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Genetics of Neuronal Migration in the Cerebral Cortex

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The development of the cerebral cortex requires large-scale movement of neurons from areas of proliferation to areas of differentiation and adult function in the cortex proper, and the patterns of this neuronal migration are surprisingly complex. The migration of neurons is affected by several naturally occurring genetic defects in humans and mice; identification of the genes responsible for some of these conditions has recently yielded new insights into the mechanisms that regulate migration. Other key genes have been identified via the creation of induced mutations that can also cause dramatic disorders of neuronal migration. However, our understanding of the physiological and biochemical links between these genes is still relatively spotty. A number of molecules have also been studied in mice (Reelin, mDab1, and the VLDL and ApoE2 receptors) that appear to represent part of a coherent signaling pathway that regulates migration, because multiple genes cause an indistinguishable phenotype when mutated. On the other hand, two human genes that cause lissencephaly (*LIS1*, *DCX*) encode proteins that have recently been implicated as regulators or microtubule dynamics. This article reviews some of the mutant phenotypes in light of the mechanisms of neuronal migration.
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The formation of the cerebral cortex involves a series of dramatic cellular movements, because the neurons that are born progressively later in gestation must travel increasingly long distances to reach their correct location. The proper timing and navigation of these migrations are essential for normal brain function, since defects of neuronal migration are associated with cognitive defects and/or epilepsy in humans and mice. Recently, there has been rapid progress in understanding the ever-surprising phenomenology of this migration, as well as its molecular basis, and this review will briefly touch on both of these issues.

Studies of neurogenesis in the cortex have long shown that cortical neurons are born in an orderly sequence. The earliest-formed cortical neurons form a precocious organization referred to originally as the primordial plexiform layer [Marin-Padilla, 1978], but now commonly referred to as the preplate [Luskin and Shatz, 1985]. These early born neurons form connections with subcortical targets [Marin-Padilla, 1978; McConnell et al., 1989; McConnell et al., 1994] that are essential for development of later connections [Ghosh and Shatz, 1992]. The preplate is subsequently divided into two layers—an outer marginal zone beneath the pial surface, and a deeper subplate layer—by the arrival of a later-generated neuronal population called the cortical plate.

The cortical plate neurons are added in a peculiar, ''inside-out'' sequence that appears to be particularly susceptible to genetic disruption. The earliest-born cortical plate neurons form a dense, essentially close-packed array of cells. Later-born cohorts of cortical plate neurons must migrate up to this array and then must squeeze past the earlier-born cortical plate neurons, arresting their migration at the top of the cortical plate, between the cortical plate cells and the marginal zone cells. Subsequent cohorts of neurons repeat this pattern, migrating through an ever-thicker cortical plate, so that the newest neurons are always at the top of the cortical plate facing the marginal zone cells.

Modes of Neuronal Migration

Studies of cell lineage and migration in cortical neurons have demonstrated strikingly diverse clonal and migratory patterns. Morphological [Rakic, 1971, 1972] and electron microscopic studies [Rakic et al., 1974], and in vitro analysis of cerebellar cultures [Edmondson and Hatten, 1987; Gregory et al., 1988] have long shown that radial glia provide a substrate for migrating neurons. However, studies of cell lineage using retroviral vectors [Luskin et al., 1988; Price and Thurlow, 1988; Walsh and Cepko, 1988; Walsh and Cepko, 1992; Reid et al., 1995] or X-inactivation mosaic analysis [Tan and Breen, 1993; Tan et al., 1995] have provided a picture of diverse migratory routes including both directly radial and less direct patterns. Studies of cortical cell migration in explant or slice cultures [O'Rourke et al., 1992; Fishell et al., 1993; O'Rourke et al., 1995; Neyt et al., 1997] have also shown the predominantly radial routes of some cells, but the strikingly nonradial routes of other cells. How these apparently diametrically opposed patterns of neuronal migration might relate to one another has been a persistent question for a decade.

