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Review article

Reconstruction of ancestral brains: Exploring the evolutionary process of encephalization in amniotes

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ABSTRACT

There is huge divergence in the size and complexity of vertebrate brains. Notably, mammals and birds have bigger brains than other vertebrates, largely because these animal groups established larger dorsal telencephali. Fossil evidence suggests that this anatomical trait could have evolved independently. However, recent comparative developmental analyses demonstrate surprising commonalities in neuronal subtypes among species, although this interpretation is highly controversial. In this review, we introduce intriguing evidence regarding brain evolution collected from recent studies in paleontology and developmental biology, and we discuss possible evolutionary changes in the cortical developmental programs that led to the encephalization and structural complexity of amniote brains. New research concepts and approaches will shed light on the origin and evolutionary processes of amniote brains, particularly the mammalian cerebral cortex.

Contents

1. Introduction

Extant animals exhibit a huge diversity in body size in accordance with unique physiological traits adapted to the environment. For example, in mammals, a type of small shrew has only 2 g in adult body weight, whereas blue whales weigh over 170 tons and are the largest animals ever to have lived on earth. Despite the great variation in adult body size, all species arise from a tiny fertilized egg at the beginning of development. Thus, size control is primarily due to the regulation of cell proliferation, differentiation and cell death during organogenesis, which has been an attractive issue in developmental biology for a long time, although the underlying cellular and molecular mechanisms have not been clarified.

In addition to the body size, the size of the brain is also divergent in animals. Generally, brain size increases with body size. The average brain weight is approximately 0.5 g in mice, 1400 g in humans, and 7000 g in whales (see also Fig. 1 of Borrell and Calegari, 2014). Plotting brain size against body size reveals a positive

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correlations between the two; brain mass increases allometrically rather than isometrically (Jerison, 1973). This "brain–body scaling" has been repetitively examined with various species in different vertebrate groups, which provides taxon-specific rules for the scaling (Hofman, 1982; Hopson, 1977). Particularly, the actual amount of brain mass exceeding the expected brain–body ratios provides an "encephalization quotients (EQ)", which is a simple but relevant criterion for evaluating comparative brain–body scaling within taxon (Jerison, 1985). In amniotes (terrestrial animals in which embryogenesis proceeds in amniotic membranes), mammals and birds have relatively larger brains against body mass when compared with other animal groups such as reptiles (Jerison, 1973). This suggests that genetic (or epigenetic) mechanisms underlie the taxon-specific brain scaling, which could be resulted from significant changes in developmental programs during evolution.

Brain structures are also highly divergent among animal groups. Particularly in amniotes, the dorsal part of the telencephalon displays distinct anatomical architectures (Aboitiz, 2011; Molnar et al., 2006; Nieuwenhuys, 1994; Nomura et al., 2013b; Puelles, 2001; Striedter, 2005). The mammalian neocortex established conspicuous anatomical hallmarks with tangential expansion of surface area and a six-layered lamination. In contrast, the dorsal part of the avian telencephalon forms nuclear compartments or slabs rather than multi-layered sheet structures. Furthermore, the lateral part of the reptilian and avian telencephalon protrudes inward to form bulge structures, called the dorsal ventricular ridge (DVR) (also called nidopallium in birds), which significantly contribute to the increase of brain size in non-mammalian amniotes. However, the developmental and evolutionary origins of the DVR have been debated extensively.

In this review we discuss how different animal groups have acquired bigger and more complex brains during evolution. First, we will introduce paleontological data on brain mass in ancestral amniotes, particularly focused on mammalian and avian lineages. Fossil evidence has provided valuable information on the ancient forms of brains and the process of encephalization. Next, we will summarize the findings provided by comparative developmental analyses of amniote cortex/pallium and regulatory mechanisms of cortical neural stem/progenitor cell behaviors. Changes in the regulation of neural stem/progenitor cells play a key role in the control of brain scaling. We also introduce recent comparative studies on layer-specific neuronal subtypes, and discuss critical points on interpretation of cellular homology and convergent evolution. Finally, we will propose a possible scenario of the evolutionary steps of encephalization in distinct amniote lineages, based on currently available information. Combining classic and modern biology and unifying interdisciplinary approaches including paleontology, molecular phylogeny and developmental biology, this study provides valuable insights into the origin and evolution of the brain, in particular, the cerebral cortex.

2. Fossil evidence of ancestral brains

Paleontological evidence has demonstrated that all extant mammals are derived from an ancient synapsid lineage, which is thought to have evolved from ancestral amniotes in the Carboniferous, approximately 300 million years ago (Mya) (Carroll, 1988; Falcon-Lang et al., 2007; Ruta et al., 2013). All modern reptiles, (here, "reptiles" include non-avian reptiles, such as lizards, turtles and crocodiles) and birds have also evolved from sauropsid (diapsid), another amniote lineage (Fig. 1). Unfortunately, fossilized brains of ancient amniotes have not been identified; we therefore cannot address the brain architectures of ancestral amniotes directly. However, endocast analysis of fossil brain cases provides valuable information on the size and outer morphology of brains in extinct animals. Recently, the X-ray scanning technology has been much advanced, with which we can collect digital endocast data without destroying the specimen. Comprehensive endocast analyses of ancestral mammalian lineages suggest that the brain volumes of primitive mammals were much smaller than that of modern mammals. For example, *Cynodontia*, a pre-mammalian lineage that lived in the late Permian (approximately 260 Mya), possessed a small olfactory bulb and a narrow cerebrum. EQs of *Cynodontia* were estimated from 0.16 to 0.23 compared to those of modern mammals (Rowe et al., 2011). Detailed 3D-tomographic analyses of fossil cavities suggest that enhanced olfactory and tactile senses contributed to the massive elaboration of the olfactory and neocortex during mammalian evolution. (Rowe et al., 2011).

Endocast analyses also show the evolutionary steps of encephalization in avian lineages. Birds have evolved from a group of ancestral archosaurs that includes extinct dinosaurs (Fig. 1). Recent comparative tomographic analyses of brain cavities indicate that *Archaeopteryx*, an ancestral species close to avian lineages lived at Jurassic (approximately 150 Mya), had a smaller brain volume compared to modern birds (Alonso et al., 2004; Balanoff et al., 2013). Because extinct dinosaurs such as *Tyrannosaurus rex* (Cretaceous period, approximately 67 Mya) or *Oviraptor* (approximately 75 Mya) also had smaller brain volumes, these data suggest that encephalization occurred rapidly in the avian lineage (Balanoff et al., 2013; Witmer and Ridgely, 2009). Although a classic study estimated EQ values extinct archosaurs including dinosaurs (Hopson, 1977), some data must be revised according to recent endocast analyses. Interestingly, *Pterosaurs*, flying reptiles that lived in the late Triassic to Cretaceous (220–65 Mya), had relatively larger brains with an enlarged forebrain and cerebellum compared to similar sized other reptiles, suggesting that the adaptation to powered flight contributed to the convergent evolution of encephalization in different reptilian lineages (Witmer et al., 2003).

