REVIEW

Normal and abnormal neuronal migration in the developing cerebral cortex

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Abstract : Neuronal migration is the critical cellular process which initiates histogenesis of cerebral cortex. Migration involves a series of complex cell interactions and transformation. After completing their final mitosis, neurons migrate from the ventricular zone into the cortical plate, and then establish neuronal lamina and settle onto the outermost layer, forming an "inside-out" gradient of maturation. This process is guided by radial glial fibers, requires proper receptors, ligands, other unknown extracellular factors, and local signaling to stop neuronal migration. This process is also highly sensitive to various physical, chemical and biological agents as well as to genetic mutations. Any disturbance of the normal process may result in neuronal migration disorder. Such neuronal migration disorder is believed as major cause of both gross brain malformation and more special cerebral structural and functional abnormalities in experimental animals and in humans. An increasing number of instructive studies on experimental models and several genetic model systems of neuronal migration disorder have established the foundation of cortex formation and provided deeper insights into the genetic and molecular mechanisms underlying normal and abnormal neuronal migration. J. Med. Invest. 49 : 97-110, 2002

Keywords **:** *cerebrum, ectopia, migration disorder, radial glia*

INTRODUCTION

The development of the mammalian cerebral cortex is a remarkably complex process, and mainly consists of three steps, (i) production of neuronal precursor cells, (ii) migration to their laminar position and (iii) finally differentiation and development of their morphological and functional properties. The cerebral cortex of higher vertebrates is organized in to six layers. The layering is produced by variations in the densities and sizes of cell bodies through the cortical depth. All neuronal cells, with few exceptions, are generated the surface of the embryonic cerebral ventricles at sites far from their ultimate positions in the adult mammalian brain (1, 2). Therefore, neuronal migration is considered to be necessary and an essential step in the genesis of the nervous system, particularly in laminated brain regions (3-6). Migration of neurons is a distinct cellular phenomenon. By this migrating process many billions of newly generated neural cells are addressed to their proper position mainly in nuclear masses or in the cerebral cortexes. General or topical loss of control over this process generally called abnormal neuronal migration or neuronal migration disorder. Abnormal neuronal migration will result in either

Received for publication May 31, 2002; accepted July 10, 2002.

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cell death or improper positioning of functional cell groups. This in turn will result in failing connections or improper wiring (misconnection) responsible for functional deficiencies and epilepsy. Abnormal migration had been linked to congnitive deficits, mental retardation, and motor disorders (7-11). Recently, there has been rapid progress in understanding the ever-surprising phenomenology of this neuronal migration, as well as its molecular basis. Herein we will review the normal process of neuronal migration, disruptions in such neuronal migration process that results several cerebral cortical disorders, and the current understanding of the molecular mechanisms of neuronal migration and its relationship to cerebral cortical development and neuronal migration disorder.

NORMAL NEURONAL MIGRATION IN THE CEREBRAL CORTEX

(1) Mode of neuronal migration

Neurons that come to populate the six-layered cerebral cortex are born deep within the developing brain in the ventricular zone that lines the lateral ventricle of each telencephalic hemisphere. The ventricular zone of the telencephalon provides the neuronal and glial stem cells (1, 2, 12-14, 17, 24). The cortical neurons are generated in an orderly sequence. The earliest-formed cortical neurons from a precocious organization referred to as the preplate. These early born neurons from connections with subcortical targets that are essential for development for later connections. The preplate is subsequently divided into two layers : an outer marginal layer composed largely of Cajal-Retzius neurons beneath the pial surface, and an inner layer composed of subplate neurons-by the arrival of a later-generated neuronal population called the cortical plate (future cortex). Once the preplate is established, subsequent cells which complete their final mitotic division migrate out of the ventricular zone and settle between these two layers to engage into a long migration with radial centrifugal fashion through the intermediated zone (future white matter) toward the cortical plate where they settle and differentiate (20). The first cells to arrive will eventually reside in the deepest layer, layer VI. Later born cells will migrate past the existing cells to reside in progressively more superficial layers. Subsequent cohorts of neurons repeat this mode, migrating through an ever-thicker cortical plate, so that the newest neurons are always at the top of the cortical plate facing the marginal layer cells.