Several lines of evidence have begun to reconcile the divergent patterns of neuronal migration by showing that cortical neurons derive from heterogeneous progenitor cells with very different migratory properties and mature progeny. For example, retroviral studies suggested that distinct progenitors give rise to pyramidal and nonpyramidal neurons [Parnavelas et al., 1991] but this idea was extended with the observation that clones of pyramidal and nonpyramidal neurons showed distinct patterns of clonal organization [Mione et al., 1994], with pyra-

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midal neurons tending to form radial clusters, whereas nonpyramidal neurons tend to be more scattered [Mione et al., 1994, 1997]. The notion that distinct progenitors preferentially produce widespread clones of mainly GABAergic neurons, or radial clones of mostly glutamatergic neurons, has recently been very elegantly extended and refined using highly unbalanced chimeras and X-inactivation mosaics [Tan et al., 1998]. Large radial clones consisted of >90% glutamatergic neurons, whereas widespread "horizontal" clones contained 51% to 92% GABAergic (average = 75%) neurons, with the remaining cells glutamatergic [Tan et al., 1998]. The general notion that cortical clones consist of two fundamentally distinct types both topographically and physiologically appears able to reconcile most of the existing data from retroviral lineage studies, retroviral library analysis, and in vitro time-lapse studies. Although large radial clones form no more than 70% of cortical neurons—and probably less—and are apparently absent from far lateral neocortex [Tan et al., 1995], large radial clones include most pyramidal neurons and form a potential source of positional information between the ventricular zone and cortex, as first proposed by Rakic [Rakic, 1978, 1988].

In contrast to the notion of positional signaling between the progenitor cells and the mature cortex, however, is the recent observation that a substantial fraction of GABAergic, inhibitory cortical interneurons actually originates outside of the cortex altogether, in the proliferative zone that gives rise to the striatum, called the lateral ganglionic eminence (LGE) [Anderson et al., 1997; Tamamaki et al., 1997]. Neurons that express the homeobox genes *Dlx-1* and *Dlx-2* arise here, and migrate through the striatum and into the overlying cerebral cortex [Anderson et al., 1997]. The formation of inhibitory neurons outside of the cortex is especially intriguing because the same proliferative region, the SVZ of the striatum, is a persistent source of inhibitory interneurons for the olfactory bulb and elsewhere [Doetsch and Alvarez-Buylla, 1996; Lim et al., 1997; Reid et al., 1999; Wichterle et al., 1999] suggesting that inhibitory interneurons destined for large portions of the forebrain could arise from a common progenitor pool. The origin of some cortical neurons from the LGE begs the question whether all widespread/inhibitory cortical clones derive from the LGE, or whether widespread clones have more than one origin (e.g., from both the VZ of the LGE and the VZ of the cortex proper). In chimera experiments [Tan et al., 1998] most, though not all, experiments with widespread clonal patterns also showed labeled cells in the underlying striatum, suggesting that the striatum is the major, if not only, source of widespread clones. This question is difficult to address with current techniques, since there is no simple in vivo method that selectively labels just the striatal VZ or cortical VZ progenitors in clonal fashion.

Studies of cell lineage and migration in cortical neurons have demonstrated strikingly diverse clonal and migratory patterns.

Are similar patterns of widespread and radial clones conserved among species with larger cerebral cortices? Cell lineage studies in primate [Kornack and Rakic, 1995] have shown both radial and horizontal patterns of retrovirally labeled neurons. However, the very large radial clusters seen in mice have not been reported in primate, and in ferrets (members of the order Carnivora), retroviral library analysis of cortical clones at mid- to late-corticogenesis demonstrated striking numbers of widespread clones that covered large portions of the cortical mantle with little evidence for radial clustering [Reid et al., 1997]. However, recent studies of cell lineage in the early ferret cortex [Ware et al., 1999] confirm the occurrence of large radial clones of up to 150 cells in the early cerebral cortex of ferrets as well. The large clusters represent a small portion of all clones, but a significant fraction (38%) of all retrovirally labeled cells [Ware et al., 1999]. Thus, large radial clones and widespread clones (presumably deriving predominantly from the LGE) are likely to be evolutionarily conserved features of cortical development. What controls the apparent ability of two different neuronal populations to follow opposite rules for migration in the same subcortical intermediate zone is, however, an unsolved problem, and will probably not be understood until we have a firmer understanding of the mechanisms controlling neuronal migration in general.

