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Review

Lissencephaly: Mechanistic insights from animal models and potential therapeutic strategies

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ABSTRACT

Lissencephaly is a severe human neuronal migration defect characterized by a smooth cerebral surface, mental retardation and seizures. The two most common genes mutated in patients with lissencephaly are *LIS1* and *DCX*. *LIS1* was the first gene cloned that was important for neuronal migration in any organism, and heterozygous mutations or deletions of *LIS1* are found in the majority of patients with lissencephaly, while *DCX* mutations were found in males with X-linked lissencephaly. In this review, we will discuss how an understanding of the molecular and cellular pathways disrupted in model organisms with *Lis1* and *Dcx* mutations or knock-down not only provide insights into the normal processes of neuronal migration, including neurogenesis, but they also may lead to potential novel therapeutic strategies for these severe cortical malformations.

Contents

The human brain is the most elaborate structure known and comprised of an integrated network of more than 100 billion neuronal cells. The formation of this intricate neuronal network requires the precise choreography of neurogenesis, neuronal migration, pruning and synaptogenesis during development. A fundamental problem in developmental neurobiology is to understand the genetic and biochemical pathways that regulate the carefully choreographed production and migration of immature neurons to their final location in the adult brain. In this review, we will briefly discuss normal neurogenesis and neuronal migration. Then we will discuss the cloning the two most common genes mutated in the severe neuronal migration lissencephaly, *LIS1* and *DCX*. Then, functional studies of these genes in model organisms will be described, which have led to a basic understanding of many of the pathways and processes that these genes involved in. Remarkably, these studies also led to two therapeutic approaches in model organisms that provided substantial phenotypic rescue, and provide additional support for the argument that a complete understanding of

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mechanisms of actions of disease genes can lead to novel therapeutic strategies, even when those diseases are severe neurogenetic disorders.

1. Neurogenesis and neuronal migration during cortical development

Neurogenesis and neuronal migration have been studied extensively for over 30 years in diverse mammalian species from the mouse to human (reviewed in [1–3]). The basic sequence of events that occurs during cortical development is shared by these species, although the timing of events is species dependent: in humans they occur between 5th and 22nd gestational weeks, while in the mouse they occur between embryonic day 11 (E11) and 19 (E19). Prior to E11 in the mouse, the neural tube consists of a single layer of neuroepithelial stem cells (NESCs) that proliferate rapidly. Each NESC stretches from the apical to the basal surface of the neuroepithelium, and as the cell progresses through the cell cycle, the nuclei display interkinetic nuclear migration (Fig. 1). Nuclei divide at the apical surface, and synthesize DNA at the basal surface of the neural epithelium. Consequently, nuclei from cells in G1 migrate from the apical to basal surface, while nuclei from cells in G2 move from the basal to apical surface. At about E11, shortly after closure of the rostral neural tube, the neuroepithelial stem cells further differentiate into a more restricted progenitor, radial glial progenitor cells (RGPCs), that also display interkinetic nuclear migration, similar to the neuroepithelial stem cells, but only in the VZ, a proliferative zone at the apical surface (Fig. 1). A subpopulation of these cells become post-mitotic and begin to move radially out from the VZ at about E12 along the extensions of the radial glial progenitors, which are bipolar-shaped in the VZ but then convert to a multipolar morphology within the subventricular zone (SVZ) and migrate into the intermediate zone (IZ). A switch from the multipolar state back to a bipolar morphology accompanies the radial glia guided locomotion of projection neurons towards the cortical plate (CP), with the trailing process concomitantly developing into the axon. Once the neuron arrives in the CP, the leading process attaches to the pial surface and the neuron undergoes a terminal somal translocation step to reach its final location [4,5,64]. Classical studies have established that the cerebral cortex is formed by an "inside-out" migration of cells from the ventricular zone to form layers 6 through 2. The early arising neuroblasts that migrate first to the cortical plate occupy the deepest cortical layers in the adult. The later born migrating young neurons migrate past the earlier established cortical plate cells to occupy more superficial layers of the adult cortex. In addition to radial migration of cortical projection neurons, the inhibitory interneurons migrate tangentially from the medial (MGE) and lateral (LGE) ganglionic eminences.