Neuronal migration in the neocotex takes place for the greater part between the 8th and the 20th weeks of gestation in humans (15) and between embryonic day 14 (E14) and postnatal day 5 (P5) in rats (19). The migration of young neurons is guided from an early stage by a system of radial glial fibers that span the width of the thickening telecephalon (16-18). Radial glia is a specialized cell type belonging to the astroglial cell lineage. During cortical development, these long bipolar cells expand radially across the thickness of the cerebral wall. Radial glia are bipolar cells with one short process extended to the adjacent ventricular surface and a second projecting to the pial surface. The perikarya of the radial glial cells are in the ventricular and subventricular zones (21-23, 25, 26). Neurons of layer I--the giant Cajal-Retzius neurons and layer VIb--the lower part of layer VI are laid down as a single neuronal network, the primordial plexiform layer (27, 28, 33-36, 39). This primordial plexiform layer is thought to provide a cytoskeleton for the successive neuronal migration waves as these become sandwiched between the upper and the lower part of the lower part of cerebral structure (Fig. 1). Neurons migrate along the elongated radial glial fibers, which disappear after neuronal migration has been completed, when the morphology of radial glial cells changes into that of astrocytes.

(2) Determining correct position of migrating neurons within the cerebral layers

As description above, neurons are generated in sites different from those in which they will later reside, so the intervening neuronal migration is necessary for this shift. On the other hand, neuronal migration into the cortical plate must also stop at the appropriate location. This choice point and determining this point is a key for normal cerebral cortical development and brain functions. Some studies have suggested that neurons completing migration appear to require a stop signal, which appears to be provided by the most superficial cortical layer or the pial membrane. This process of the neuronal migration stop involves the detachment from the radial glial fibers triggered by local signals (Fig. 2) (29, 33, 42, 43), some of them emitted by the Cajal-Retzius cells of the marginal zone (27, 39). The study of mouse mutants has led to identify some of the molecules that regulate neuronal positioning.

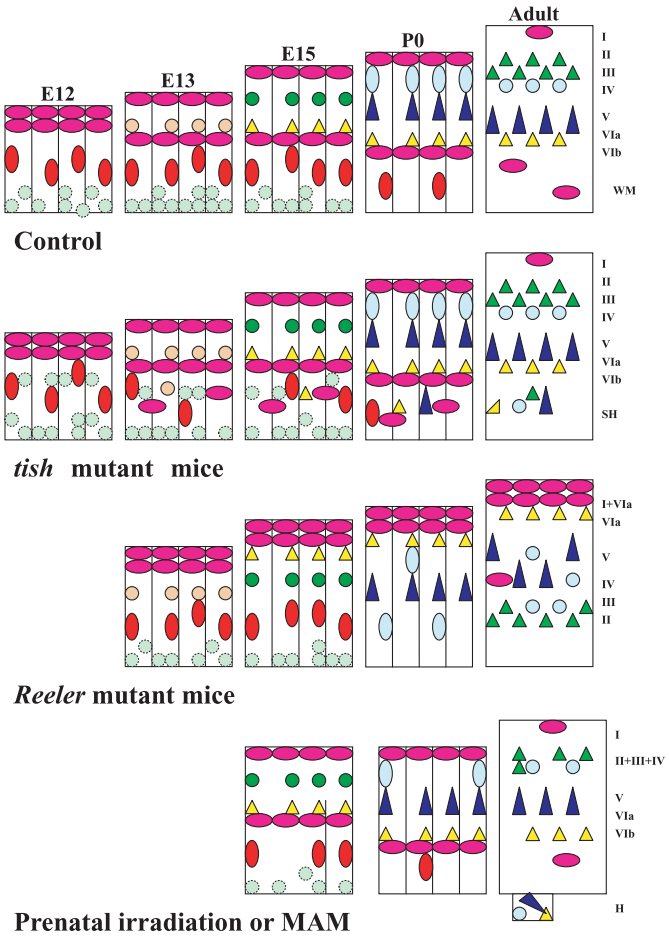

Fig. 1. Diagrammatic representation of cortical development in three current rodent models of neuronal migration disorder from embryonic day (E) 12, 13, 15, postnatal day 0 (P 0) to adult stage. Experiment rats for nongenetic models are treated on E 14-15 with methylazoxymethanol (MAM) or irradiation. Three models (*tish* mutant rat, *reeler* and *reeler*-like mutant mouse and the prenatal irradiation-or MAM-treated rat) show that neuronal migration disorders can result from an abnormal neurogenesis (*tish*), a failure of preplate splitting (*reeler*) or a lesion of radial glia cells (X-ray, MAM). WM : white matter, SH : subcortical band heterotopia, H : heterotopia.

