ, and later become layer I) is populated by Cajal-Retzius (CR) neurons which are derived mostly from cortical hem (Zhao et al., 2006), while the lower zone becomes subplate (SP) which mainly functions to mediate axon targeting during development (Kanold and Shatz, 2006). A layer is created between MZ and SP, giving rises to the cortical plate (CP). In the newly formed CP, neurons of the deeper layers (layer V and VI) are generated earlier than neurons of the upper layers (layer II–IV), and these upper-layer neurons migrate past the deeper-layer neurons in the CP. Thus, it appears that fate potential of both neural and neuronal progenitors are finely programmed within NSCs, such that progressive restriction or acquisition of fate potential limits or enables, respectively, their differentiation into specific cell types.

Abbreviations: GABA, gamma-aminobutyric acid; FGF, fibroblast growth factor; BMP, bone morphogenetic protein; WNT, wingless int; SHH, sonic hedgehog; RA, retinoic acid; PRC1/2, polycomb repressive complexes 1/2; EED, embryonic ectoderm development; SUZ12, suppressor of zeste 12; EZH1/2, enhancer of zeste homolog 1/2; RING1A/B, ring finger protein 1a/b; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; gp130, glycoprotein 130; BRN1/2, brain-specific homeobox/POU domain protein 1/2; SATB2, special AT-rich sequence binding protein 2; RELN, reelin; CTIP2, COUP-TF-interacting protein 2; FOXP2, forkhead box P2; SIP1, survival of motor neuron protein interacting protein 1; MTA2, metastasis-associated gene family, member 2; *Emx1/2*, empty spiracle homologues 1/2; *Pax6*, pair box domain 6; *COUP-TF1*, chicken ovalbumin upstream promoter-trascription factor 1; *Sp8*, specific protein 8; *Fezf2*, FEZ family zinc finger 2; *Gfap*, glial fibrillary acidic protein; *Dnmt1*, DNA methyltransferase 1; *S100β*, s100 calsium-binding protein beta; *Nfia*, nuclear factor I/A; *Neurog1/2*, neurogenin 1/2; *Foxg1*, forkhead box G1; *Otx1*, orthodonticle 1; *Svet1*, subventricular-expressed transcript 1; *Cux1/2*, cut-like homeobox 1; *Ntf3*, neurotrophin-3; *Sox5*, sex determining region Y-box5; *Tbr1/2*, T-box transcription factor 1/2; *Ski*, sarcoma viral oncogene homolog.

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Extensive studies in this phenomenon suggest that the regulation of NSC differentiation is orchestrated by an array of intrinsic mechanisms and extrinsic cues. In particular, the involvement of intrinsic mechanism such as epigenetic regulations in fate specification has not only enriched our knowledge, but provide another line of rationale in addition to changes in DNA sequences, in elucidating the complexity of developmental processes. Moreover, alterations of these kinds are retained through meiosis and heritable from generation to generations (Russo et al., 1996). Although this definition is commonly used at present, the dynamic flux of chromatin structure has prompted us to put forward a broader definition which includes chromatin modifications that are not necessarily perpetual, but are still able to cause changes in gene expression. Hence, Bird (2007) has proposed a revised definition of epigenetics as 'adaptations of chromosomal structures so as to register, signal or perpetuate altered activity state'.

There are three major types of epigenetic mechanisms: DNA methylation, histone modifications and non-coding RNA-mediated regulations (Bird, 2002; Goldberg et al., 2007; Wu and Sun, 2006). It is worth to mention that epigenetic modifications display dual mode of actions: exerting direct effects on gene transcription, and/or serve as platforms for the recruitment of chromatin remodeling complexes, resulting in persistent changes in chromatin state. Eventually, these changes activate or repress transcriptional programs either globally or specifically, which ultimately affect cellular phenotypes (Bird, 2002; Robertson, 2005). In this review, we introduce the key mechanisms and machineries, together with epigenetic modifications, that are responsible for the NSCs fate switch during corticogenesis.

2. Forebrain development

The cerebral cortex arises from dorsal telencephalon (pallium) of the prosencephalon (forebrain) during embryonic development. Upon closure of neural tube, the rostral portion of the neural tube (prosencephalon) differentiates into telencephalon and diencephalon. This is followed by regionalization of telencephalon *via* dorso-ventral mechanism, establishing dorsal progenitor and ventral progenitor domains. While the dorsal telencephalon develops into cerebral cortex as mentioned above, the ventral telencephalon (subpallium) becomes the basal ganglia (Götz and Sommer, 2005). Hence, dorso-ventral patterning plays pivotal roles in the early fate determination of telencephalic progenitors, and the initial specification of cortical progenitor identity.

