

Review Article

LIS1 and DCX: Implications for Brain Development and Human Disease in Relation to Microtubules

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Proper lamination of the cerebral cortex requires the orchestrated motility of neurons from their place of birth to their final destination. Improper neuronal migration may result in a wide range of diseases, including brain malformations, such as lissencephaly, mental retardation, schizophrenia, and autism. Ours and other studies have implicated that microtubules and microtubule-associated proteins play an important role in the regulation of neuronal polarization and neuronal migration. Here, we will review normal processes of brain development and neuronal migration, describe neuronal migration diseases, and will focus on the microtubule-associated functions of LIS1 and DCX, which participate in the regulation of neuronal migration and are involved in the human developmental brain disease, lissencephaly.

1. Introduction

Defined cell polarization is the key for the function of multiple cell types in the body, for example, the gut epithelium and the neuroepithelium, which both display an apicobasal orientation. Neurons, which part of them are generated from neuroepithelial cells, are also highly polarized cells with two distinct main structures that emerge from the cell body: usually a thin single axon, which is the key for signal transmission, and multiple shorter dendrites, which are designed for signal reception. The basic polarity of neurons was first recognized by Ramon y Cajal, who studied and described the morphology of neurons more than one hundred years ago [1]. In the cerebral cortex, two major types of neurons were defined: the excitatory or the glutamnergic neurons which compose the majority of the neurons in the cerebral cortex, and the inhibitory or the GABAergic interneurons composing the minority of the neurons. These two types of neurons are born in physically distinct areas of the brain, therefore, they need to migrate, sometimes very long distances, to reach their final destinations (reviews [2–6]). Genetic mutations, which affect polarity regulation and processes of neuronal migration in the developing brain, result in a wide array of human diseases. The range of diseases includes on the more severe end brain

malformations, such as the lissencephaly-pachygyria spectrum, which defines the variety of diseases that cause relative smoothness of the brain surface and includes lissencephaly (smooth brain surface), agyria (no gyri), and pachygyria (broad gyri). In other cases, the brain surface may appear normal, but neurons can be mislocalized, which will be defined as cortical dysplasia. The position and the extent of the heterotropic neurons will further define the type of the brain malformation, for example; periventricular heterotopia (close to the ventricle), subependymal heterotopia (beneath the ependyma), subcortical heterotopia, or band heterotopia (neurons located in the white matter beneath the cortex as focal concentrations or a band) (reviews [7–13]). Patients with brain malformations will usually exhibit developmental delay, epilepsy, seizures, and intellectual disability depending on the severity of the brain malformation. These conditions usually can be diagnosed using brain imaging such as MRI (magnetic resonance imaging). However, neuronal migration diseases are not always detected by current noninvasive imaging techniques. Microscopic malpositioning of neurons could have been detected in many cases of childhood epilepsy following surgical procedures [14, 15]. Neuronal polarity and neuronal migration abnormalities are among the most common underlying primary defects in many cases of mental

retardation or intellectual disability [16, 17]. Furthermore, autism and schizophrenia are also part of the spectrum of diseases involving neuronal polarity and neuronal migration regulation [18–21]. The prevalence of either mental retardation or schizophrenia is estimated to be about 1% of the population; the burden on society is huge since the patients live with the impairment over decades. Collectively, it can be appreciated that the wide range of neuronal polarity and neuronal migration diseases significantly impacts our society. Therefore, the understanding of the molecular mechanisms involved in these diseases, which also may affect therapeutic strategies, is of wide public interest.

Here, we will review the normal process of neuronal cell birth and migration, then will highlight the role of microtubules in this process, and will describe what happens when things go awry with special emphasis on the microtubule-associated functions of LIS1 and DCX.

2. Birth of Neurons of the Cerebral Cortex

The majority of neurons in the cerebral cortex, the pyramidal or the excitatory neurons, are born either within the ventricular zone or the subventricular zone (reviews [22–26]). During early development, neuroepithelial cells proliferate mainly to generate additional progenitors (reviewed [22, 26]). Later, two types of progenitors in the ventricular zone are defined; most of them are the radial glial cells that span the entire neocortical wall and maintain contact both at the ventricular and pial surfaces throughout mitotic division, and the minority of them are the short neural precursors that possess a ventricular endfoot and a basal process of variable length that is retracted during mitotic division [27, 28] (Figure 1). The radial glia is the major population of neural progenitor cells occupying the proliferative ventricular zone in the developing mammalian neocortex [29–31]. Radial glia cells serve as progenitors in all regions of the central nervous system [32]. Radial glia cells exhibit typical interkinetic nuclear migration, where the nucleus moves within the cytoplasm of elongated neuroepithelial progenitor cells in synchronization with the cell cycle phase [33, 34] (review [35]). The nucleus ascends to the upper region of the proliferative zone, the ventricular zone, during S phase and later descends to the apical part of the ventricular zone (Figure 2). Mitosis is restricted to the most apical regions of the ventricular zone after the nucleus completed its descent. The variable positioning of the nucleus within the ventricular zone is the basis for the pseudostratified appearance of the progenitor-cell layer known as the ventricular zone (Figure 2).