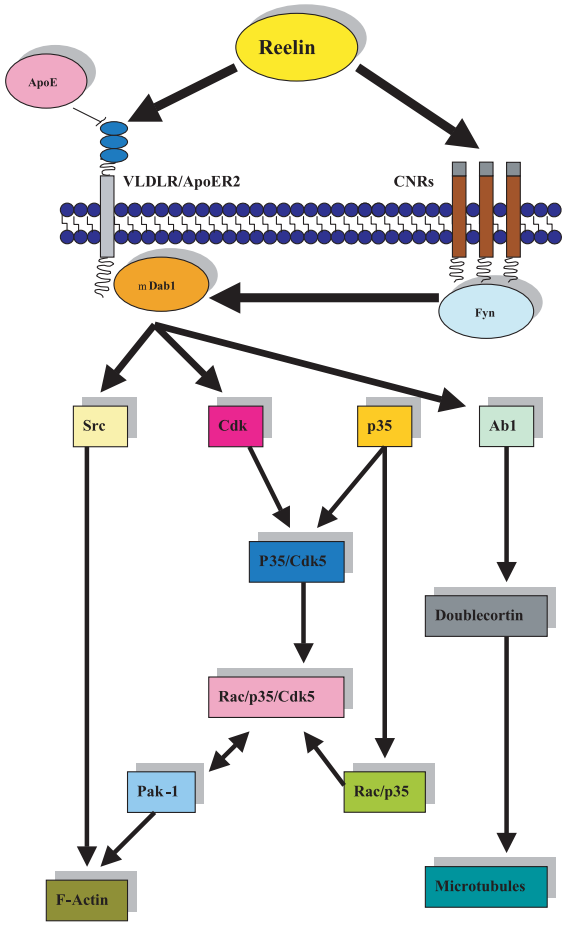

Fig. 2. Diagram to illustrate Reelin signaling pathway. Reelin is expressed by Cajal-Retzius cell in cortical layer I and binds the cadherin-related receptors (CNRs) and the VLDL receptor or ApoE receptor-2, or both. CNR binding initiates phosphorylation of a Scr family kinase, possibly Fyn, which is considered to phosphorylate mDab-1 associated with VLDLR/ApoER 2. Reelin binding to VLDLR and ApoER2 also appears to result in phosphorylation of mDab-1 through kinase domains in the cytoplasmic region of the receptors. Activated mDab-1 is then though to interact with Cdk 5, Src, and Ab 1 to regulate cyotskeletal remodeling, directly or indirectly.

In particular, the characterization of the Reeler mouse mutant provided the first insights into the process of laminar organization. The Reeler mouse was first identified as a postnatal behavioral defect (40), and the neuropathological studies have showed that the cortical layering pattern is just opposite from the normal inside to outside migrating pattern (41, 44, 45). It has been known that Reelin is pressed by Cajal-Retzius cells in layer I (30-32). As one of extracellular matrix molecule, Reelin plays a role to form a Reelin's zone to stop migration of the earliest generated neurons in the cerebral cortex. However, Cajal-Retzius cells in the Reeler mice were found to be remained at the top of the undivided preplate, or superplate. These heterotopic Cajal-Retzius cells are thought to be the reason to form the inverted cortical layering in the Reeler mutant mouse (Fig. 1). Detail description of the Reelin signaling pathway to end cell migration will be described below.

ABNORMAL NEURONAL MIGRATION INDUCED BY DISTINCT ENVIROMENTAL, CHROMOSOMAL AND GENETIC CAUSES

(1) Teratogenic, physical and biological influences

The process of neuronal migration involves four key steps : (i) neuronal migration onset, (ii) ongoing neuronal migration, (iii) neuronal penetration into preplate and (iv) neuronal migration completion. One can imagine that a disruption in any step upon which brain formation is dependent can result in a profound and stereotypical malformation. Various environmental factors (teratogenic, physical and biological factors) which can affect neuronal migration have been tested in the animal experiments. The use of teratogenic (e. g. alcohol or cocaine) (46-48, 55, 110), physical (e. g. irradiation, heat) (49-53) and biological (e. g. viral infection) (54) agents has provided animal models for studying neuronal migration disorder. These animal experiments have involved different species and different protocols of exposure the environmental agents to the potentially damaging effects on the neuronal migration of the cerebral cortex. Most of these nongenetic model were generated by exposure of pregnant females during the early period of migration to irradiation or toxic substances such as the antimitotic agent methylazoxymethanol (MAM) (56-58), cocaine(110) or ethanol (46-48, 55). Whatever their respective mechanisms, all these influences will lead neurons to differentiate in an abnormal heterotopic position.

