

Normal and Disordered Formation of the Cerebral Cortex : Normal Embryology, Related Molecules, Types of Migration, Migration Disorders

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The expansion and folding of the cerebral cortex occur during brain development and are critical factors that influence cognitive ability and sensorimotor skills. The disruption of cortical growth and folding may cause neurological disorders, resulting in severe intellectual disability and intractable epilepsy in humans. Therefore, understanding the mechanism that regulates cortical growth and folding will be crucial in deciphering the key steps of brain development and finding new therapeutic targets for the congenital anomalies of the cerebral cortex. This review will start with a brief introduction describing the anatomy of the brain cortex, followed by a description of our understanding of the proliferation, differentiation, and migration of neural progenitors and important genes and molecules that are involved in these processes. Finally, various types of disorders that develop due to malformation of the cerebral cortex will be discussed.

Key Words : Cerebral cortex · Embryology · Malformations of cortical development.

ANATOMY OF THE CEREBRAL CORTEX

More than 90% of the surface area of the human cerebral cortex is composed of the 6-layered neocortex. Roughly two-thirds of the cortical surface is folded and located inside the sulci. Cortical folding not only enables a reduction of brain volume but also optimizes brain connectivity²⁶⁾. The thickness of the neocortex ranges from 1 to 3 mm, with thicker sections at the top of the gyri than deep inside the sulci⁴⁴⁾. Regarding the cell composition of the cerebral cortex, pyramidal neurons (glutamatergic, excitatory), which establish long circuits, are

the most abundant (80%). Interneurons, on the other hand, are gamma-aminobutyric acid-ergic (GABAergic), inhibitory neurons that establish local, intracortical connections between pyramidal neurons. The neurons are arranged primarily in a columnar unit but become organized in layers due to the horizontal, intracortical development of cortical fibers⁴⁾.

The basic six layers are as follows.

- 1) layer I : molecular layer, contains local connecting fibers.
- 2) layer II : external granular layer, receives corticocortical afferents (association and commissural fibers).
- 3) layer III : external pyramidal layer, sends corticocortical

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efferents (association and commissural fibers).

4) layer IV : internal granular cell layer, receives thalamocortical afferents.

5) layer V : internal pyramidal layer, sends the cortico-subcortical efferents (to the striatum, brainstem, and cord).

6) layer VI : Fusiform or multiform layer, sends corticothalamic efferents.

NORMAL DEVELOPMENT OF THE CORTEX

The cerebral cortex is formed from neuroepithelial cells (NECs). In humans, NEC proliferation begins in the 4th week of development in the neural plate. NECs proliferate in a symmetric fashion (one stem cell divides into two stem cells) until neural tube closure is complete⁹. Afterwards, proliferation changes to asymmetric division in which one stem cell produces one stem cell and one neuron. The differentiated neurons are located in the periphery (primordial plexiform layer or preplate [PP]), and as a consequence, the stem cells are placed in the deep germinative zone called the ventricular zone (VZ)⁵⁴. In early developmental stages when the distance between the VZ and PP is short, the neurons move by somal translocation (nucleokinesis). Nucleokinesis occurs by the neuron extending a process toward the PP meningeal surface, and the nucleus moves toward the surface as the ventricular process shortens and is detached from the ventricle. Cajal-Retzius cells are one of the neurons in the PP that establish the first extracortical connections and play a major role in controlling the migration of neurons in the cortical plate (CP). The PP is divided into two layers : the superficial marginal zone (MZ) and the subcortical layer of the subplate (SP). The MZ contains Reelin-positive Cajal-Retzius cells, and the SP contains Reelin-negative Cajal-Retzius cells^{28,34}.

New-born excitatory, pyramidal neurons must migrate from the VZ where they are born, to near the surface of the cortex. This migration is accomplished through a process called radial migration⁴¹. Radial migration uses radial glial fibers of radial glial cells (RGCs) as a scaffold. RGCs are neuroepithelial progenitors that form bipolar radial fibers between the ventricular and meningeal surfaces. The newly formed neurons travel along the radial glial fiber in the direction perpendicular to the cortical surface and are induced to detach from the radial glia. The cell-cell interaction between the trav-

elling neuron and RGC is under tight molecular control, and also affected by external signals such as Reelin provided by Cajal-Retzius cells. The trajectory of the fibers is a key factor in defining the migratory route and the final location of the new neurons along the cortical surface. The cells that leave the ventricular zone in the early stages of development settle in the deep layers of the cortex. The cells that exit the ventricular zone at later times travel longer distances, passing over previously born neurons, and settle in the superficial layers of the cortex^{2,15,35}. This system explains the inside-out pattern of the cortical layers.

One of the major forces of the migration of neurons on RGCs is microtubular assembly and function. As a neuron wraps around the shaft of an RGC using its leading process, the nucleus of the cell moves within the cytoplasm of the leading process. The leading process slowly extends, and the nucleus follows in a rather stepwise fashion. The conduit for nuclear movement in the cytoplasm is a system of microtubules and centrosome-like structures termed the basal body. Another important player in neuronal migration along RGCs is adhesive interactions between cells, as adhesive receptors such as integrins promote neuronal extension on the scaffold³⁶.