The radial glia precursor stem cells undergo symmetric and asymmetric divisions while producing large numbers of diverse cortical cell types. However, the relative orientation of the cleavage plane does not define whether the divisions are symmetric or asymmetric [36, 37], but rather the relative inheritance of the apical plasma membrane dictates whether the daughter cell fate will be symmetric or asymmetric [38–42]. Asymmetric divisions will result in self-renewal of the progenitors, but will also produce more committed daughter cells, intermediate progenitor cells (also known as

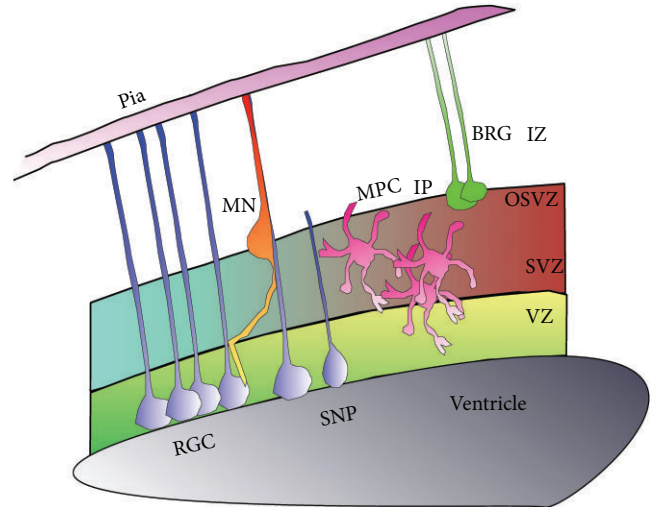


FIGURE 1: Schematic presentation of progenitors in the developing cerebral cortex. Radial glia cells (RGCs) extend their processes from the ventricular zone (VZ) to the pial surface. These cells proliferate in a symmetrical fashion to produce additional RGC or asymmetrically to produce a progenitor and a multipolar cell (MPC), which may be either a postmitotic neuron or an intermediate progenitor (IP), which can further divide in the subventricular zone. The VZ contains additional short neuronal progenitors (SNP). In the SVZ and the outer SVZ (OSVZ), an additional type of progenitors was described, basal radial glia (BRG), which lack the connection to the ventricle. A bipolar migrating neuron (MN) is moving towards the intermediate zone (IZ).

basal progenitors), outer subventricular zone progenitors, or postmitotic neurons [43] (review [24]). During development, there is a gradual shift from proliferative divisions to neurogenic divisions. This has been accompanied with progressive lengthening of the cell cycle [44]. Further studies indicated that artificial lengthening of the cell cycle can be sufficient to switch neuroepithelial cells from proliferative to neurogenic divisions [45, 46].

The second proliferative area for excitatory neurons of the cerebral cortex is the subventricular zone. Within this area, progenitors usually divide in a symmetrical way, and in contrast with the radial glia, their processes do not make contact with the apical or pial surfaces. These intermediate or basal progenitors are daughter cells of either neuroepithelial or radial glial cells located in the ventricular zone [43, 47–49] (reviews [22, 24, 50]). Mitotic intermediate progenitor cells are largely found in the subventricular zone, but it should be noted that they can also undergo division in the ventricular zone and the intermediate zone [51, 52]. Typical intermediate progenitors in the developing neocortex usually undergo one terminal symmetric division that produces two neurons, while some cells undergo two rounds of symmetric divisions (Figure 1).

In primates and humans, the subventricular zone is widely expanded and they develop an additional proliferative region known as the outer subventricular zone [53–55]. Cell-labeling studies in primates have shown that cell divisions in both the outer subventricular zone and the ventricular zone

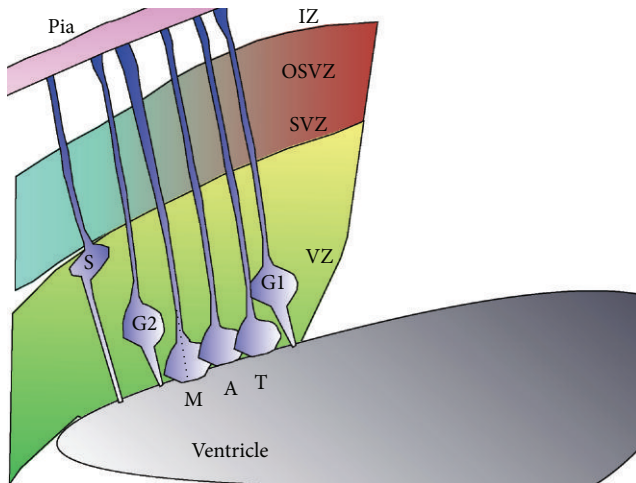


FIGURE 2: Schematic presentation of interkinetic nuclear movements in the ventricular zone (VZ). Nuclei of RGC are found at the upper surface of the VZ during S phase (S). The nuclei of the cells undergoing mitosis (M phase) are located close to the ventricle, where they complete anaphase (A) and telophase (T). Nuclei in G1 and G2 phases are found in intermediate positions.

coincide with the major wave of cortical neurogenesis, suggesting that outer subventricular zone cells produce neurons [56, 57]. The outer subventricular zone was found to contain two types of progenitors: radial glia-like cells and intermediate progenitor cells [58, 59]. The outer subventricular zone radial glia-like cells have a long basal process; however, the contact with the ventricular surface is lacking. These cells undergo proliferative divisions and self-renewing asymmetric divisions to generate neuronal progenitor cells that can proliferate further and can also generate neurons. Initially it was thought that these cells exist only in primates, but similar progenitors have also been observed in nonprimates, such as ferrets [59] and mice [40, 60].