It is believed that the most primitive amniotes with terrestrial life styles evolved during the early Carboniferous period (Carroll, 1988; Falcon-Lang et al., 2007; Laurin, 2004; Ruta et al., 2003). Molecular phylogenetic analyses suggest that all extant amniotes have evolved from a common origin, although it is still uncertain that which species is corresponding to the "stem" amniotes. The primitive amniotes are referred to as reptiliomorphs, which include several unique species such as Solenodonsaurs (Laurin, 2004). Fossil records suggest that these animals had tiny brains with small olfactory bulb and narrower cortical region, similar to the ancestral synapsids (Ulinski, 1983). Thus, the increase in brain volume occurred independently in mammalian and avian lineages.

Although endocast analyses provide valuable information on the size and outer morphology of brains, we could not ascertain the internal structures of ancient brains, particularly the cerebrum. What was the extent of neurons formed in their cerebrum? Were there any signs of laminar structures in the primitive cortex? Currently, a possible approach to solve these challenging questions is comparative analyses of extant amniote telencephali. If particular brain characteristics are shared in all extant amniotes, these traits might be derived from common ancestors, with which we could partially reconstuct ancient cortical architectures. Comparison of cortical ontogeny in various species provides significant insights into changes in the developmental programs that contributed to diversification of cortical morphology. Furthermore, creation of phenocopies by manipulating embryogenesis provides experimental evidence of the genetic mechanism responsible for making species-specific cortical structures.

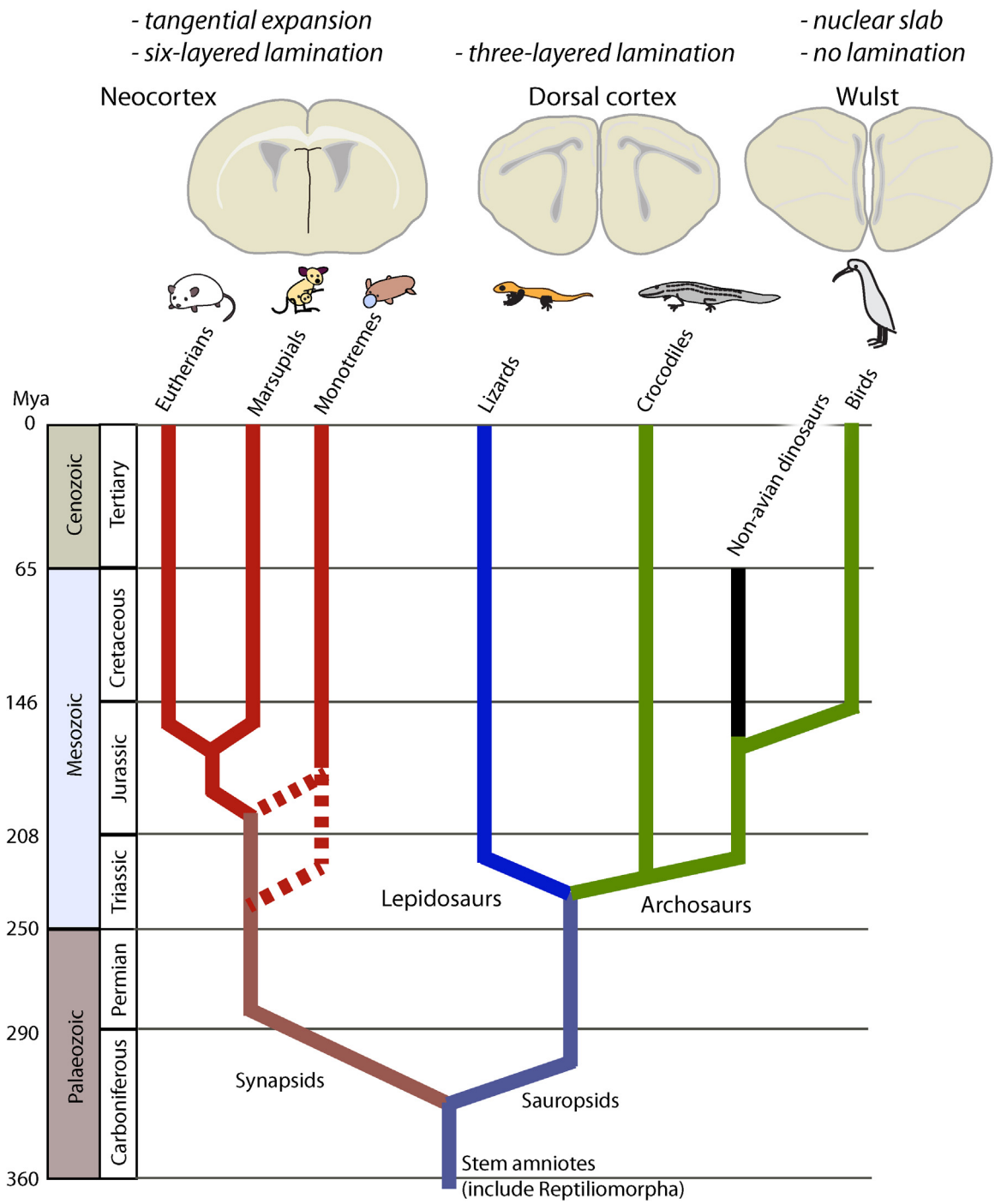

Fig. 1. Phylogenic tree of amniotes. The first amniotes appeared approximately 350 million years ago (Mya), then this animal group split into two lineages, synapsids and sauropsids. Synapsids lead to mammals, whereas sauroposids lead to reptiles and birds. The last common ancestor(s) of extant mammals could have lived at around the Jurassic or Triassic. Because all extant mammals share the neocortical structures with tangential surface expansion and six-layered lamination, the last common ancestor(s) acquired these morphological traits. The sauropsid lineage split into lepidosaurs and archosaurs: the former led to extant lizards/geckos/snakes, whereas the latter further diverged into several groups including crocodiles and extinct dinosaurs. During the Jurassic, the first avian lineages diverged from dinosaurs. Because fossil evidence suggests that primitive amniotes had small brains compared to body weights, encephalization could have occurred in mammalian and bird lineages independently. The illustration was based on Warren et al. (2008) and O'Leary et al. (2013) with slight modification.