Genetic Disorders of Neuronal Migration in Mice

The recent past has witnessed an explosion in our understanding of the genes that are required for normal neuronal migration to the cerebral cortex, although we are still a considerable way from having a comprehensive understanding of how these genes relate into biochemical pathways. The best-characterized animal model of abnormal neuronal migration is the reeler mouse, identified several decades ago [Falconer, 1951]. Reeler shows abnormalities in cortical lamination patterns creating a cortex that is roughly inverted from normal, with additional defects of neuronal positioning in other brain regions, as well as profound cerebellar hypoplasia [Caviness and Sidman, 1973; Caviness, 1982; Goffinet, 1984, 1992]. The reeler mouse harbors an autosomal recessive mutation mapped to mouse chromosome 5 [Goffinet, 1992; Beckers et al., 1994]. The responsible gene was identified as a result of a transgene insertion into the reeler locus, as well as by physical mapping across the candidate gene region [Bar et al., 1995; D'Arcangelo et al., 1995; Hirotsune et al., 1995]. The reeler protein, Reelin, is a large secreted polypeptide with homology to extracellular matrix molecules involved in cell adhesion [D'Arcangelo et al., 1995]. Reelin is synthesized and secreted by the Cajal-Retzius cells of the marginal zone of the cerebral cortex, at a distance from the migrating cells which appear to require Reelin for appropriate guidance [D'Arcangelo et al., 1995; Ogawa et al., 1995], and blockage of Reelin secretion appears to be sufficient to cause loss of Reelin function [de Bergeyck et al., 1997]. Electron microscopic observations have suggested that cells in the reeler brain have difficulty releasing from radial glia [Pinto-Lord et al., 1982], although exactly how Reelin may regulate neuron-glia adhesion and migration is uncertain.

More recently another mouse mutant, called scrambler (*scm*), which has a phenotype similar to reeler, has promised to help unravel the Reelin signaling pathway. The scrambler mutation arose spontaneously [Sweet et al., 1996] and like reeler, the mutant animals show an unstable, ataxic gate and whole body tremors. In addition, scrambler brains have cytoarchitectural abnormalities in the layering of the cerebral cortex and cerebellum [Sweet et al., 1996]. Histological analysis and birthdating experiments demonstrate the absence of a marginal zone as well as an inverted inside-out pattern of cortical development

[Gonzalez et al., 1997]. Similar to reeler, the hippocampus is disorganized with the appearance of two indistinct pyramidal layers rather than one precise layer. The cerebellum is hypoplastic, reduced in size, and lacking normal folia [Goldowitz et al., 1997]. Although *scm* mice present with physical and morphological abnormalities indistinguishable from reeler mice, *scm* maps to a location on mouse chromosome 4 distinct from reeler [Sweet et al., 1996]. Furthermore, *scm* mice express normal levels of Reelin mRNA and protein suggesting that the *scm* gene product may act downstream of Reelin [Goldowitz et al., 1997; Gonzalez et al., 1997].

Another recently identified mouse mutant, yotari (*yot*), has a similar behavioral phenotype and neuropathology to scrambler and reeler [Yoneshima et al., 1997]. Yotari is caused by an autosomal recessive mutation independent of reeler based on genetic crosses between yotari and reeler mice. In addition, yotari mice have normal Reelin expression, suggesting that, like scrambler, yotari acts downstream to Reelin. Subsequently, yotari was shown to be allelic to scrambler [Sheldon et al., 1997].

Construction of a genetic and physical map across the *scm* candidate region allowed identification of the gene responsible for scrambler [Ware et al., 1997]. The YACs which span the region were analyzed by interspersed repetitive sequence PCR (IRS-PCR) [Hunter et al., 1994], identifying an exon of the mouse disabled gene (*mdab1*) [Howell et al., 1997a; Ware et al., 1997]. A splicing abnormality was detected in *scm* mice that inserted a portion of a retroposon-like element into the coding region of *mdab1* [Ware et al., 1997]. In another approach, *mdab1* was analyzed as a candidate gene because it mapped to the *scm* candidate region and is expressed almost exclusively in the brain during development [Sheldon et al., 1997]. Furthermore, targeted disruption of *mdab1* resulted in disturbed lamination of the brain, indistinguishable from the phenotype seen in *scm* and *yot* mice [Howell et al., 1997b]. *scm* and *yot* express mutated forms of *mdab1* mRNA and little to no mDab1 protein [Sheldon et al., 1997]. Taken together these results implicated *mdab1* as the gene responsible for the *scm* and *yot* phenotype.