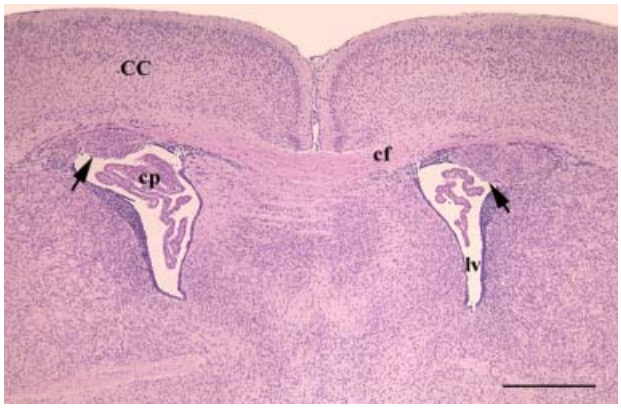

Fig. 3. An example of a typical heterotopica (arrows) located bellow the cerebral cortex (cc) of a 1-week-old mouse irradiated on embryonic day 13 (E 13), which corresponds to E 15 in the rat. Heterotopia is separated from the cerebral cortex by a band of fibers of corpus callosum (cf). cp : choroids, lv : lateral ventricle. Hematoxylin and eosin stain. Scale bar=400 μm.

Absence, interruption or excessive migration will lead neurons to differentiate respectively in a subcortical (i. e. along the ventricle), intracortical (i. e. in the white matter or in an inappropriate layer) or extracortical (i. e. in the submeningeal space) position. Pregnant mice subjected to X-irradiation at a single dose of 1.5 Gy on embryonic day 13 which is the radiosensitive stage produced offspring with neuronal heterotopia located in enlarged lateral ventricles of the cerebral hemispheres (Fig. 3) (49, 51, 53, 63). Midkine (MK) is a 13 kDa heparin-binding growth factor specified by a retinoic acid-responsive gene. It is mitogenic for certain fibroblastic cell lines, and enhances neurite outgrowth and survival of various embryonic neuron types (121-123). Increased expression of MK was detected on the processes of radial glial cells in the developing rat cerebral cortex (124). Thus, MK is used for analysis of gliogenesis in the early stages of the developing brain. MK-immunocytochemical staining (59-62) was carries out to confirm a course corresponded to the distribution of the radial glial fibers (neuronal pathway). These MK-staining fibers radially traversed the distance between the ventricular zone and the pial surface. They were straight and perpendicular to the pial surface, oriented in the direction of neuronal migration in the normal brain (Fig. 4 A). However, in the brain of the irradiated mice, MK-staining radial glial fibers (examination from 6 hr after irradiation) were crumpled and no longer regularly distributed to the pial surface (Fig. 4 B). It is well know that radial glial cells play a role as guides for migrating neurons (50, 53), while a large number of young neurons migrated