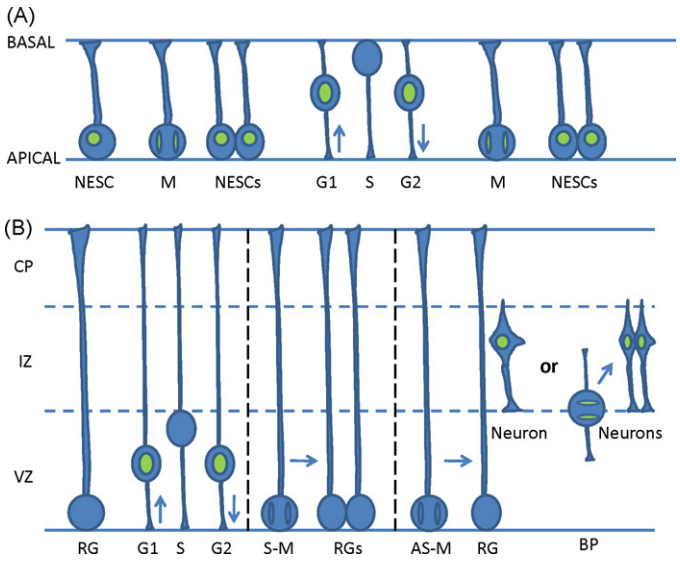

Fig. 1. Neurogenesis in (A) neuroepithelial stem cells (NESC) and (B) radial glial progenitor cells (RGPC). In NESC, nuclei undergo interkinetic nuclear migration from apical to basal surfaces, and divide symmetrically and vertically to produce NESCs. In RGPCs, interkinetic nuclear migration occurs only in the ventricular zone (VZ). At the ventricular zone, the RGPCs divide mostly vertically, but this division can be symmetric (S-M) to produce two RGPCs, or asymmetric (AS-M) to produce one RGPC and either one neuron or one basal progenitor (BP). This BP moves to the subventricular zone at the border of the VZ and intermediate zone (IZ), where it divides once symmetrically and horizontally to produce two neurons. Neurons produced by either of these two ways migrate into the cortical plate (CP), where they set up the cortical layers in an inside-out fashion.

2. Human lissencephaly: identification of *LIS1* and *DCX* as causative genes

One of the most striking abnormalities of human neuronal migration is lissencephaly (or "smooth brain"), a term originally used to describe the smooth cerebral surface of lower mammals (reviewed in [6]). Lissencephaly of the human brain is a severe malformation in which the brain has a smooth cerebral surface rather than the characteristic gyri and sulci that make the human and primate brain instantly recognizable. The primary defect underlying the smoothening of the brain of lissencephalic patients is defective neuronal migration, although defective neurogenesis may also contribute. The inability of post-mitotic neurons to reach their final destination and correctly populate the cortical plate of the cerebral cortex consequently leads to abnormal cortical thickness and reduced or absent gyri and sulci of its surface. There are two major types of classical lissencephaly: isolated lissencephaly sequence (ILS) and Miller–Dieker syndrome (MDS). Isolated lissencephaly sequence (ILS) is a heterogeneous disorder consisting of variably severe lissencephaly with no other major malformations such as craniofacial dysmorphism. Miller–Dieker syndrome (MDS) consists of more severe lissencephaly than ILS patients, characteristic facial anomalies (high forehead, a small nose with anteverted nares, thin vermilion border, and micrognathia), and occasionally other malformations [7]. Children with ILS and MDS are severely retarded and suffer from epilepsy [8]. These disorders are fatal in early childhood. MDS (100%) and some cases of ILS (40%) are the result of haploinsufficiency at human chromosome 17p13.3, with visible or submicroscopic deletions detectable by FISH [9]. The *LIS1* gene was cloned from this region [10]. *LIS1* was disrupted in an ILS patient with a translocation, and several other key MDS patients [11,12].

There are X-linked forms of lissencephaly. The major cause of X-linked lissencephaly is mutation of the *Doublecortin* (*DCX*) gene [13,14]. Mutations in the *DCX* gene cause gross neocortical disorganization and lissencephaly in hemizygous males, while heterozygous females show a mosaic phenotype with a normal cortex as well as a second band of misplaced (heterotopic) neurons beneath the cortex ("double cortex syndrome"). Although several other lissencephaly genes have been identified, the majority of patients with lissencephaly display mutations in either LIS1 or DCX [15].

3. Mouse models for *Lis1* and *Dcx*: *in vivo* functional studies

3.1. *Lis1*

Mouse models for lissencephalies have aided in the understanding of the function of LIS1 and the pathways associated with it during brain development [16,17]. We produced two knock-out and one conditional knock-out *Lis1* mutant alleles by gene targeting