3. Progenitor dynamics of the amniote telencephalon

Extant amniotes have homologous regions in their dorsal part of the telencephalon, namely the pallium. The pallium is subdivided into four regions including the medial, dorsal, lateral and ventral pallium. In mammals, the dorsal and lateral pallium increased its their size and the neocortex was elaborated with a six-layered laminar structure (Nieuwenhuys, 1994; Puelles et al., 2000). These cortical characteristics are unique to three mammalian groups, including eutheria (placental mammals), marsupials and monotremes, which suggests that the neocortex was acquired in the common ancestors of modern mammalian groups (Nieuwenhuys, 1994; Puzzolo and Mallamaci, 2010). In contrast, the dorsal pallium of reptiles and birds give rise to distinct anatomical structures. In reptiles such as lizards and turtles, the dorsal pallium becomes a small cortex between the medial and lateral

pallial derivatives, with a three-layered laminar structure (Ulinski, 1990). In the lateral part of the reptilian DVR, a conspicuous neuronal bulge-like structure is protruded into the ventricle (Ulinski, 1990). In birds, the dorsal pallium gives rise to a thick neuronal mass called the Wulst, in which no tangential laminar structures are formed (Medina and Reiner, 2000). Additionally, the DVR dramatically increases in size and give rises to the major telencephalic component.

Expansion of the neocortical surface area is primarily due to an increase of the progenitor population during the embryonic period. Based on computer simulation analyses, Fujita suggested that the growth rate of matrix cells (neural stem/progenitor cells) during the neurogenic period is a key parameter for determining the brain size: larger brains, such as the human cortex are generated by a slower growth rate with smaller decay of growth retardation, compared to those of smaller brains such as mouse cortex (Fujita, 1990). Consistently, several lines of evidence revealed inter-species differences in the rate of progenitor proliferation and neuronal differentiation and in the length of the cortical neurogenic period (Caviness et al., 1995; Fujita, 1962; Kornack and Rakic, 1998; Takahashi et al., 1996). In the developing mouse cortex, neurogenesis starts at embryonic day 11 (E11) and is completed at around embryonic day 17 (E17). Total cell cycle length in neural stem/progenitor cells is increased from 8 to 19 h by the progression of embryogenesis, primarily due to the increase of the G1- and S-phases of the cell cycle (Arai et al., 2011; Takahashi et al., 1996). Interestingly, total cell cycle length in the developing monkey cortex is 5 times longer than that in mouse (Kornack and Rakic, 1998). However, the prolonged neurogenic period in monkey corticogenesis results in increased cell numbers, which contributes to an enormous expansion of the neocortex (Kornack and Rakic, 1998).

A few pioneering studies reported the neurogenic periods and cell cycle lengths in the developing brains of other amniotes. ^{3}H-thymidine labeling demonstrated that in the developing chicken telencephalon, massive neurogenesis occurred between embryonic days 4–9, and terminated at around day 10 (Tsai et al., 1981). In the dorsal cortex of developing Chinese softshell turtles (*Pelodiscus sinensis*), neurogenesis occurs between the stages 11–17 (Xi et al., 2008). Limited periods of cortical neurogenesis were also reported in other species of turtles (*Emys orbicularis*), lizards (*Lacerta trilineata*), and geckos (*Parodedura pictus*) (Goffinet et al., 1986; Nomura et al., 2013a). Cumulative BrdU labeling indicated that in the developing quail telencephalon, cell cycle duration increases from 11 h at stage 24 to 22 h at stage 28 (Charvet and Striedter, 2008). S-phase duration also increases from 3.6 to 8 h, as observed in the developing mouse cortex (Arai et al., 2011).

These lines of evidence provide significant insights into the evolution of cortical neurogenic programs. First, the cortical neurogenic period and the total embryonic period vary among amniote species, which suggests that these periods might be regulated by distinct developmental programs. In reptiles and birds, cortical/pallial neurogenesis terminates much earlier than the end of embryogenesis, suggesting that this trait could be derived from common ancestral characteristics in non-mammalian lineages. Second, the total duration of neurogenesis and cell cycle length are differentially regulated, and the shortening and/or lengthening of these two parameters had been occurred independently in distinct amniote lineages. Particularly in placental mammals, these parameters change dynamically in accordance with gestational period (Charvet et al., 2011). This is also the case in birds, in which different avian species such as parakeets and quail exhibit different cell cycle lengths and neurogenic periods (Charvet and Striedter, 2008).

Although the cell cycle length has not been extensively analyzed in reptiles, we recently reported that total cell cycle duration in the developing gecko cortex is approximately 50 h at 18 days post oviposition (Nomura et al., 2013a), which is much longer than that in mouse embryos. In geckoes, cortical neurogenesis terminates by the middle stages of embryogenesis, similar to other reptilian species (Goffinet et al., 1986; Nomura et al., 2013a; Xi et al., 2008). These results suggest that the total numbers of rounds of cell division during cortical neurogenic period is limited in geckos, although cell cycle parameters in early stages of corticogenesis have yet to be elucidated. Further analyses of cell cycle length in reptiles are required to ascertain whether the similar proliferation dynamics in mammals and birds, such as the increase of cell cycle length during the progression of corticogenesis, are derived from common origin(s), or are provided by convergent evolution. The role of cell cycle regulation in cortical expansion is further discussed by Borrell and Calegari (2014).

4. Shape and polarity of neural stem cells: comparative views

Polarized morphology is a characteristic of neural stem/progenitors in the developing vertebrate nervous system. A “typical” cortical neural stem/progenitors in the ventricular zone exhibit bipolar morphology with apical–basal polarity, in which apical membrane faces ventricular surface, whereas a long basal process extends toward the basal lamina (Fietz and Huttner, 2011; Gotz and Huttner, 2005). This unique morphology of neural stem/progenitors is prerequisite for maintaining stem/progenitor compartment, by which proliferation and differentiation are tightly controlled (Kosodo et al., 2004; Okamoto et al., 2013). In addition, recent studies clarified that several types of progenitors can be classified in the developing mammalian cortex, based on their morphology and molecular characteristics (Fietz and Huttner, 2011; Stancik et al., 2010). Particularly, neural stem/progenitors in the outer subventricular zone of the developing primate and carnivore cortex are intriguing, which are distinguished by the lack of apical surface contact with ventricular surface, a long basal process, and self-renewal capacity together with the expression of neural stemcell makers (Betizeau et al., 2013; Fietz et al., 2010; Hansen et al., 2010; Reillo et al., 2011).

Although detailed characterization of neural stem/progenitors in non-mammalian amniote pallium has not been performed, a few pioneering works reported that a bipolar stem/progenitors exist in the developing reptilian and avian pallium (Striedter and Beydler, 1997; Weissman et al., 2003). We have previously shown that a unique feature of avian neural stem/progenitors with curled morphology of basal process in the pallial neuronal layer (Nomura et al., 2008). Similar morphology of neural stem/progenitors is also evident in the developing gecko pallium (Fig. 2), suggesting that curved extension of basal process is common phenotype among the developing non-mammalian amniotes. Although functional relevance of basal fiber projections and cortical evolution is not well understood, our previous study suggested that differences in basal fiber morphology are linked to the polarity of mature neurons (Nomura et al., 2008). Interestingly, this unique projection pattern of basal process is obvious in the reptilian/avian dorsal pallium, but not in the septum and DVR regions (Striedter and Beydler, 1997; our unpublished data), implicating that spatially distinct regulatory mechanisms influence the polarized morphology of neural stem/progenitors.