The inhibitory neurons, or the GABAergic neurons, are born in a different position than that of the excitatory neurons. Most of the GABAergic neurons are born in the ventral part of the telencephalon, in the subpallium [61] (for reviews see [62–64]). More specifically, the medial ganglionic eminence (MGE) and the caudal aspect of the lateral ganglionic eminence (cLGE) (also known as the dorsal aspect of the caudal ganglionic eminence (dCGE)) generate most of the cortical GABAergic interneurons [65]. However, additional sources of cortical GABAergic interneurons are the rostral LGE, the subpallial septum, and the embryonic preoptic area (POA) [66–68] (Figure 3). Radial glia cells are progenitors for inhibitory neurons as well as for excitatory neurons [32] (for reviews see [69–71]). These progenitors not only share structural similarities, but the ventral progenitors in the MGE were shown to also undergo asymmetric cell divisions to produce neocortical interneurons [72]. Furthermore, neocortical inhibitory interneurons were produced as spatially organized clonal units in the developing ventral telencephalon. However, although the radial glia cells in different areas of the cerebral cortex appear morphologically similar, they do not

share the same molecular identity. Radial glia cells in the ventricular zone of the telencephalon express the transcription factors Pax6 and Emx1 [73, 74]. In their absence, the cells convert their fate to that of ventral telencephalon cells [75]. Radial glial cell in the ventral telencephalon express different sets of transcription factor genes, for example, Gsx1/Gsx2 and Olig2 [73, 76, 77]. In addition to proliferating radial glial cells, the ventral telencephalon contains multiple intermediate progenitors, which divide symmetrically to produce interneurons [76, 78]. These proliferating progenitors are an important source of the interneurons since the subventricular zone in the ventral telencephalon is larger than that in the neocortex.

3. Migration of Neurons of the Cerebral Cortex

As mentioned above, neurons are usually born in a position, which differs from their terminal destination. Thus, neurons need to migrate from their place of birth to their final position using several types of cellular motility (reviewed [2, 4, 6, 79–82]). The position of neurons within defined layers of the cerebral cortex is dependent upon their birth date and their proper movement from their place of birth to their accurate placement. The six layers of the cerebral cortex are composed of neurons that are born in different areas but are subsequently organized according to their birth dates [83, 84]. Interestingly, this organization is not unique to excitatory neurons. Many interneurons and excitatory neurons that are born at a similar time end up occupying the same neocortical layer; however, little is known how this amazing coordination is achieved [85–88] (review [69]). Neurons born relatively late during corticogenesis reside in more superficial layers on top of the older neurons, thus composing an inside-out organization. Early in development, these cells usually move using cellular locomotion. Later, neurons migrating along this route attach to radial glia, which provide a transient scaffold for directed migration [2–4, 89, 90]. Neurons migrating along radial glia exhibit a bipolar structure. Once these cells reach the pial surface or their correct position, they detach from the radial glia and continue to move towards their correct laminar position. A different mode of migration, known as tangential migration, is employed by the interneurons, which migrate tangentially across the plane of the glial fiber system [2, 4, 80, 85, 91]. Once they reach the cerebral cortex, they employ the radial route and migrate along radial glia to their proper laminar position [66, 92–100] (routes of migration are schematically shown in Figure 3). Thus, even if only the radial route of migration is disrupted, the position of inhibitory neurons in the cerebral cortex will be affected, since they use both the tangential and the radial route.

Newly formed neurons in the ventricular zone undergo an initial morphological transition to a pin-like structure following their final mitoses [101]. These cells are still lacking a leading edge, and their centrosomes are localized towards the ventricular endfoot. The ventricular endfoot is then retracted, and the cells adopt a multipolar structure where cells extend neurites in multiple directions. Live imaging of