Mouse Dab1 was originally identified in a two-hybrid screen by virtue of its binding with c-Src, a non-receptor tyrosine kinase [Howell et al., 1997a]. mDab1 represents the murine homolog of Drosophila *disabled* (Dab) which was originally identified as an enhancer of a disrupted Drosophila abl (D-abl) gene, thus the name *disabled* [Gertler et al., 1993; Howell et al., 1997a]. Dab and D-abl are co-localized within the Drosophila CNS and double mutants display serious defects in axonogenesis [Gertler et al., 1993]. mDab1 contains a phosphotyrosine binding (PTB) domain and binds other non-receptor tyrosine kinases such as Fyn and c-Abl. The mDab1 protein is intensely expressed and tyrosine phosphorylated in developing neurons throughout the nervous system and is concentrated in developing neurites [Howell et al., 1997a, 1997b; Sheldon et al., 1997]. mDab1 has no known catalytic activity. However, the ability of mDab1 to bind c-Abl directly suggests the existence of a signaling pathway dependent upon c-Abl or some other Abl-related tyrosine kinase and essential for normal neuronal migration.

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The Beginnings of a Biochemical Pathway in Murine Neuronal Migration

Given the remarkable similarities in phenotype between reeler and scrambler mice, it has been suggested that Reelin and mDab1 share a common biochemical signaling pathway with mDab1 downstream of Reelin. Like reeler, newer neuronal precursors in scrambler mice fail to properly migrate past older cortical plate neurons, leading to an approximate inversion of cerebral cortical layering. Both Reelin and mDab1 are expressed very early during the development of the cerebral cortex, hippocampus, and cerebellum and Reelin is expressed in cells adjacent to the mDab1 expressing cells [Rice et al., 1998]. Analysis of the expression patterns of mDab1 during development suggested that mDab1 accumulates in the ectopically migrating neurons in reeler mice. Although the levels of *mdab1* mRNA are comparable, the mDab1 protein is overexpressed in the brains of reeler mice as compared to normal mice [Rice et al., 1998; Howell et al., 1999a]. The accumulation of mDab1 in the absence of Reelin implies that Reelin regulates the levels of mDab1. For example, mDab1 is phosphorylated in response to Reelin [Howell et al., 1999a], and phosphorylated signaling proteins are often more unstable than unphosphorylated ones. The absence of Reelin may therefore result in excess mDab1 due to failure of mDab1 degradation after fulfilling a signaling function, or perhaps the absence of a normal decrease in the rate of translation of mDab1 protein in response to Reelin. It is unlikely that there is a direct physical interaction between mDab1 and Reelin since Reelin is secreted while mDab1 is a cytoplasmic protein. Thus, an additional protein such as a Reelin receptor may be involved, with mDab1 acting as an adapter protein between the Reelin receptor and downstream signaling pathways.

Very recently comes a remarkable recapitulation of the reeler phenotype in all of its features, from yet a third mouse mutation, implicating additional molecular players in signaling downstream from Reelin. Two different studies showed that mDab1 can bind to the cytoplasmic portions of the low density lipoprotein receptor (LDL) family of membrane proteins [Trommsdorff et al., 1998; Howell et al., 1999b]. mDab1 and the other adapter proteins appear to bind the LDL receptor family through the PTB domain of mDab1, and through an NPxY motif on the cytoplasmic tail of the LDL receptors [Trommsdorff et al., 1998; Howell et al., 1999b]; interestingly, the Alzheimer precursor protein (APP) shares this same NPxY motif and the same Dab1 binding [Trommsdorff et al., 1998; Howell et al., 1999b]. Surprisingly however, engineered mutations in two of the LDL superfamily genes that show high expression in the brain—the VLDL receptor and the ApoE2 receptor—each individually show defects in neuronal migration. Finally, the double-mutant mice, lacking both VLDL receptor and ApoE2 receptor function, have a phenotype indistinguishable from reeler, with inversion and disruption of the cortical layers, hypoplasia of the cerebellum, and disruption of the hippocampus [Trommsdorff et al., 1999]. Moreover, the double mutants show intact Reelin synthesis as in *scm* mutants, and upregulation of mDab1 protein as in reeler mutants, suggesting that VLDL/ApoE2 receptors may be required for intact signaling between Reelin and mDab1. One possibility is that these two membrane proteins represent definitive receptors for Reelin, though efforts thus far have not shown direct binding of Reelin to either receptor [Trommsdorff et al., 1999]. Another possibility is that the VLDL/ApoE2 receptors are required for

endocytosis, which may be an essential component of signaling following binding of Reelin to some other definitive receptor [Cooper and Howell, 1999].