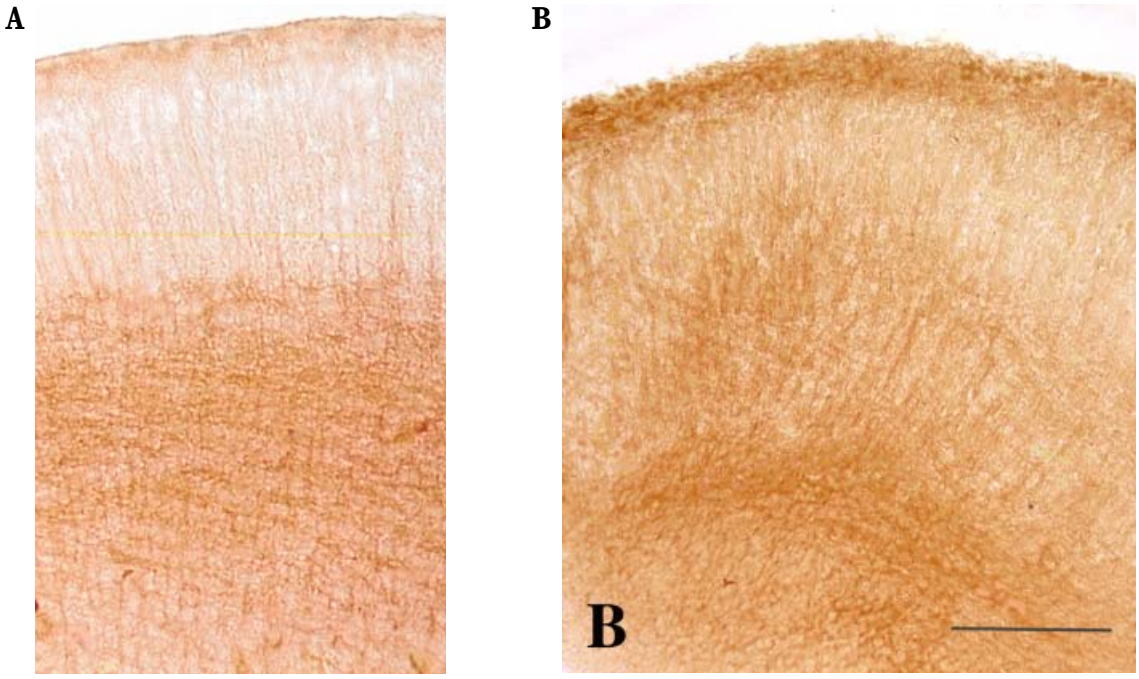

Fig. 4. An example of anti-Midkine (MK)-immunoreactive radial glial fibers in the mouse brain mantle on embryonic day 17. A : radial glial fibers are straight and perpendicular to the pial surface in the control mouse. B : Radial glial fibers are crumpled and no longer regularly distributed to the pial surface in the mouse irradiated on embryonic day 13. Scale bar=100 μm.

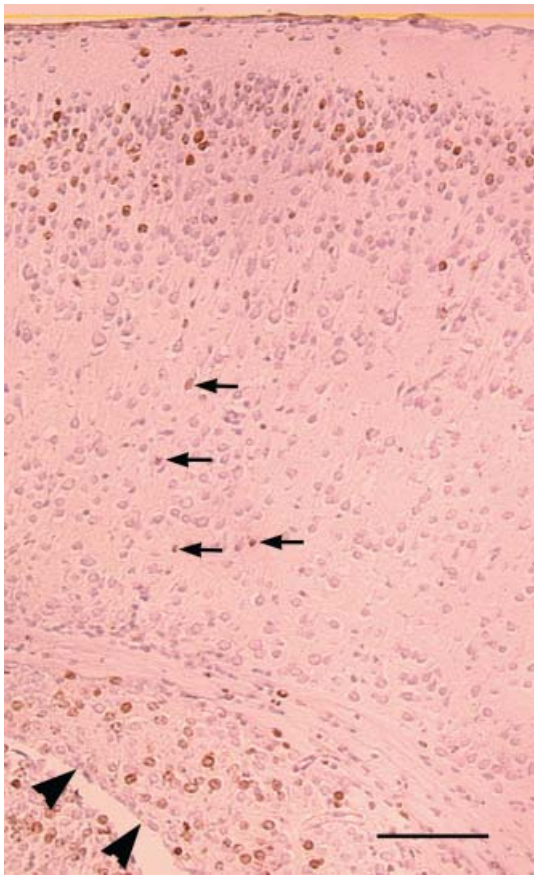

Fig. 5. An example of anti-bromodeoxyuridine (BrdU)-labeled young neurons migrated along disturbed pathways in a 1-week-old mouse irradiated on embryonic day13. Some of these neurons could not move far from the place of their origin around the lateral cerebral ventricle and remained in the lower inappropriate layer (arrows) or near the ventricle to form heterotopic cell mass (arrowheads). Scale bar=100 μm.

along such a disturbed pathway, some of them could not move far from the place of their origin around the lateral cerebral ventricle and remained in the lower inappropriate layer or near the ventricle to form heterotopic cell mass (Fig. 5).