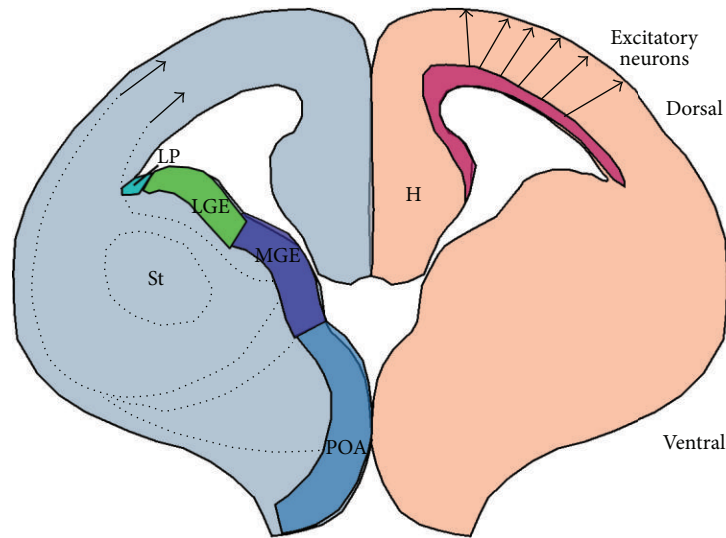


FIGURE 3: Schematic presentation of migratory routes of excitatory and inhibitory neurons in the developing brain (adapted from a review by Tan and Shi, *WIREs Dev Biol* 2012. doi: 10.1002/wdev.88). Inhibitory neurons are shown in the left side. Most of the GABAergic neurons are born in the ventral part of the telencephalon, in the subpallium, and more specifically in the medial ganglionic eminence (MGE) and the lateral ganglionic eminence (LGE), in the subpallial septum, and the embryonic preoptic area (POA), and they migrate in a tangential way to the cortex. St: striatum; LP: lateral pallium; H: hippocampus.

in utero transfected cells reveals that each of the radially migrating neurons undergoes this complex morphological transition [4, 102, 103]. It has become apparent that this transient morphology is particularly sensitive to genetic manipulations, as knockdown of several genes resulted in accumulation of stalled neurons with multipolar morphology (reviews [104, 105]). The multipolar stage is transient and is followed by acquisition of bipolar morphology [43]. Neurons redefine their polarization; they first extend an axon, which will be the future trailing edge, orient the centrosome in front of the nucleus, and generate a leading edge, which has some characteristics of a dendrite [106]. In radially migrating cerebral neurons, the centrosome moves in a very processive manner, whereas the nucleus, which composes most of the cell body, follows this movement in a stepwise manner [107–110]. Failure to translocate the nucleus will translate to abnormal migration and will affect the proper laminar organization of the developing cortex. Thus, during the normal course of migration, the cells will change their morphology to a bipolar one and continue to migrate along radial glia in an ordered fashion (Figure 1). Therefore, acquisition of polarity is imperative both for initiation and continuity of directed motility of neurons to their targets.

4. Neuronal Microtubules and the Centrosome

The morphological changes that take place in migrating neurons require coordinated regulation of the cytoskeleton (review [18]). We will focus on the microtubules, which are key components of the neuronal cytoskeleton. Microtubules are long cellular polymers composed of subunits of alpha- and beta-tubulin. They exhibit dynamic instability, which can be visualized both *in vitro* [111, 112] and *in vivo* [113–115]. Microtubules exhibit an inherent polarity, where tubulin

subunits are preferentially added to the plus ends. The microtubule cytoskeleton participates in structuring of the cell and provides directional rails for transport of intracellular organelles and different cargoes (review [116]). In neuronal progenitors and in early born neurons, most of the microtubules emanate from the microtubule organization center, the centrosome, and its proper function and intracellular localization are believed to be of great importance both in proliferating and migrating cells (reviews [18, 35, 81, 105, 117, 118]).

In polarizing neurons, it has been proposed that the position of the centrosome may predict the location of the future axon [119, 120]. However, this notion has been questioned following several findings. In neurons from the tegmental hindbrain nuclei in zebrafish, axon outgrowth occurs at clear distance from the centrosome [121]. Probably, an earlier cue for polarization is the relative position of N-cadherin. Endogenous N-cadherin was found to localize to one pole of the newborn neuron, from where the first neurite will emerge [122]. The Golgi and centrosome move towards this newly formed morphological pole in a second step, which is regulated by PI3K (phosphoinositide 3-kinase) and the actin/microtubule cytoskeleton.

In mature neurons, the proportion of acentrosomal microtubules is significantly higher (review [117]). In contrast with migrating neurons, the axons of mature neurons contain microtubules that form a continuous array, extending from the cell body into the growth cone at its distal tip (comprehensive review [123]). It has been shown that the centrosome loses its function as a microtubule-organizing center in developing hippocampal neurons [124]. Most importantly, microtubule arrays in mature neurons are highly organized in regard to their intrinsic polarity. Early studies have determined the orientation of microtubules in mature neurons by electron microscopy-based techniques [125].

Most of the microtubules in the axon are oriented with their plus-ends facing the growth cone, while in the dendrites the microtubules are oriented in both directions. Thin and distal dendrites exhibit unipolar microtubule orientation similar to the axonal ones (review [116]). Live imaging using a fluorescently tagged plus-end tracking protein (EB3-GFP) confirmed these findings and enhanced the capability to rapidly evaluate the orientation of growing microtubules in culture and *in vivo* [126].

5. Neuronal Migration and Brain Developmental Deficits in Humans

Deficits in neuronal migration in humans have provided us with insights on the regulatory mechanisms involved in this process. Abnormal neuronal migration may result in cortical malformations, and in extreme cases, the brain is smooth (lissencephalic) lacking most of the normal typical brain convolutions. Lissencephaly (i.e., smooth brain) is a severe human neuronal migration disorder (review [127]). Based on brain histology; two types of lissencephaly were defined: type I or classical lissencephaly and type II or cobblestone lissencephaly [128]. Whereas in type I the cerebral cortex consists of four layers, in type II no discrete layers are formed. Moreover, in type II lissencephaly, the manifestation of the phenotype including the cerebellum and the brainstem as well as other organs, such as eyes and muscles, has been noted [129]. Disorganization of the cortical layers reflects mainly migration deficits in excitatory neurons. Yet it should be noted that the migration of inhibitory neurons is also diminished [130]. Imbalances between excitatory neurons and inhibitory neurons are one of the underlying causes of epilepsy. Therefore, it is not surprising that epilepsy is a common feature among lissencephalic patients [131].