Additional genes that are crucial for normal neuronal migration include cyclin-dependent kinase-5 (cdk5) and p35. Cdk5 is a serine threonine kinase that phosphorylates histone H1, tau, or neurofilaments, and is highly expressed in the axons of post mitotic neurons [Tsai et al., 1993; Nikolic et al., 1996]. Disruption of *cdk5* results in abnormal lamination of the cerebral cortex and altered foliation of the cerebellum similar to the scrambler and reeler phenotypes [Ohshima et al., 1996; Gilmore et al., 1998]. P35 is a regulatory subunit that associates with Cdk5 to activate kinase activity [Tsai et al., 1994; Delalle et al., 1997]. Engineered mutations in p35, which eliminate Cdk5/P35 kinase activity, cause migration defects of the cerebral cortex, as well as sporadic seizures and adult lethality, but spares the cerebellum [Chae et al., 1997]. The *cdk5* and *p35* mRNAs are expressed in axons of the developing and mature nervous system, and Cdk5/P35 kinase activity is essential for neurite outgrowth during neuronal differentiation [Nikolic et al., 1996; Delalle et al., 1997], perhaps by acting as an effector for small GTPases of the Rho superfamily [Nikolic et al., 1998]. Although the P35/Cdk5 knockouts share some similarities to the reeler phenotype, there are also prominent differences [Chae et al., 1997; Gilmore et al., 1998; Kwon and Tsai, 1998]: unlike *rl* and *scm* mice where cells fail to penetrate the cortical plate, the cortical lamination fails after the formation of the cortical plate in *cdk5* and *p35* null mice. One possible interpretation of these phenotypic differences might be that the Cdk5/P35 kinase functions downstream of mDab1 during neuronal migration, but the connections between mDab1 and Cdk5 are at present unknown.

A number of membrane proteins have been implicated in neuronal migration based upon genetic and antibody perturbation studies [Hatten, 1999]. For example, antibodies to astrotactin [Zheng et al., 1996], a membrane receptor protein, disrupt migration along glial cells [Edmondson et al., 1988; Fishell and Hatten, 1991; Fishman and Hatten, 1993]. Antibodies to β1 integrin disrupt migration of cortical [Anton et al., 1999] and other neuronal cell types [Fishman and Hatten, 1993; Cann et al., 1996] and retroviral antisense experiments [Galileo et al., 1992], and experiments on β1 integrin mutant mouse cells [Andressen et al., 1998] also suggest a role in neuronal migration. Recent analysis of an engineered mutation in the alpha3 integrin gene also suggests a role in cortical neuronal migration [Anton et al., 1999]. Perhaps some of these membrane proteins provide the receptor systems for signaling through mDab1 and Cdk5, but the phenotypes in the several loss of function experiments are difficult to compare.

Recently, a secreted factor called neuregulin (NRG) has been shown to be produced by migrating neurons in the cerebellum and cortex, and to be required for normal migration in these regions [Anton et al., 1997; Rio et al., 1997]. NRG is a member of a family of secreted factors related to EGF that bind to a family of receptors called the erbB family. In the cerebellum, NRG is expressed in radially migrating granule cells while the cognate receptor is expressed in radial glial cells [Rio et al., 1997]; in the cortex NRG is secreted by cortical neurons and appears to act on radial glial cells as well [Anton et al., 1997]. Obstructing NRG signaling to erbB receptors blocks the normal elongation of radial glial by NRG, and blocks the radial migration of neurons along the glial fibers [Anton et al., 1997; Rio et al., 1997].

Disorders of signal transduction may be a common denominator in the human and mouse disorders of neuronal migration.

Another secreted protein that has recently been critically implicated in regulating neuronal migration is slit. Slit, which actually represents a family of at least three related genes in vertebrates, was first identified in flies as a gene required for commissural axon formation, and was shown to be chemorepulsive for commissural axons [Kidd et al., 1999; Van Vactor and Flanagan, 1999]. Interestingly, members of the slit gene family are expressed in the septum of the forebrain [Wu et al., 1999], which had previously been shown to secrete a factor that repels nonradially migrating neurons formed in the anterior SVZ and forming the RMS. Slit appears to represent this repulsive activity [Wu et al., 1999]. Moreover, slit appears to be formed in the LGE as well, and to repel nonradially migrating LGE neurons that migrate from the LGE into the cerebral cortex [Zhu et al., 1999].