A subtype of progenitors in the subventricular zone of mammalian cortex exhibits a multi-polar shape and called as basal progenitors (Miyata et al., 2004; Noctor et al., 2008; Pontious et al., 2008; Tabata and Nakajima, 2003). The majority of this progenitor subtype behaves as fate-committed intermediate progenitors and contributes to the expansion of neuron numbers in the mammalian cortex. The massive number of basal progenitors (or basal mitotic

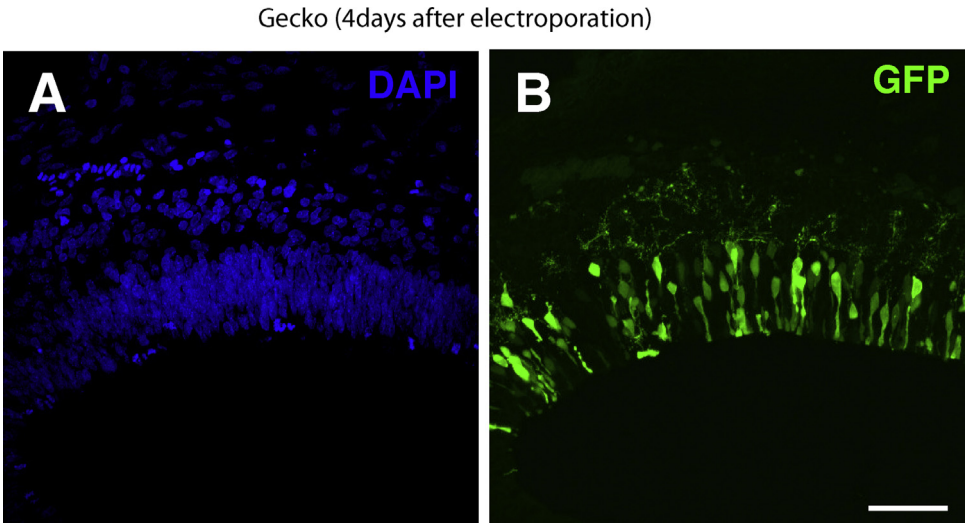

Fig. 2. Morphology of neural stem/progenitors in the developing gecko cortex. GFP-expression vector was electroporated into the dorsal pallium of developing gecko (*Paroedura pictus*, d.p.o. 14). An embryo was collected 4 days after electroporation. (The sample is same embryo in Nomura et al., 2013a). This figure shows Z-stack images of a section (14 μm thickness) captured with a confocal microscopy. Note that basal processes of GFP-positive neuroepithelial cells project toward the pial surface in curled manner. Scale bar: 50 μm.

cells) has been confirmed only in the developing pallium of placental mammals and birds, but not in marsupials, geckos, turtles, and alligators (Charvet et al., 2009; Cheung et al., 2007; Nomura et al., 2013a; Puzzolo and Mallamaci, 2010), suggesting that basal progenitors have evolved independently during amniote evolution (Charvet et al., 2009).

5. Regulation of neural stem/progenitor cell dynamics

Recent studies clarified the molecular mechanisms that underlie the dynamics of neural stem/progenitor cells in mammalian cortical development (Gotz and Huttner, 2005; Kriegstein et al., 2006). Several extrinsic and intrinsic factors of neural stem/progenitor cells tightly control cell cycle length and the timing of cell division. In particular, secreted growth factors such as fibroblast growth factors (FGFs), Sonic hedgehog (Shh) and Wnts have strong impacts on neural stem/progenitor cell proliferation in the developing cortex. These growth factors are released from the specific tissue-signaling centers and/or are broadly distributed in the cortical ventricular zone. Experimental depletion or overexpression of these growth factors in mice altered cell division frequency, which caused a dramatic reduction or enlargement of neocortical structures (Chenn and Walsh, 2002; Komada et al., 2008; Paek et al., 2011; Rash et al., 2013; Sahara and O'Leary, 2009). These lines of evidence suggest that changes in the expression timing, duration or amplitude of these growth factors during cortical neurogenesis contributed to morphological diversification of pallial structures. Aboitiz suggested that morphogenic signals that facilitate the development of the dorsal pallium were amplified in ancestral mammals, which provided radial expansion of the neocortex (Aboitiz, 2011). In contrast, enhanced morphogenic signals from the anti-hem region (the border between the pallium and subpallium) induced massive growth of the ventral pallium in reptiles/birds, which gave rise to the formation of the DVR in these animal groups (Aboitiz, 2011). This intriguing theory explains the mechanisms underlying differential morphology of amniote brains, although quantitative analyses of growth factor expression and signaling amplitudes across species are required to prove this theory.

Signals mediated by cell-cell interaction also controls cellular dynamics during cortical development. Various types of cell membrane-associated molecules, such as Notch receptors, Eph receptors and ephrin ligands, cadherin and integrin family molecules play pivotal roles in progenitor proliferation, neuronal differentiation and apoptosis during mammalian corticogenesis (Marthiens et al., 2010; North et al., 2013; Pierfelice et al., 2008). Experimental manipulation of these signaling molecules significantly altered the progenitor dynamics and morphology of developing mammalian neocortex (Depaepe et al., 2005; Imayoshi et al., 2010; Kadowaki et al., 2007). In particular, Notch signaling is an evolutionary conserved pathway in fate determination of neural stem/progenitor cells. Upon activation of Notch receptors via multiple ligands, the cleaved Notch intracellular domain (NICD) translocates into the nucleus and associates with transcription factors such as Rbpj-k (CBF-1) and Mastermind-like 1 (MAML) to regulate various downstream target genes (Pierfelice et al., 2008). We have recently identified differential activation levels of Notch signaling in cortical neural stem/progenitor cells that correlate with the proportion of neuronal outputs among various amniote species (Nomura et al., 2013a). Notably, gecko cortical progenitors exhibited high level of Notch activity in accordance with their lower rate of neuronal differentiation. Blocking of Notch signaling by using dominant-negative Rbpj construct enhanced neuronal differentiation in the gecko cortex, suggesting that differential activation of Notch signaling underlies species-specific neuronal outputs.

Recent studies have shown that the expression of Notch downstream target genes oscillates in mouse cortical neural stem/progenitor cells (Kageyama et al., 2008). Live cell imaging with reporter system revealed that the expression of bHLH factors such as Hes1, Neurogenin1 and Ascl1 oscillates with approximately 2 h intervals (Shimojo et al., 2008). The oscillatory expression of these genes is critical for maintaining neural stem/progenitor states, whereas stable down- or up-regulation of these genes triggers neuronal differentiation. Notch signaling plays a pivotal role in the oscillation of these factors because pharmacological blocking of Notch signaling induces sustained expression of Ascl1 and neuronal differentiation in mouse neural stem cells (Imayoshi et al., 2013). Dynamic expression of Notch signaling pathway genes in other mammalian and non-mammalian species has yet to be elucidated, which would provide insights into the evolutionary conservation and diversification of cell fate determination machinery.