Along with their role as a guiding scaffold, RGCs have been shown to act as progenitor cells that generate both neurons and astrocytes. These cells undergo asymmetric division in the VZ, producing another RGC and a neural progenitor⁴⁰. The neural progenitors move to the SVZ (subventricular zone) and become multipolar, establishing multiple cellular contacts. Then, the neural progenitors move tangentially to detach from the radial glia and scatter throughout the SVZ³³.

Interneurons move by another mode of migration in the developing cortex, tangential migration, in close association with the radial migration of the pyramidal neurons. The major cellular substrate seems to be the axonal projections that connect pre-existing neurons. Tangential migration follows specific navigation routes. Interneurons are generated in the medial ganglionic eminence and travel parallel to the surface of the hemisphere toward the cortex. From the lateral ganglionic eminence, the interneurons rostrally migrate and contribute to the interneurons of the olfactory bulb^{28,44}. During this process, the interneurons are speculated to acquire laminar address or positional information. The interaction of some interneurons with some pyramidal neurons during their migration may allow for the transmission of such positional information. Hence, this type of migration may

have evolved as a mechanism for increasing the complexity of neuronal circuits^{27,34}).

MOLECULES AND GENES

Lis1 and doublecortin (DCX) proteins have been localized to microtubules, suggesting that they are involved in microtubule-dependent nuclear movement³⁹. Reelin is an extracellular matrix protein that is secreted from Cajal-Retzius cells and plays a crucial role in the migration of cortical neurons^{11,14}. Without Reelin, neurons fail to detach from the RGC and accumulate underneath the cortical plate.

Fibroblast growth factor (FGF) and its pathway block the maturation of cortical progenitors and promote their proliferation⁴⁸. FGF also plays a role in the self-amplification of cortical progenitors, resulting in cortical expansion^{42,43}. Other important signaling pathways suspected to regulate cortical progenitor proliferation and self-renewal include the Wnt, bone morphogenetic protein (BMP), MAPK, and Notch pathways^{19,32,38}. The Notch pathway and retinoic acid signaling are known to regulate the balance between progenitor proliferation and neurogenesis⁵².

The specific genes associated with cortical malformation are listed in Table 1.

MALFORMATIONS

The size and folding of the cerebral cortex have a significant impact on brain function and apparently intellectual ability^{1,21}. It should be noted that the classification of malformations varies between reports in addition to the one used in this review. For example, microcephaly, megalencephaly, and dysplasias may be classified as malformations of brain size; lissencephaly and polymicrogyria may be classified as cortical folding failure; and subcortical band heterotopia, cobblestone brain, and periventricular heterotopia may be classified as ectopia¹⁷. The variation may be caused because many of the anomalies overlap, and the pathomechanisms cannot be simplified into clear-cut categories.

Failure of proliferation/apoptosis

Alterations in proliferation and survival of the neural progenitor may result in abnormal brain size, namely defective (microcephaly), excessive (megalencephaly), or imbalanced (focal cortical dysplasia [FCD] type II) brain size⁷.

Microcephaly is a rare condition in which affected patients display a significantly small brain size. Genes known to be important for various cellular processes, such as DNA repair efficiency, cell cycle length, mitotic spindle positioning, and centrosome function, are associated with microcephaly⁵⁶. For instance, microcephalin (MCPH1), which lengthens the cell cycle and alters the alignment of chromosomes, is one of the common causes of primary microcephaly^{20,25,59}. Mutation in

Table 1. Types of human cortical malformation, altered molecular pathway, associated genes

Malformation	Molecular Mechanism	Genes
Microcephaly	DNA repair efficiency/cell cycle length/mitotic spindle positioning/centrosome maturation, duplication, and position	MCPH1/ASPM, AKT3/ASPM, STIL, WDR62/NDE1, CDK5RAP2
Megalencephaly	Cell growth	PI3K-AKT signaling AKT3, PIK3R2, PIK3CA
Dysplasia	Cell cycle and growth, ribosome biogenesis, mRNA translation	mTOR pathway activation
Lissencephaly type I	Radial migration/cortical lamination	LIS1, DCX, TUBB3, TUBA1A, RELN/RELN
Cobblestone (Lissencephaly type II)	Pial surface stability	POMT1, POMT2, FKTN, FKRP
Periventricular heterotopia	Actin cytoskeleton/vesicle trafficking/neuronal migration/molecular adhesion	FNLA, ARFGEF2, C6orf70, FAT4, DCHS1
Polymicrogyria	Cell adhesion, regulation of phosphorylation, cell motility, synaptogenesis, angiogenesis/cytoskeleton regulation/neurite outgrowth	SPRX2/GPR56/TUBB2B, TUBB3, TUBA1A/KBP

Modified from Fernandez et al.¹⁷ with permission. PI3K : phosphatidylinositol 3-kinase, mTOR : mammalian target of rapamycin

Abnormal Spindle-like, Microcephaly-associated (ASPM), which is important in maintaining the orientation of the mitotic cleavage plane is also found in microcephaly patients^{23,29}.