Mutations in several genes have been associated with type I lissencephaly, among them *lissencephaly-1 (LIS1)* [132], the X-linked gene *doublecortin (DCX)* [133, 134], and *tubulin alpha 1A (TUBA1A)* [135–137]. The phenotype is characterized by absent (agyria) or decreased (pachygyria) convolutions, producing a smooth cerebral surface with thickened cortex [138]. Some differences were noted in cases of lissencephaly due to mutations in *LIS1* versus mutations in *DCX*. In case of *LIS1* mutations, the brain is more affected in the dorsal portion of the brain, whereas *DCX* mutations affect the more rostral part [139, 140]. Furthermore, a limited study of two fetal brains, one mutated in *LIS1* and the other mutated in *DCX*, revealed differences in the histology [141]. In the *LIS1* mutated brain, the cortical ribbon (the grey matter) displayed a characteristic inverted organization, also called “four-layered cortex”, while in the *DCX* mutated brain, the cortex displayed a roughly ordered “six-layered” lamination. It was suggested that additional studies, especially of *DCX* mutant, brains may help to clarify this issue. Subcortical band heterotopia (SBH) is a related disorder in which there are bilateral bands of gray matter interposed in the white matter between the cortex and the lateral ventricles. SBH (double cortex) is very common among females with mutations in *DCX* [133, 134]. SBH can also be observed in cases of somatic or mild mutations in *LIS1* [142, 143]. Lissencephaly and SBH

have been observed in different regions of the same brain, defining an “agyria-pachygyria-band” spectrum [140]. Mutations in *TUBB2B* have been associated with a different brain malformation, asymmetrical bilateral polymicrogyria [144]. Polymicrogyria is characterized by a disorganized cortical lamination and the presence of multiple small, partially fused gyri separated by shallow sulci that produce an irregular cortical surface [145]. A partial duplication of *LIS1* has been detected in a patient with microcephaly (reduced brain size), neurodevelopmental delays, and profound white matter atrophy in the absence of lissencephaly [146]. All of the protein products of the genes mentioned above, tubulin, *LIS1*, and *DCX* are involved in formation and regulation of microtubules, which play an important role in the developing brain.

Less noticeable deficits in neuronal migration are responsible for a significant proportion of cases of mental retardation and epilepsy in children [8, 14, 147]. Furthermore, it is proposed that abnormal neuronal migration also plays a role in schizophrenia and autism spectrum disorders (ASDs) (reviews [148–150]). Thus, there are multiple examples indicating a strong link between intellectual disability and abnormalities in neuronal migration [2, 105]. *MARK1/Par1* has been proposed as a susceptibility gene for autism [151]. MARK (microtubule-associated protein/microtubule affinity-regulating kinase) composes a small family of proteins [152], which were first identified to regulate the dynamics of microtubules [153, 154]. Increased dosage of *LIS1* also impairs processes of normal brain development and results in delayed development, mental retardation, and autism [155–157]. One of the reported patients with increased *LIS1* dosage exhibited epileptic seizures, which fitted the diagnosis of classical West syndrome [131].

In addition, microdeletions of a region encompassing the *MAPT* (microtubule-associated protein tau) gene, encoding for the tau protein, result in moderate mental retardation with associated dysmorphic features [158–162]. The frequency of the microdeletion syndrome was estimated to be 1:13,000 to 1:20,000, thus suggesting it to be a common underlying cause for mental retardation. *MAPT* is one of the few genes within the microdeletion locus; it is strongly expressed in the developing brain [163, 164], and it has been suggested to play a role in neuronal migration. Tau is a well-studied, brain enriched, microtubule-associated protein, which was initially identified by virtue of its capability to enhance microtubule polymerization *in vitro* [165, 166]. Tight regulation of the dynamic instability of microtubules allowing for rapid transition between the growing and shrinking phases is essential for proper neuronal migration. Furthermore, it should be noted that regulation of proper microtubule dynamics and axonal transport plays an important role in multiple neurodegenerative diseases; this topic has been extensively reviewed and is not the focus of this current review (e.g., [123, 167–174]).

6. LIS1 and DCX: Microtubules and Cellular Polarity

A tight relationship between *LIS1*, microtubule regulation, and microtubule-based motor proteins has been demonstrated in many organisms. The first functional insights on

LIS1 and their role in regulation of microtubules and microtubule-based motors came from studies conducted in a fungus, *Aspergillus nidulans*, during a screen conducted by the Morris lab. Fungi mutated in LIS1, designated in *Aspergillus nidulans* as nudF (nuclear distribution gene F) exhibited impairments in the ability to move nuclei along microtubules in the growing hyphae. Interestingly, a mutation in the alpha-tubulin gene suppressed mutations in nudA (dynein heavy chain), nudC (LIS1 interacting protein), nudG (dynein light intermediate chain) and nudF [175]. We have shown that LIS1 interacts with tubulin and modulates microtubule dynamics *in vitro* [176], suggesting an evolutionary conserved LIS1 function. The role of LIS1 in preserving the normal microtubule network organization *in vivo* has been shown both in mammalian cells [177–179] and in cells of the simple organism *Dictyostelium* [180]. LIS1-microtubule interaction and probably other LIS1 interactions are regulated by phosphorylation [181]. In addition to a direct role for LIS1 in regulating tubulin dynamics, LIS1 interacts with a plethora of microtubule-associated proteins (MAPs). This includes interactions with DCX [182], CLIP-170 [183], and MAP1b [184]. Furthermore, LIS1 may affect actin polymerization through Cdc42 and IQGAP [185, 186].