Several studies have clarified that Wnt or Notch signaling pathways directly regulates the expression of Cyclin and/or Cdk family genes, which are essential gate controllers for cell cycle progression (Cohen et al., 2010; Das et al., 2010; Davidson and Niehrs, 2010). Overexpression of Cdk4 and Cyclin D1 in the developing mouse cortex increased the number of progenitors and resulted in a dramatic expansion of cortical surface area (Lange et al., 2009; Nonaka-Kinoshita et al., 2013), suggesting that the regulation of cell cycles via these molecules played a significant role in the tangential expansion of the neocortex in mammals during evolution. Interestingly, cyclinD2 mRNA is transported to the basal process of neural stem/progenitor cells in the developing mouse and human cortex (Tsunekawa et al., 2012). Asymmetric inheritance of basal process to daughter neural stem/progenitor cells after cell division results in unequal distribution of cyclinD2, by which daughter cell fates might be determined. Basal localization of cyclinD2 mRNA in neural stem/progenitor cells has not been detected in the developing chicken pallium (Tsunekawa and Osumi, 2012), suggesting that specific regulatory mechanisms for transporting cell determinants have been established during mammalian cortical evolution.

6. Conservation and diversification of pallial neuron subtypes among amniotes

Mature vertebrate brains contain numerous types of neurons that are distinguished by morphological and functional characteristics. Cortical neurons are largely classified into two groups, glutematergic excitatory neurons and GABAergic inhibitory neurons. In the developing telencephalon, the glutamatergic neurons emerge from the pallial region, whereas the GABAergic neurons are born in the subpallium (the lateral, medial and caudal ganglionic eminences and the preoptic area) and dorsally migrate into the pallium (Marin and Rubenstein, 2001; Wilson and Rubenstein, 2000). The genetic programs govern the production and migration of these two neuronal populations is evolutionarily conserved among amniotes (Cobos et al., 2001; Fernandez et al., 1998; Metin et al., 2007; Puelles et al., 2000; Tanaka and Nakajima, 2012; Tanaka et al., 2011; Tuorto et al., 2003). However, the distribution of glutamatergic neuron subtypes in the pallium varies among mammals, reptiles and birds, which makes it difficult to address homologous neuronal components across species.

The classification of glutamatergic neuron subtypes has been well established in the mammalian neocortex, in which laminar specific neurons can be distinguished by their specific characteristics, including morphology, descending and ascending pathways, and specific gene expression (Molyneaux et al., 2007; Nieuwenhuys, 1994). During mammalian corticogenesis, these distinct neuronal subtypes are sequentially born from cortical neural stem/progenitor cells and migrate toward the pial surface. At the beginning of corticogenesis, the earliest born neurons spread out at the surface of the telencephalon and form primitive neuron layer called the preplate. Subsequently, other types of neurons migrate into the preplate and form a distinctive neuronal layer called the cortical plate. Consequently, the preplate split into the marginal zone (layer I) and the subplate, which are the superficial and deepest layers of the cortex, respectively. The early-born cortical plate neurons give rise to deep cortical layers, which are marked by the expression of Tbr1, FoxP2 (layer VI), er81, Fezf2 and Ctip2 (layer V). However, the later-born cortical plate neurons migrate to the pial surface and pass through the territory of the early-born neurons. These neurons constitute the superficial cortical layers and are distinguished by the expression of Cux2, Brn1 and Brn2 (layer II/III). Functional analyses by using mouse molecular genetics demonstrated that these transcription factors play essential roles in the specification of layer specific neurons in cortical development (Leone et al., 2008).

Recently, expression patterns of these laminar-specific genes have been examined in non-mammalian telencephali (Dugas-Ford et al., 2012; Jarvis et al., 2005; Nomura et al., 2008, 2013a; Suzuki et al., 2012). Layer-specific genes are expressed in discrete pallial regions of the developing and adult avian pallium, which coincide with morphologically discernible tissue compartments (Fig. 3). Intriguingly, gene expression is partially associated with specific neuronal characteristics across species. For example, Rorβ is expressed in thalamo-recipient neurons (layer IV in mammals and Field L, entopallium and IHA in birds), whereas er81 is expressed in descending neurons (layer V in mammals and arcopallium in birds) (Dugas-Ford et al., 2012; Nomura et al., 2008) (Fig. 3). Furthermore, birthdate analyses indicated that the temporal order of neuron subtype production is conserved between mouse and chicken (Suzuki et al., 2012).

We have recently shown that the expression of CTIP2 and SATB2 proteins are also present in the dorsal pallium of Madagascar ground gecko and Chinese softshell turtle, and these neuronal subtypes are born in a chronological order during gecko corticogenesis (Nomura et al., 2013a). Interestingly, CTIP2 and SATB2-positive neurons are clustered medio-laterally in the gecko dorsal pallium, as in the case of other neuronal subtypes in the developing red-ear turtles (Dugas-Ford et al., 2012; Nomura et al., 2013a) (Fig. 3). These lines of evidence indicate that temporally regulated systems for neuron subtype specification are conserved among various amniote lineages, which might be derived from their common ancestors. Furthermore, the temporally controlled neuron production system is spatially constrained in the reptilian and avian pallium, by which discrete compartments with specific neuronal subtypes are established (Medina and Reiner, 2000; Nomura et al., 2009; Suzuki et al., 2012).

Combining ontogenic and phylogenic views of cortical development, in the late 70s, Marin-Padilla hypothesized that the mammalian neocortex has dual cell population origins, from which preplate (primordial plexiform layer) neurons and cortical plate neurons have evolutionary distinct derivatives: the former are derived from ancestral neuron subtypes that originated from amphibian or reptilian cortical neurons, whereas the latter evolved specifically in mammalian lineages as an evolutionary novelty (Marin-Padilla, 1978). However, accumulating data revealed that the reptilian cortex does not solely consist of preplate-like neurons, but comprises a variety of neuronal subtypes distinguished by multiple excitatory neuron markers (Dugas-Ford et al., 2012; Nomura et al., 2013a). Our cell-tracing experiments also demonstrated that in the developing quail telencephalon, early-born neurons tangentially migrate on the pallium and constitute the primitive neuronal layer, which are followed by later-born neurons that radially migrate toward the pial surface (Nomura et al., 2008). Thus, it is possible that two types of pallial neurons (the preplate and cortical plate neurons) commonly develop in different amniote groups.