Megalencephaly patients show an abnormally enlarged brain. It is speculated that megalencephaly is caused by the overproduction of progenitor cells and cortical neurons due to a shortened cell cycle that results in increased re-entry into the cell cycle or to decreased apoptosis^{12,24,58}. Apart from severe cases, typical megalencephaly cases show excessive cortical folding (polymicrogyria) due to the abundance of progenitor cells⁶. The causal genetic error is under investigation and recent reports suggest that phosphatidylinositol 3-kinase (PI3K)-Akt signaling may play a central role in controlling brain size^{13,30,45}.

FCD is the most common type of malformation of cortical development and frequently presents as epilepsy in children. FCD has two features of malformation, cortical disorganization and the presence of abnormal cells (neuronal heterotopia, balloon cells, neuronal cytomegaly) in abnormal locations³⁷. In FCD type II (the subtype with balloon cells or dysmorphic neurons), defective proliferation and/or apoptosis of cortical progenitors seem to be the pathomechanism. mTOR pathway genes are revealed to play important roles in the formation of FCD^{3,10}. In contrast, the pathomechanism of FCD type I is speculated to be organizational failure, such as lack of tangential lamination or abnormal retention of radial cortical pattern⁴⁴.

Failure of migration

Regulation of variables during migration is critical for the proper positioning of cortical neurons, including both the location and timing of their positioning. In other words, the neurons must migrate through the entire thickness of the cortex and stop at the surface of the cortex¹⁷. Such a 'fate' is known to be determined by the time and place of their birth. Errors in these events may misplace the neurons, resulting in heterotopias. Heterotopias are described by their appearance (laminar, nodular) and location (periventricular, transcerebral, subcortical, cortical, marginal, and extracortical meningeal).

Lissencephaly includes several types of 'simplified folding pattern' diseases: agyria, pachygyria, and subcortical band heterotopia. Agyria refers to a brain with a complete absence of folds, and pachygyria shows a simplified gyral folding pattern²². In subcortical band heterotopia, broad convolutions

and a thickened cortex are observed in either a normal or simplified gyral pattern.

Type I or classic type lissencephaly is associated with the mutation of genes related to the cytoskeleton and cell migration. LIS1 or DCX are the most commonly mutated genes³⁹. A small portion of type I lissencephaly (1–4%) is caused by the mutation of TUBB3 or TUBA1A³³. Mutations in Reelin (RELN), a critical gene for radial migration and cortical lamination, are also found in a minority of type I patients^{11,14}. These genetic mutations hinder the proper migration of newborn neurons, resulting in the accumulation of neurons below the PP into disorganized and thickened, 4-layer cortex. The thickened cortex is the hallmark finding of lissencephaly, differentiating it from the simplified gyral pattern of primary microcephaly¹⁷.

Type II lissencephaly or cobblestone brain is different from other migration disorders (caused by undermigration) in that they are formed by overmigration. The anchoring and attachment of the radial glial fibers to the pial membrane is anomalous, resulting in the disruption of the basement membrane. As the cortical basement membrane is the end point of the radial migration of neurons, the disruption leads to the overmigration of the neurons beyond the pia and into the meningeal space. This results in the 'cobblestone' appearance of the cortical surface^{31,60}. There is a wide spectrum of phenotypes, but the known driver genes are related to the attachment of the radial glial fiber to the pial surface or are associated with the glycosylation of alpha-dystroglycan, which is fundamental in the anchoring of the dystrophin complex to the extracellular matrix^{8,47,55}.

Periventricular heterotopia is caused by the failure of the radial migration of cortical neurons. It is speculated that defective remodeling of the actin cytoskeleton inhibits the proper change in cell shape and the locomotion of newborn neurons required for migration. This results in the complete failure of the neurons to depart from the germinal zone, and instead the neurons reside near the ventricular zone clustered into nodules^{1,49,51}. The most frequent genetic alteration in periventricular heterotopia is the mutation of Filamin A (FLNA) and ARFGEF2. FLNA is known to act on the actin skeleton, and ARFGEF2 plays a role in the trafficking of intracellular membranes and vesicles^{16,18,50}.

Polymicrogyria is a group of cortical malformations showing abnormally abundant and small cortical folds and the in-

terdigitation of white matter causing abnormal lamination⁷⁾. The polymicrogyria cortex is either 4-layered or unlayered^{5,57)}. It is characterized by a malarrangement of the cell layers and intracortical fiber plexus. The excessive folding of the upper or all cellular layers under the continuous smooth molecular layer is also observed. Due to excessive folding, the CP may appear thick, although it is actually thinner than under normal conditions⁴⁴⁾. The causative genes for polymicrogyria have not been identified; however, associations with several genetic errors, such as mutations in *SPRX2* and genes related to the cytoskeleton, have been suggested⁴⁶⁾.

CONCLUSION

The development of the cerebral cortex is a complex process involving the proliferation, migration, and differentiation of neural progenitors regulated by multiple genes and molecules in a time- and location-specific manner. A clear understanding of this process will lead us to better understand related malformations, resulting in more effective treatments and preventative therapies for these diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

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