Dorso-ventral patterning is orchestrated by the concerted actions of various morphogens such as FGF, BMP, WNT and SHH. These morphogens are secreted from distinct patterning centers, including the anterior neural ridge, the roof plate, hem, and antihem (Grove and Fukuchi-Shimogori, 2003; Rubenstein et al., 1998). For dorsal patterning, FGF8 regulates the antero-posterior (A-P) axis (Fukuchi-Shimogori and Grove, 2001; Garel et al., 2003), while BMP and WNT molecules induce medio-lateral (M-L) axis (Furuta et al., 1997; Hebert et al., 2002; Rubenstein et al., 1999). SHH and RA instruct the surrounding tissue to acquire ventral and lateral identity, respectively (Shimogori et al., 2004). By spreading in a concentration dependent manner across telencephalic neuroepithelium, such regulatory molecules act in part, in promoting differential yet combinatorial graded expression of selective transcription factors (TFs) which confer positional identities within cortical progenitors that lead to functional arealization (the specification of functional areas) in the adult cerebral cortex. Among the candidate TFs that have been shown to be directly involved in cortical arealization are *Emx1* and *Emx2* (Bishop et al., 2000; Mallamaci et al., 2000), *Pax6* (Bishop et al., 2000), *COUP-TF1* (Zhou et al., 2001), *Sp8* (Zembrzycki et al., 2007), and *Fezf2* (Hashimoto et al., 2000; Jeong et al., 2007).

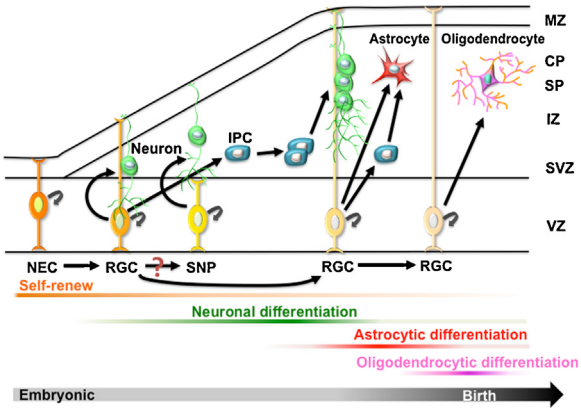

Fig. 1. Schematic representation of the diversity of progenitor populations and sequential developmental stages in the mammalian cortex. Neural development in cortex involves more than one type of progenitors which resided in respective proliferative niche and contribute to distinct cell types in mammalian central nervous system. At early embryonic stage prior to neurogenesis, NECs undergo self-renewal symmetric divisions, resulting in the expansion of neural progenitor pool. Following the onset of neurogenesis, NECs progressively switch into another types of progenitors namely, RGCs and SNPs. Later on, RGCs then give rise to another progenitor cell type, IPCs. All RGCs, SNPs and IPCs contribute to the neurogenic phase during cortical development. At late embryonic stage, gliogenesis is initiated when progenitors progressively differentiate into glial cells, such as astrocytes and then oligodendrocytes.

It is worth mentioning that these morphogens and TFs, do not work independently but cross-regulate each other in conveying defined positional identities to cortical progenitors. For instance, FGF8 of the anterior telencephalic source and WNT and BMP of the cortical hem interact antagonistically (Shimogori et al., 2004). Similar mutually repressive interaction has also been reported between *Pax6* and *Emx2* (Mallamaci and Stoykova, 2006). Intriguingly, numerous studies have indicated that the efficacy of regulatory mechanism is confined within a crucial time window, right before regional cell identity is intrinsically fixed by cell autonomous mechanisms (Backman et al., 2005; Li et al., 2005). Taken together, these facts show that the early stages of forebrain development are fundamentally governed by cross-regulation of morphogens and selective sets of TFs, in a spatially and temporally dependent manner.

3. Diversity and differentiation of NSCs and their progenitors

During embryonic development, the projection neurons arise exclusively from progenitors located within the dorsolateral wall of the telencephalon. Four main types of cortical progenitors have been identified within the developing cortex: neuroepithelial cells (NECs), radial glial cells (RGCs), intermediate progenitor cells (IPCs) and most recently, short neural precursors (SNPs). Each cell type harbors distinct proliferative features, molecular markers and laminar fate of their progeny (Götz and Huttner, 2005).

Prior to neurogenesis, the developing telencephalon is composed of a single pseudostratified layer of NECs lining the lateral ventricles, a region widely known as VZ. NECs contribute to most of the major cell types in the nervous system: neurons, astrocytes and oligodendrocytes. NECs divide symmetrically at the apical surface, producing two daughter cells (Fig. 1). Subsequent continuous self-renewal symmetric divisions then resulted in the expansion of neural progenitor pool and lead to the increased surface area of the VZ. Following the onset of neurogenesis around embryonic day (E)11, NECs progressively switch into another types of apical