Although the dual cortex theory underestimated the neuronal diversity of the non-mammalian cortex, possibly because it was substantially influenced by the recapitulation theory (ontogeny recapitulates phylogeny), recent findings revealed that the mammalian neocortex consists of a heterogeneous neuronal population with multiple developmental origins. For example, Cajal-Retzius cells, a major neuronal subtype in cortical layer I, originate from the outside of the neocortex and tangentially migrate into the neocortical region (Takiguchi-Hayashi et al., 2004; Yoshida et al., 2006). Furthermore, it is noteworthy that cortical plate neurons with a unipolar migratory shape are unique in the mammalian cortex because the majority of migrating neurons in non-mammalian pallium exhibit a multipolar shape (Nomura et al., 2008). Indeed,

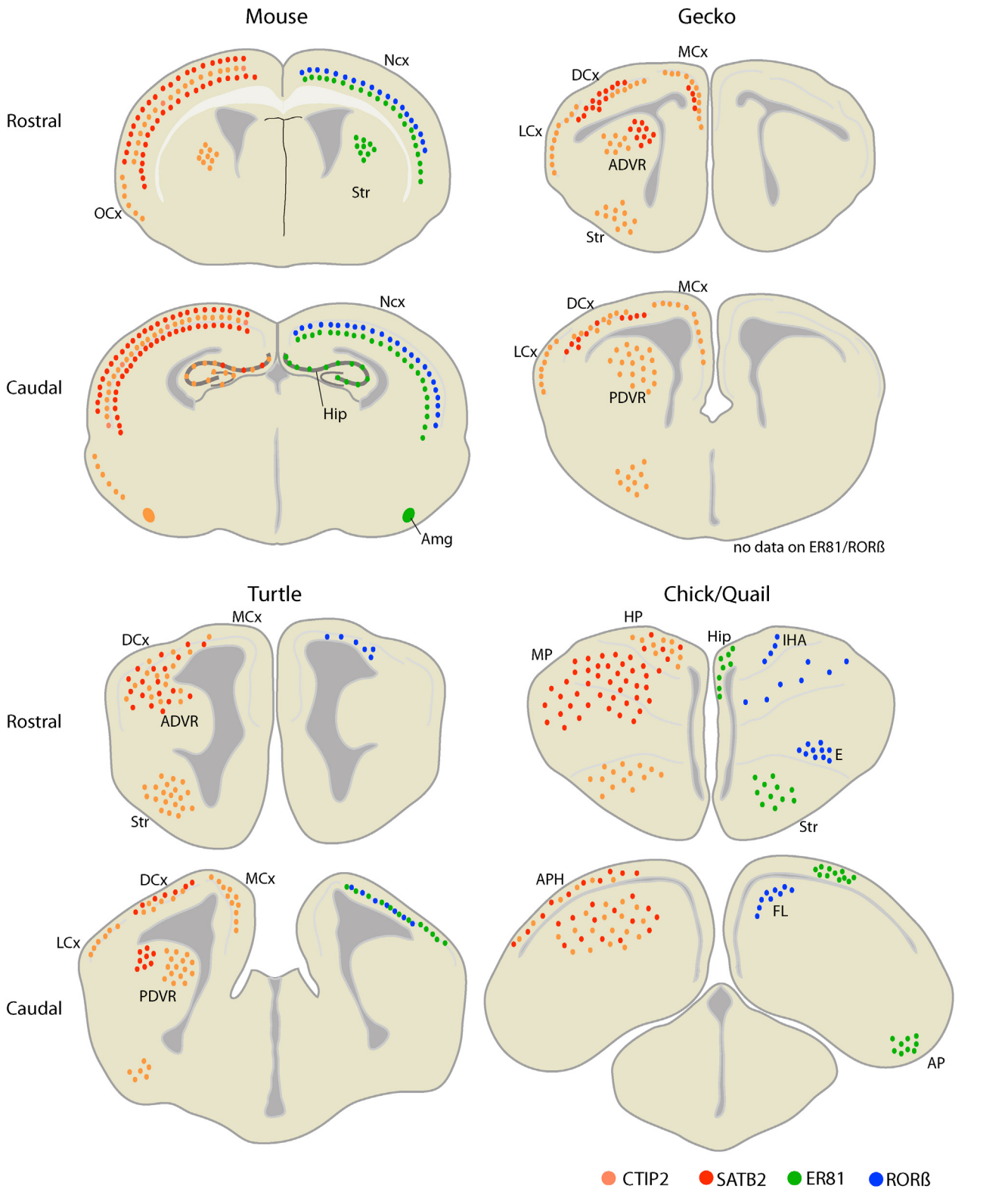

Fig. 3. Distribution of distinct neuron subtypes in the amniote telencephalon. The illustration summarizes the distribution of neuron subtypes in mouse, gecko, turtle and chick/quails telencephali. Orange, red, green and blue dots indicate CTIP2, SATB2, ER81 and RORβ-positive neurons, respectively. Upper panels show the rostral parts, and lower panels show the caudal parts of the telencephalon. Note that these transcription factor-positive neurons are distributed in various regions of the telencephalon. The data are based on previous reports by Nomura et al. (2008, 2013a,b), Dugas-Ford et al. (2012), Suzuki et al. (2012), Belgard et al. (2013) and Jarvis et al. (2013). The distribution of neuron subtypes in turtles summarizes the combined data of two species: red-eared turtle (*Trachemys scripta*, Dugas-Ford et al., 2012) and Chinese softshell turtle (*Pelodiscus sinensis*, Nomura et al., 2013a,b). The distribution of ER81 and RORβ-positive neurons in the gecko telencephalon has not been reported. The data represent later embryonic to postnatal/adult stages at which neuronal differentiation and migration completed in each species (mouse: P4, gecko: d.p.o. 44, chinese softshell turtle: st25, red-eared turtle: adult, chick/quail: E16 or P0). Ncx: neocortex, OCx: olfactory cortex, Hip: hippocampus, Amg: amygdala, MCx: medial cortex, DCx: dorsal cortex, LCx: lateral cortex, ADVR: anterior dorsal ventricular ridge, PDVR: posterior dorsal ventricular ridge, HP: hyperpallium (described as Wulst in the text), MP: mesopalliun, APH: area parahippocampalis, FL: field L, E: entopallium, IHA: interstitial part of the hyperpallium apicale.