(2) Abnormal neuronal migration in mutant mice

Several studies on neurological mutant murine with brain malformation (64, 65) provide a new approach to the discovery of genetic loci that contribute to neuronal migration in developing brain. Classical studies of mutants, Reeler, Scrambler, Yatari, have been assumed to be models for neuronal migration in cerebral cortex. In Reeler mutant mice, the cortical layering appears inverted (41). In other words, the first cells of definitive cortex to migrate out of the ventricular zone end up residing in the superficial cortical plate and subsequent cells migrate to and stop in progressively deeper positions. This migration pattern is opposite of the normal inside to outside development of the cerebral cortex. The affected gene in Reeler mice was found to encode for a large extracellular matrix protein named Reelin (29, 31, 66, 67). Reelin has homology to F-spondin and contains epidermal growth factor-like repeats similar to those of tenascin C, tenascin X, restrictin, and the integrin βchain (31). Reelin is expressed by Cajal-Retzius cells and is found extracellularly in the molecular layer (layer I) (29, 31, 33). These

data suggest that Reelin is required for the normal inside to outside positioning of cells as they migrate from the ventricular zone (25, 68). This was the first component of a signaling pathway guiding cells to the correct location in the cortex. Because Reelin is an extracellular matrix molecule, a receptor for Reelin would be required for signaling to the migrating cells. Reelin signaling pathway was summarized in Fig. 2. Reelin has been found to bind to cadherin related receptor (CNRs) (69) and at least two members of the LDL receptor family (70-72) and $\alpha 3\beta 1$-integrin (73). Binding of Reelin to $\alpha 3\beta 1$-integrin functions as a stop signal ; however, the downstream components within the cell that regulate the migration stop are not known. Upon contact with Reelin, the CNRs initiates phosphorylation of the cytoplasmic second messenger mDab1, possibly through a CNR-associated tyrosine kinase Fyn (69) or through the LDL receptor (71, 72). The scrambler and Yotari mutant mice have been identified as mutations in the mDab1 gene (8). Scramber, Yotari, and mDab 1-/-all show a Reeler phenotype further supporting the notion that they lie the same pathway. Phosphorylated mDab1 can interact with a variety of proteins including the SH2 domain of Src (74). Src has been shown to interact with actin and affect cytoskeletal remodeling (75-77). Src-deficient cells exhibit strong adhesion to surfaces and low migration capacity (78). Therefore, these data tie Reelin signaling pathway to cell migration and enable neurons to be targeted to the appropriate layer of the cortex. mDab1 also activates the proto-oncogene c-Ab1. Once activated, c-Ab1 can phosphorylate Cdk5, a process that is enhanced by Cable, thus activating Cdk5 (79). Cdk5 and p35 (another activator of Cdk5) have also been implicated in directing neurons to the appropriate location within the cerebral cortex (80-82). Cdk5 has several putative kinase substrates and several other potential biochemical interactions, in addition to an effect on neurite outgrowth, all of which might have some role in neuronal migration. Cdk5 can phosphorylate both neurofilaments (115, 116) and the microtubule-associated protein, tau (117, 118). Although the mechanism by Cdk5 or p35 has its effects on migration is not clear, all of the effects are related to cytoskeletal changes. Cdk5 and p35 are highly expressed in the developing central nervous system and mice engineered to be homozygous mutant for Cdk5 or p35 also show a cortical defect similar, although not identical, to the Reeler phenotype (80). Nikolic *et al*. have shown co-localization of Cdk5, p53, Rac and Pak-1 in neurons (83). They suggest that a Rac-dependent hyperphosphorylation of Pak-1 results in a dynamic down-regulation of actin polymerization and enhancement of new focal complex formation during cell migration and process outgrowth (83). Activation of Pak has also been shown to result in a loss of stress fibers and focal adhesions (84). These data indicate that the Rac family of GTPases along with Scr family members can regulate cytoskeletal remodeling and therefore transduce guidance signals from the cell membrane to the cytoskeleton.

(3) Abnormal neuronal migration in the human brain

The genes mutated in several human disorders of neuronal migration also provided a basis for linking neuronal migration. In man, more than 25 syndromes with neuronal migration disorders have been described (37). Neuronal migration disorders primarily affect development of the cerebral cortex, but the extent and nature of the cortical malformation varies greatly (38). Table1 summarized genetics of neuronal migration, characteristics of the pathologic alterations and underlying defect in some of these syndromes both in mutant rodent models and humans. It can provide important insights into the histogenesis of the cerebral cortex and the molecular etiology for the cerebral malformations.