An evolutionary conserved function of LIS1 in regulation of cytoplasmic dynein was first noted in the fungus, *Aspergillus nidulans*. Three of the *Aspergillus nidulans* nud genes (nudA, nudI, and nudG) are subunits of cytoplasmic dynein, a microtubule-based motor protein, and a fourth gene, nudK, is a part of the dynein regulatory complex dynactin [187–189]. Genetic interaction of LIS1 with dynein/dynactin/microtubule-mediated pathway has also been suggested from work on early development in *Drosophila* [190–192], demonstrating that LIS1, like dynein heavy chain, is essential for germ-line division, nuclear positioning, and oocyte differentiation. Moreover, also in *Saccharomyces cerevisiae*, the LIS1 ortholog was found to be involved in nuclear migration [193], which is mediated by microtubules and regulated by the dynein pathway [194]. The evolutionary conservation of LIS1 with the dynein pathway has been extended to mammals, where it interacts with several subunits of the retrograde, microtubule-based motor complex dynein/dynactin [177, 178, 195, 196]. It regulates cytoplasmic dynein activity [177] and participates in several dynein-mediated activities, such as intracellular transport [197, 198], organization of intracellular organelles [199–201], and mitosis [195, 202–204].

In contrast to other known proteins interacting with dynein, LIS1 binds to dynein motor domain [205] (review [206]). LIS1 was found to strengthen the dynein-microtubule interaction [205, 207] (reviewed in [208]). In addition, it has been proposed that LIS1 may have a role in initiating dynein-driven motility [209]. Single-molecule laser bead trap analysis revealed that LIS1 substantially prolonged dynein stalls under load [207]. With LIS1 bound, dynein is arrested in a strongly microtubule-bound state, although ATP hydrolysis can still go on [205].

LIS1 and cytoplasmic dynein play an important role in the regulation of the polarity of microtubules. As mentioned above, axonal microtubules are normally oriented uniformly

plus-end-distal; however, without dynein or LIS1, axons contained both plus- and minus-end-distal microtubules [210]. Probably this mixed polarity of the microtubules allowed for the entry of dendritic organelles and proteins to the axon [210].

LIS1 itself has been shown to be a cargo for the anterograde motor Kinesin-1 [211, 212]. Kinesin-1 interacted with the NUDEL (nuclear distribution protein nudE-like 1)/LIS1/14-3-3epsilon complex through DISC1 (disrupted in schizophrenia 1), and interference with the complex affected protein localization and axonal outgrowth.

DCX was characterized as a microtubule-associated protein (MAP) [213–215] shortly following its discovery as a gene mutated in cases of X-linked lissencephaly [133, 134]. DCX promotes nucleation and the assembly, and stability of 13-prot filament microtubules [216, 217]. DCX interacts with the sides of the lattice of microtubules and stabilizes the 13-prot filament structure through a cooperative interaction, wherein DCX molecules decrease the dissociation rate of their neighbors [218]. DCX is part of a small superfamily of proteins, characterized by the existence of one or two conserved DCX domains [219, 220]. Interestingly, most mutations that are found in lissencephaly patients cluster in the well-defined DCX domains [221, 222]. We have shown a physical interaction between LIS1 and DCX, and *in vitro* both proteins enhance tubulin polymerization in an additive manner [182]. A genetic interaction between LIS1, DCX, and cytoplasmic dynein has also been suggested [223]. DCX is also involved in the regulation of the actin cytoskeleton, in a direct and indirect way [224–226]. Additional interactions have been observed between DCX and mu subunits of clathrin adaptor complexes [227]. In developing cultured neurons, DCX modulated endocytosis and thereby the surface distribution of neurofascin. Interestingly, this activity has been shown to be independent of DCX's interaction with the microtubules [228].

The interaction between DCX and microtubules is regulated, at least in part, by phosphorylation. DCX is phosphorylated by at least four different kinases: JNK [229], Cdk5 [230, 231], protein kinase A (PKA) and/or the MARK/PAR-1 family of protein kinases [232], and GSK3 β [233]. Protein phosphatase 1 (PP1) has been shown to dephosphorylate some of the sites [234, 235]. *In vitro* analysis indicated that DCX's phosphorylation by Cdk5, PKA, and MARK reduced the affinity of DCX to microtubules [230, 232]. Phosphorylation of DCX by different kinases yielded different outputs; Cdk5-mediated phosphorylation inhibited the ability of DCX to promote microtubule bundling and suppressed axon branching [230, 234], while GSK3 β -induced phosphorylation of DCX promoted the function of DCX in the regulation of axon branching and self-contact [233]. The effect of DCX on branching may be associated also with its interaction with the actin cytoskeleton. DCX depletion significantly delayed collateral branching in hippocampal neurons and also significantly lowered the frequency of actin-rich patches along hippocampal axons [236]. DCX not only affects the development of the axon but also the dendritic arborization [237].