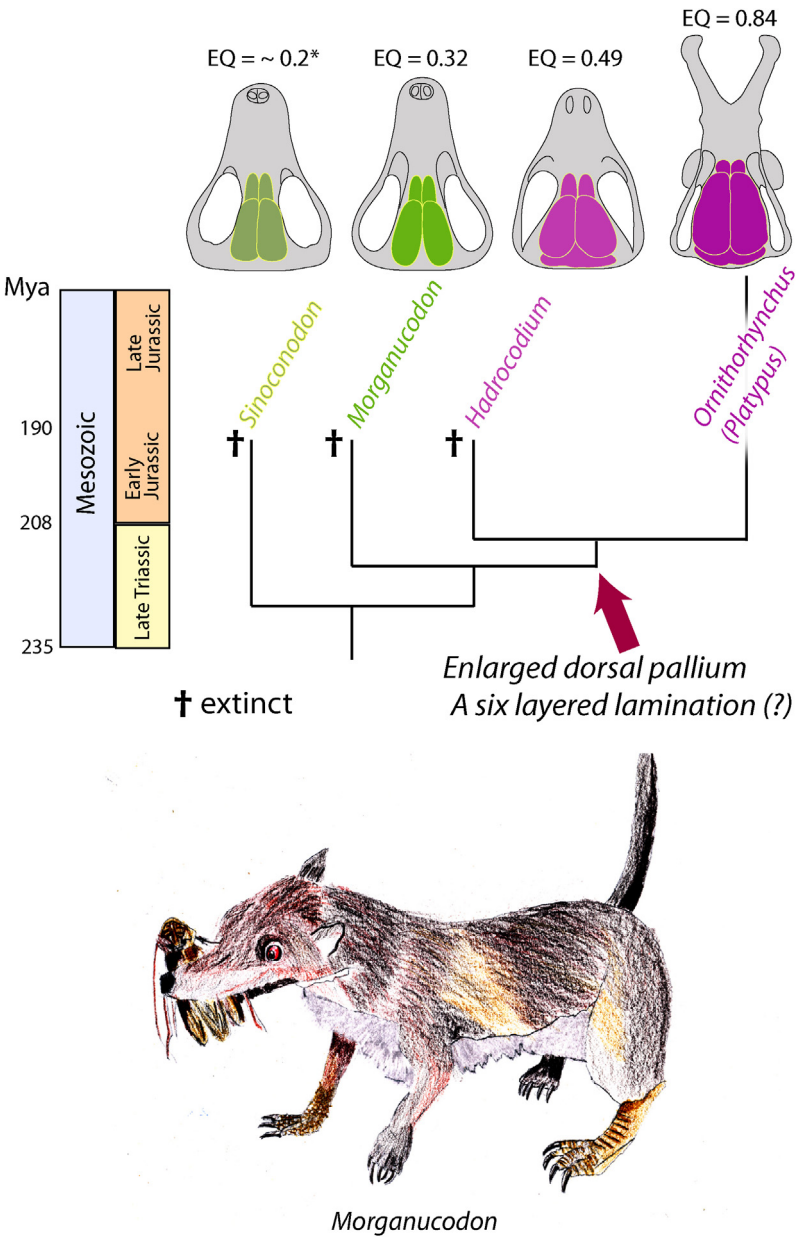

Fig. 4. Primitive mammals and evolution of the neocortex. Upper images: phylogenic trees of primitive mammals with their endocasts. The illustration was modified from Luo et al. (2001). The divergence time of *Sinoconodon*, *Morganucodon*, *Hadrocodium* and *Ornithorhynchus* were based on Luo et al. (2001), Ruta et al. (2013) and O'Leary et al. (2013). EQ values of each species are based on Rowe 2011. Because exact EQ of *Sinoconodon* has not been reported, we referred EQ values of related species in *Cynodontia* (an asterisk). A lower image: *Morganucodon*, a mammaliaform that lived at around the late Triassic to early Jurassic. The illustration was based on Levy et al. (2008).

reptilian and avian palliogenesis proceed in roughly an outside-in manner, which does not resemble the developmental process of the mammalian cortical plate (Goffinet et al., 1986; Tsai et al., 1981).

These data suggest that the mammalian and non-mammalian cortical plate neurons are not simply comparable, although currently we could not state which neuronal subtypes are ancestrally or evolutionarily derived populations during evolution. A recent study has shown that in the developing mouse telencephalon, the transcription factor Foxg1 plays a critical role in the fate determination of Cajal-Retzius cells by its suppressive activity (Hanashima et al., 2004; Kumamoto et al., 2013). Comparative analysis of Foxg1 functions in the developing pallium will shed light on the evolutionary process and the regulatory system for preplate and cortical plate neurons.

7. Critical points of comparative gene expression and cellular homology

Although comparative analyses of gene expression patterns across species provided molecular profiles of diverse sets of neuron subtypes, it is still unclear whether the cells expressing orthologous genes in different animals can be considered as homologous cell types or not. In particular, the neurons in the DVR of reptiles and birds are being discussed regarding the interpretation of homologous counterparts in the mammalian telencephalon (Karten, 1969, 2013; Puelles, 2001; Puelles and Medina, 2002). Importantly, nearly all genes specifying excitatory neurons in the neocortex are expressed elsewhere in the telencephalon, such as the hippocampus, the amygdala, the olfactory bulb, and also the subpallium (Aboitiz and Zamorano, 2013; Medina et al., 2013; Nomura et al.,

2008). Thus, homologous cell components cannot be addressed due to the lack of topological information, even within same species. For example, granule cells in the olfactory bulb exhibit similar molecular profiles to those of cortical interneurons (because both are GABAergic), but usually we can distinguish two types of interneurons based on their topology in the brain. However, in homozygous Pax6 mutant mice, the olfactory bulb is ectopically localized at the lateral cortical surface, which makes it difficult to address neuronal subtypes without specific markers or morphological landmarks for olfactory interneurons, particularly granule cells (Jimenez et al., 2000; Nomura and Osumi, 2004). Returning to the argument of a neocortex homologue among amniotes, the lack of specific markers for the dorsal pallium and its derivatives across species is a major problem for identifying neocortical homologues in non-mammalian animals (Medina et al., 2013).

Notably, organisms frequently exploited similar regulatory mechanisms to evolve analogous structures with distinct developmental origins. For example, genetic mechanisms regulating appendage development are highly conserved between vertebrates and insects, although the appendage of these two animal groups had been evolved independently (Shubin et al., 1997). This evidence implies that basic regulatory systems have been repetitively recruited (co-opted) to evolve functionally related organs. Thus, similarities of gene expression patterns associated with neuronal functions among distinct species might be the results of parallelism or convergent evolution. Accordingly, recent comparative transcriptome analysis of neuron subtypes revealed the divergence of gene expression patterns between mouse and chicken pallium, which implies that similar characteristics of adult neurons evolved independently in non-homologous regions (Belgard et al., 2013; Chen et al., 2013; Jarvis et al., 2013). If this was the case, how can we compare different types of brains based on the concept of homology? Homology always depends on a hierarchical level of comparison, and one of fascinating concept for addressing this issue is “deep homology”, in which highly conserved genetic regulatory networks across phyla might be derived from ancient regulatory systems in common ancestor(s) (Carroll, 2008; Shubin et al., 1997). In this case, the ancestral regulatory networks are not necessarily to be associated with specific structures or biological events in descendants. The best example is the highly conservative role of Pax6 in the eye development among phyla, which suggests that this transcription factor has been functionally associated with the development of primitive photosensitive organs in common ancestor(s) of metazoans (Gehring and Ikeo, 1999).