Lissencephaly represents a broad class of neuronal migration disorders. It can be described as a brain with a macroscopically smooth cortical surface in which a more or less layered cortex can be observed on microscopical examination. It occurs as an isolated abnormality (isolated lissencephaly sequence) or in association with dysmorphic facial appearance in patients with Miller-Dieker lissencephaly (85). These abnormalities have been attributed to defects in neuronal migration (86). A hemizygous chromosomal deletion at band 17 p13.3 led to identification of lissencephaly-1 (LIS-1) as the causative gene in this anomaly. The LIS-1 gene codes for the LIS1 protein, which contains eight WD-40 repeats of the type found in G-protein βsubunits. It is a regulatory subunit of brain intracellular Platelet-Activating-Factor acetyllhydrolase (PAF-AH1B1) (87), a G-protein-like trimer that regulates cellular levels of the lipid messenger PAF (88). The importance of PAFAH 1 B 1 in the developing brain is supported by the high-level expression of mRNA transcripts for all three subunits during neuronal migratory epochs in cerebrum. The LIS-1 gene product is prominent in Cajal-Retzius cells and ventricular neuroepithelium

Table 1 Genes implicated in neuronal migration disorder

Mutation	Symbol	Chromosome	Position	Description	Source (No. of references)
Mice					
Reeler	*rl*	5	8.0 cM	Migration arrest in early development with subsequent failure of cortical plate formation. Reeler encodes a large ECM molecule produced by Cajal Retzius cells in the molecular layer.	29, 103, 104.
Scrambler	*scr*	4	49.7 cM	Phenotype is identical to that of reeler. Scrambler is a mutation in a disabled gene that encodes a phosphoprotein that binds nonreceptor tyrosine kinases.	105, 106.
Yotari	*yot*	4	49.7 cM	Allele of scrambler.	8, 107.
Disabled	*mdabI*	4	49.7 cM	Allele of scrambler.	8.
Lissencephaly	*Lis 1*	ND	ND	Failure of forebrain neuronal migration via deletion of th ebeta subunit of platelet activatingfactor acetylhydrolase (PAFAH1B1, also known as Lis1)	104.
Zellweger	*PEX 1, PEX 2*	ND	ND	Failure of forebrain neuronal migration via defective peroxisomal biogenesis.	101, 102.
Rats					
Double cortex	*tish*	ND	ND	Cortical neurons are seen in a bilateral heterotopia that is prominent below the frontal and parietal neocortex ; heterotopoas rare beneath the temporal cortex.	111.
Humans					
MD syndrome	LIS 1	17	17 p 13.3	A class of spontaneous and inherited disorders (MD) with failure of migration in forebrain, fewer gyri, and smoother gyri in cerebral cortex. In a murine model, the mechanism involves the deletion of the beta-subunit of platelet activating factor acetyldehydrogenase (PAFAH1B1).	112.
Lissencephaly	LIS			Subset of MD with failure of migration in forebrain. Individuals that express the gene have a smooth brain, i.e. fewer gyri in the cerebral cortex.	113.
X-Linked Lissencephaly	xLIS	X	Xq 22.3-q 23	Males show lissencephalic phenotype. Females have a double cortex phenotype with disorganized forebrain gray matter and an extra layer of cells located underneath the white matter. The defective gene encodes the doublecortin protein. Doublecortin is homologous to the amino terminus of a predicted protein kinase, which suggests a role for signal transduction.	92, 93, 94.
Zellweger syndrome	At least 10 genes proposed	ND	ND	Failure of cortical migration, neuronal laminae do not form. In two murine models, the molecular mechanism involves defects in the PEX 2 or PEX 5 genes, both genes required for neuronal peroxisomal biogenesis.	112.
Bilateral Periventricular Nodular band Heterotopias	BPNH	X	Xq 28	Forebrain neurons form heterotopias in the subependymal zone. The cellular mechanism is unknown.	96, 97, 114.
Microencephaly	ND	1	1 q 25	A class of disorders resulting in reduced brain size due to smaller neuronal lamina. The pattern of lamination isnormal ; the thickness of the layers is reduced. (Nor involving head structures.) One subgroup of families has been mapped.	

ECM : extracellular matrix, EGF : epithelial growth factor, ND : not determined, MD : miller-Dieker.