Microtubules stabilized by DCX are preferred substrates for kinesins [238]. Furthermore, DCX has been recently found to associate with a member of the kinesin superfamily, namely Kif1a, which is a Kinesin-3 molecular motor protein that traffics synaptic vesicles [239]. Neurons lacking *Dcx* and/or its closed family member, *doublecortin-like kinase 1* (*Dclk1*), showed impaired Kif1a-mediated transport of Vamp2, a cargo of Kif1a [239]. The same study demonstrated that DCX specifically enhanced binding of the ADP-bound Kif1a motor domain to microtubules.

7. The Roles of LIS1 and DCX in Processes of Brain Development

7.1. Neurogenesis in the Developing Brain. LIS1 levels affect cell proliferation in the developing brain at multiple stages [108, 155, 240–245]. Neuronal progenitors knocked down for LIS1 failed to proliferate [108]. In addition, mosaic analysis demonstrated the requirement of LIS1 for the proliferation of all neuronal lineages and astrocytes [246]. At the initiation of mitosis, *Lis1*^{+/-} neuroblasts exhibited impaired prophase nuclear envelope invagination. This process, which occurs at prophase, is dynein-dependent and facilitates nuclear envelope breakdown [245]. Abnormal interkinetic motility was observed in knockdown, knockout, and increased dosage of LIS1 [108, 155, 241]. LIS1 was found to be essential for precise control of mitotic spindle orientation in both neuroepithelial stem cells and radial glial progenitor cells [247]. Conditional gene knockout of *Lis1*, specifically in neuroepithelial stem cells, resulted in rapid motility of the spindle followed by cell death. Radial glial progenitors were somewhat less affected [247]. Proliferating cells in the ventricular zone with increased LIS1 dosage lost most of their polarity markers and exhibited abnormal adherens junctions [155]. LIS1 genetically interacts with Ndel in proliferating cells in the ventricular zone; mice with an allelic series of *Lis1* and *Ndel* double mutations displayed a striking dose-dependent size reduction and delamination of the cerebral cortex [248].

DCX participates in the regulation of proliferating neurons in the developing brain in coordination with LIS1. *Dcx*^{-/-} radial glia cells displayed spindle orientation abnormalities similar to *Lis1*^{+/-} cells that in turn lead to moderate proliferation defects both *in vivo* and *in vitro*. Thus, a functional genetic interaction of the two genes has been demonstrated *in vivo*, where the combined effects of *Lis1* haploinsufficiency and *Dcx* knockout leading to more severe neuronal migration and proliferation phenotypes compared with the single mutants, resulting in cortical disorganization and depletion of the progenitor pool [241]. These results were also confirmed when gene expression was examined. Differential expression analysis indicated that LIS1 and DCX mutants at E14 displayed a repression for cell-cycle processes and networks, while in wild-type embryos these processes are activated [240].

7.2. Neuronal Migration in the Developing Brain. Multiple evidence link LIS1 to the regulation of neuronal migration in the developing brain. Abnormal radial migration was noted

in an hypomorph allele of *Lis1* (*Lis1/sLis1*) [249], in *Lis1*^{-/+} [250], as well as with further reduction of LIS1 using a floxed allele [250], or by knockdown of the gene using *in utero* electroporation [107, 108, 251]. Mosaic analysis also led to the conclusion that LIS1 regulates the migration efficiency in a cell-autonomous manner [246]. In migrating neurons with reduced LIS1 levels, the centrosome and the nucleus were less tightly coupled [223, 251]. *Lis1* shRNA inhibited somal movement but not process extension [107]. In radially migrating granule cells in mouse cerebellar slices, LIS1 inhibition resulted in slightly different effects; it specifically blocked nuclear migration without affecting the coupling of the centrosome and microtubules in the leading process [252]. LIS1 also affects the migration of inhibitory neurons. It was demonstrated that LIS1 is required for proper tangential migration in *Lis1*^{-/+} [253] and also in case of increased LIS1 dosage [155]. The effects of LIS1 mutation are not limited to the cortex. Abnormal tangential migration was noted in a subset of neurons in the spinal cord [254].