In the case of brain development, the regulatory networks controlling cortical/pallial neural stem/progenitor cells are highly conserved among species. In the developing mammalian cortex, transcription factors such as Pax6, Tbr2 and Tbr1 are progressively expressed in cortical excitatory neuron lineages according to their differentiation states (Englund et al., 2005). Temporal expression patterns of these transcription factors are well conserved among amniotes, including mammals, reptiles and birds (Chen et al., 2013; Fernandez et al., 1998; Nomura et al., 2013a; Puelles et al., 2000; Puzzolo and Mallamaci, 2010; Suzuki et al., 2012). However, the characteristics of Tbr2-positive cells are not equivalent among animals. In placental mammals (eutherians), Tbr2-positve cells include basal progenitors, which are intermediate neuronal progenitors localized at the subventricular zone (Englund et al., 2005). In contrast, Tbr2-positive cells in other animal groups such as marsupials and reptiles do not show any proliferative activities (Nomura et al., 2013a; Puzzolo and Mallamaci, 2010). Thus, the temporal regulatory networks for Pax6, Tbr2 and Tbr1 expression could be inherited from common ancestor(s) of amniotes, in which sequential expression of these transcription factors might be crucial for the maintenance and differentiation of cortical neural stem/progenitor cells. However, mitotic activity of Tbr2-positive cell population in placental mammals might be a derived character that has been acquired after marsupial-eutherian diversification.

In addition to exploring conserved regulatory systems in cortical/pallial development, lineage tracing of specific pallial regions is crucial to connect the conserved regulatory networks in each developmental event and/or cellular phenotype. Furthermore, functional conservation and diversification of orthologous genes should be addressed in various types of pallial development, particularly in non-mammalian amniotes. For example, although enormous knowledge has been accumulated on the role of Pax6 in the developing mouse cortex, functions of its orthologous gene in non-mammalian cortical/pallial development has yet to be elucidated. It is highly intriguing to know the developmental functions of Pax6 in reptilian and avian DVR, where Pax6 is highly expressed at the ventricular zone (Aboitiz, 2011; Aboitiz and Zamorano, 2013). Recent advances in genome editing tools such as Zinc-finger nuclease, TALEN and CRISPR/Cas9 systems enable to perform gene targeting in various species, which will provide fascinating data on the role of homologous regulatory networks in pallial development of non-mammalian species (Gaj et al., 2013; Mali et al., 2013).

8. A possible evolutionary scenario for encephalization process in amniotes

Based on currently available data, we propose a possible scenario for encephalization during amniote evolution. Paleontological evidence implies that primitive amniotes had smaller brain volumes relative to their body weights. Thus, the dorsal pallium, a homologous region of the mammalian neocortex, could be formed as a small structure between the medial and lateral sectors of the telencephalon, as is the case in present reptiles. Based on amniote phylogenic trees, it is highly plausible that encephalization could have occurred in mammalian and avian lineages independently. The increase of brain size could have been provided by multiple changes in developmental programs, which led to a massive elaboration of the dorsal pallium in mammals and the DVR in birds. Amplification and reduction of Notch signaling, together with other pleiotropic regulatory systems of neural stem/progenitor cells could have had strong impacts on the growth rates of the specific pallial regions during embryogenesis. However, some unknown mechanisms determine the total neurogenic periods, which were also changeable in accordance with total gestational periods.

Progressive expression of Pax6, Tbr2 and Tbr1 could be detected in the embryonic pallial regions of ancestral amniotes as a core regulatory network for generating pallial excitatory neurons. Additionally, it is possible that primitive amniotes already acquired regulatory networks to evolve multiple neuron subtypes in the pallium because all extant amniotes possess multiple subtypes of excitatory neurons in their pallium, regardless of whether each neuronal subtype is homologous. The extent of laminar structures formed in the dorsal pallium of ancestral amniotes has yet to be elucidated. However, mouse mutant analyses revealed that surface expansion of the neocortex is indispensable for maintaining six-layered lamination (Chou et al., 2009), which suggests that multi-laminar structures would not be formed in ancestral amniotes if they had a small dorsal pallium. One possibility is that multiple excitatory neuron subtypes were intermingled in the dorsal pallium of primitive amniotes, similar to the “amalgam” situation in modern reptiles (Dugas-Ford et al., 2012).

When and how the tangential expansion and multi-layered lamination of the cortex evolved in mammalian lineages remains unknown. Monotremes, the most ancient derivatives of extant mammals, elaborate the tangentially expanded neocortex with a six-layered laminar structure. The divergence period of

monotremes and other mammals ranges between 160 and 210 Mya (O'Leary et al., 2013; Warren et al., 2008), suggesting that cortical lamination evolved some time before this period. However, brain endocast data implies that the telencephalon volume increased after the divergence of mammaliaforms (Fig. 4). *Morganucodon*, a basal mammaliaform that lived at around the late Triassic to Early Jurassic had a smaller forebrain and a narrower dorsal pallium. An enlarged neocortex is already evident in *Hadrocodium*, a pre-mammalian group that lived in the early Jurassic, approximately 195 Mya (Luo et al., 2001; Rowe et al., 2011). These lines of evidence suggest that tangential expansion of the cortical surface area, possibly together with multiple-layered lamination, occurred quite rapidly during the late Triassic to early Jurassic.

Currently, it is premature to discuss the origin of the DVR in the primitive amniotes. Nevertheless, it is obvious that the encephalization process of avian lineage from dinosaurs was driven by the massive elaboration of the DVR, which was inherited from the ancestral reptilian telencephalon, rather than tangential expansion of the dorsal pallium. Thus, mammalian and avian lineages are highly contrasting animal groups that increased brain size in different ways by modifying pre-existed regulatory networks of pallial development derived from common ancestor(s). However, whether or not stem amniote(s) had a DVR or not remains unknown.

9. Future directions

The recent progress of developmental biology on the nervous system provides enormous information on the regulatory system of brains, particularly the mammalian neocortex. However, data from genetic and cellular analyses of non-mammalian brains, including reptiles and birds, which are necessary to fill in the gaps of our knowledge on the evolutionary processes of the increase (or decrease) of the brain size and complexity, are still fragmentary. Recent comparative molecular approaches demonstrated new perspectives on neuronal identities in different animal groups, although we have to carefully evaluate the data based on developmental homology and functional convergence in different hierarchal levels. Nevertheless, the introduction of novel technologies is highly welcomed to enhance our understanding on the evolutionary process of amniote brains. Experimental evolutionary developmental biology will prove or dismiss old hypothesis and unveil the core regulatory systems and their modifications during the process of animal history, which also shed light on the origin of our cerebral cortex.

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