in developing human cortex (89). How the absence of the LIS-1 gene product affects PAF-AH1B1 function, PAF signaling in the cell, and ultimately neuronal migration remains to be understood. In addition, LIS-1 may have ad yet unidentified interactions in the cell, as suggested by the ability of the WD-40 repeat segments of LIS-1 to interact with the cytoskeketon. The normal gene product of LIS1 is widely distributed in the grey and white matter of the brain and spinal cord in controls. It has been found both in neurons and in glial cells (90). Prenatal diagnosis of the chromosome band 17p 13.3 deletion is now possible using Fluorescent In Situ Hybridization (FISH) and Fragment Restriction Length Polymorphism (FRLP) techniques after chorionic villus biopsy sampling. Another group of disorders with this general class of neuronal migration disorder is X-linked (86). The first X-linked malformation syndrome is X-linked LIS. In X-LIS, hemizygous males have lissencephaly and heterozygous females have subcortical band heterotopia that is also known as a double cortex (DC) syndrome. The clinical presentation in affected males is similar to that with classical lissencephaly and chromosome 17p 13.3 deletion : profound mental retardation, epilepsy with multiple seizure types, feeding problem and a shortened life span. The female carriers have mental retardation, behavior problems and epilepsy. Linkage of DC/X-LIS to Xq21-24 was first demonstrated (92, 93). Subsequent positional cloning identified a novel gene named Doublecortin (93, 94). Doublecortin is a microtubule-associated protein which is expressed widely by migrating neurons (11). It is often possible to predict this gene mutation from careful review of brain imaging studies : mutations of frontal gradient of lissencephaly, whereas mutations of X-LIS are associated with a frontal to occipital gradient (95). The second X-linked malformation syndrome is bilateral periventricular nodular heterotopia (BPNH) that consists of BPNH in females and prenatal lethality or a more severe phenotype in males. In this disorder, large neuronal masses of well-differentiated cortical neurons fill the adult subependymal zone. The syndrome is located at Xq 28 (96-98) the corresponding gene was identified as Filamin 1 (FLN 1), which encodes an actin-cross-linking phosphoprotein which is required for movements of many cell types (104).

Zellweger syndrome is a second broad class of cortical malformation, causing death within approximately six months of life (91). Like lissencephaly, Zellweger patients have characteristic gryal abnormalities in the cerebral cortex, which show a stereotypic medial pachygyria (reduced number of gyri, but they are abnormally large) and lateral polymicrogyria (excess number of small gyri). This syndrome is a genetically heterogeneous disorder that may arise from defects on at least 10 different genes (100). Recently, animal models for a human of Zellweger syndrome have provided by targeted deletion in mice of genes encoding the PEX2 peroxisomal membrane protein (101) and the PEX5 peroxisomal protein import receptor (102, 119). The PEX5-knockout mouse models for Zellweger syndrome show that deficient peroxisomal β-oxidation does not cause neuronal migration defects by itself, but there are some hints that the inactivity of some metabolic pathway may contribute to the brain pathology in mice and patients with complete absence of functional peroxisomes (108, 120).

CONCLUSION REMARKS

Neuronal migration is the critical cellular process which initiates histogenesis of cerebral cortex. Migration involves a series of complex cell interactions and transformation. Postmitotic cells must first adopt a characteristic conformation prior to movement. The cells are then guided in their ascent by contact with the surface of a specialized of the astroglial lineage, the radial glial cells. When migrating cells enter the cortical plate, neuronal cells migrate through the established neuronal lamina and settle onto the outermost layer, forming an "inside-out" gradient of maturation. The process of neuronal cell migration is highly sensitive to various physical, chemical and biological agents as well as to genetic mutations. Disturbance of neuronal migrating pathway (radial glial fiber) or extracellular factors or correct settling of Cajal-Retzius cells is considered for all types of neuronal migration. Arrested or excessive migration will lead neurons to differentiate in a hetertopic position. Such neuronal migration disorder is believed as major cause of both gross brain malformation and more special cerebral structural and functional abnormalities in experimental animals and humans. An increasing number of instructive studies on nongenetic models (e.g. MAM-or irradiation-treated rodents) and mutations (e.g. reelin-or tish-mutant animals) have established the foundation of cortex formation and provided a framework in which to understand the cerebral cortex development. These experimental analysis and genetic manipulation

have come to together to begin providing detailed explanation for the pathogenesis of several the human phenotypes resulting from abnormal neuronal migration. Linking the known genes into pathways from extracellular signaling to cytoskeletal dynamics will be important for a complete understanding of the processes involved. Finding additional molecules in these pathways along with defining the genetic defects in other families and other syndromes will also provide deeper insights into the genetic and molecular mechanisms underlying normal and abnormal neuronal migration.

ACKNOWLEDGEMENTS

The authors would like to thank Ms. Kiyoko Suzuki and Ms. Yasuko Koto of Environmental and Toxicological Sciences Research Group, National Institute of Radiological Sciences for kind help in retrieval of scientific references for this review.

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