The neuronal migration phenotype was not so obvious in case of *Dcx* mutant mice [255]. Mutant mice showed neocortical lamination that was largely indistinguishable from wild type. Nevertheless, the hippocampus of both heterozygous females and hemizygous males shows disrupted lamination that is most severe in the CA3 region. It has been speculated that the relatively mild phenotype may be due to genetic compensation (review [256]). Supporting this notion, knockdown of *Dcx* using *in utero* electroporation inhibited migration of cortical excitatory neurons both in rat and in mouse brains [4, 54]. Using the same system, it was also possible to demonstrate the genetic interactions between DCX and one of its phosphorylating kinases, MARK2/Par-1 [110]. It is postulated that whereas in case of the knockout there is plenty of time for developmental redundancy mechanisms to become operative, the knockdown involves an acute gene reduction, which may not allow sufficient time for redundancy mechanisms to evolve. This notion received additional support following findings that the knockout of *Dclk1* did not result in an observable phenotype in the migration of pyramidal neurons in the developing brain [39, 55]. Similar to *Dcx*, the knockdown of *Dclk1* impaired the migration of pyramidal neurons [55]. Nevertheless, the double knockout of *Dcx* and *Dclk1* had a clear effect on cortical development. More specifically, the double mutant mice demonstrated perinatal lethality, disorganized neocortical layering, and profound cytoarchitectural defects of the hippocampus caused by the disruption of radial neuronal migration. The possibility of gene redundancy was investigated in *Dcx* mutant mice, where the expression of transcripts and proteins, which are products of the *Dclk1* and *Dclk2* gene, was analyzed [46]. A minor change in the expression of one of the DCLK1 proteins was detected in this study. In addition, more severe phenotypes were noted in the combination of mutant alleles for *Dcx* and *Dclk2* [47]. In particular, in the absence of *Dcx* and *Dclk2*, there was a dosage-dependent phenotype in the hippocampus, where hippocampal lamination was disrupted and it was accompanied with simplification of pyramidal dendritic arborizations. Studies in primary hippocampal

neurons revealed that DCX supported the development of dendritic arbors [237].

Dcx knockout had a more pronounced effect on the migration of interneurons. Branching and nucleokinesis problems were observed in interneurons derived from *Dcx* mutant mouse brains [257]. *In utero* electroporation of *Dcx* shRNA impaired tangential migration [258]. In addition, these type of experiments also indicated the LIS1 and DCX work in the same genetic pathway in inhibitory neurons migrating through the lateral cortical stream, which supplies neurons to structures in the ventral telencephalon including the amygdala and piriform cortex [259]. DCX also plays an important role in migration of neurons in the adult mouse to the olfactory bulb using the rostral migratory stream [56]. *Dcx* RNAi reduced SVZ cell migration *in vitro*, both cell autonomously and noncell autonomously [260].

7.3. Postnatal Effects. The effects of LIS1 mutations are not confined to embryonic stages. *Lis1* mutant mice develop spontaneous seizures and enhanced excitation [261]. Several abnormalities were noted in the hippocampus: abnormal inhibitory inputs [262] and dysfunctional synaptic integration of granule cells generated in the developing and adult dentate gyrus [263]. In addition, postnatally the *Lis1/sLis1* mutant mouse exhibited alterations of the inhibitory synaptic responses recorded from cortical pyramidal neurons [264]. LIS1 has been shown to be critical for determining the synaptic distribution on interneuron dendrites [265]. Therefore, it is possible to speculate that in addition to migration deficits, LIS1-dependent regulation of synaptic mobility may promote epilepsy by disrupting excitatory inputs onto GABAergic interneurons.

The lamination defects in the hippocampus of *Dcx* mutant mice result in the development of epilepsy in these animals [266–268]. Furthermore, also *in utero* electroporation of *Dcx* shRNA revealed abnormalities in the hippocampal network [269] and spontaneous epileptic seizures [270].

7.4. Possible Reversal of the Developmental Phenotype. LIS1 protein degradation was shown to be mediated, at least in part, by the protein protease, calpain [271]. Therefore, the possibility that interference with this pathway may relieve at least part of the phenotype was tested [271, 272] (review [273]). Treatment with calpain inhibitors or knockdown of calpain expression by siRNA improved the abnormal cellular phenotype caused by heterozygous loss of *Lis1* in cell culture. Calpain inhibitors were also administered to pregnant *Lis1*^{+/-} mice during embryonic corticogenesis. Remarkably, both inhibition by drugs or knockdown of calpain *in vivo* rescued defective neuronal migration and abnormal cortical and hippocampal layering in heterozygous mutant pups born to treated mothers. Furthermore, these mutant pups also exhibited improved motor function. The therapeutic potential of a calpain inhibitor was also tested on postnatal lissencephalic cells [274]. Interestingly, application of the calpain inhibitor restored spontaneous and miniature EPSC (excitatory postsynaptic current) frequencies to wild-type levels without affecting inhibitory postsynaptic synaptic

current. However, western blot analysis of protein expression, including proteins involved in excitatory synaptic transmission, demonstrated that the cleavage of the calpain substrate alpha II-spectrin was blocked, but the levels of the LIS1 protein were not restored, suggesting the possibility that the rescue was through an indirect route, which did not involve LIS1 levels.

Delayed reexpression of *Dcx* in already formed SBH after birth led to SBH regression [275] (review [273]). Moreover, the reexpression of *Dcx* corrected the sensitivity to convulsant-inducing drugs. Reduction of the SBH demonstrated a restricted time window and was limited to early postnatal ages. An additional avenue, which was not investigated at the postnatal stage, was the demonstrated genetic interaction between DCX and Par-1/MARK2. The combined knockdown of Par-1/MARK2 and DCX significantly rescued the neuronal migration deficit and the subcellular processivity of centrosomal motility [110]. Therefore, the above-mentioned studies raise the possibility that neuronal migration disorders may be eventually treatable by molecular or pharmacological interventions.

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