Human Lissencephaly Genes: Disorders of Microtubule Regulation?

In addition to the mouse disorders of neuronal migration, there are a large group of human disorders that are most consistent with disorders of migration. Lissencephaly, meaning literally ''smooth brain'' refers to a genetically and histologically heterogeneous group of conditions that are manifested by a loss of gyri and sulci that characterize the normal human brain. The most common cause of lissencephaly is gross disruption of a gene on chromosome 17p13 called *LIS1*, or more properly *PAFAH1B1* [Reiner et al., 1993]. Most affected patients undergo spontaneous, heterozygous deletions of *PAFAH1B1*, or larger deletions encompassing adjacent genes, causing a syndrome of multiple congenital anomalies called the Miller-Dieker syndrome [Dobyns et al., 1993]. Point mutations have also been described in *PAFAH1B1* with a similar phenotype [Lo Nigro et al., 1997]. The disorder typically affects the cortex and hippocampus most severely, with the cerebellum being relatively spared; however most parts of the brain are in some way affected [Dobyns et al., 1993]. The cortex in classical lissencephaly shows a well-formed pial surface and marginal zone, with a subjacent layer of pyramidal cells that likely corresponds to some of the cells of the deeper layers of the cortex and/or subplate; beneath the pyramidal layer is a narrow, cell-poor zone, and then a dense, very deep jumble of neurons below [Dobyns et al., 1993].

The mouse homologue of *PAFAH1B1* has recently been mutated, and the mice show defects that may be considerably more complex than a mere migrational disturbance [Hirotsune et al., 1998]. Mice heterozygous for a complete loss of function mutation show a very subtle defect in cortical development, much milder than heterozygous humans. Mice with homozygous strong loss-of-function alleles are lethal at early embryonic ages whereas compound heterozygotes with incomplete loss-of-function mutations show neonatal lethality with severe migrational, architectural, and perhaps proliferative abnormalities of the cortex [Hirotsune et al., 1998]. Thus, *PAFAH1B1*, which is widely expressed in all tissues and which is expressed in dividing as well as migrating neural cells, may be required at many stages of neuronal development.

After its identification in *LIS1*, *PAFAH1B1* was re-identified as a non-catalytic subunit of platelet activating factor (PAF) acetylhydrolase, hence the use of the gene name *PAFAH1B1*. PAF acetylhydrolase is the major degradative enzyme for PAF, a bioactive lipid involved in regulating the shape and function of platelets, and which appears to mobilize neuronal calcium [Hattori et al., 1994]. However, *PAFAH1B1* was later isolated independently as a regulatory protein that binds the activated form of a tyrosine kinase related to Syk [Brunati et al., 1996]. Which of these multiple, seemingly distinct, functional interactions of *PAFAH1B1* are the critical ones directing neuronal migration are not yet certain, but are likely to be most easily sorted out by the functional connection of *PAFAH1B1* to other genes required for migration.

The evolutionary conservation of *PAFAH1B1* is remarkable, and studies in nonmammalian organisms and mammalian cells suggest a role in the translocation of the nucleus via a microtubule-based mechanism. *PAFAH1B1* has a convincing orthologue in Aspergillus nidulans, called *nudF* [Xiang et al., 1995], that is required for translocation of the nucleus along an elongated cellular process called the mycelium [Morris et al., 1998a]. *nudF* interacts genetically with tubulin, and also with *nudA*, which encodes the heavy chain of cytoplasmic dynein, a microtubule motor protein implicated in retrograde organelle transport in neurons [Hirokawa et al., 1990; Xiang et al., 1994, 1995; Morris et al., 1998a, 1998b]. These data suggest that *PAFAH1B1* may represent a link to the microtubule network in neurons. Moreover, there is direct evidence that *PAFAH1B1* can be precipitated with microtubules, and can increase microtubule stability [Sapir et al., 1997].

Another, X-linked locus causes classical lissencephaly in males that is virtually indistinguishable from *PAFAH1B1* mutations [Berg et al., 1998], and the responsible gene was mapped and recently cloned [des Portes et al., 1998; Gleeson et al., 1998; Sossey-Alaoui et al., 1998], and also regulates microtubules. Females with mutations in this X-linked lissencephaly gene, abbreviated *DCX*, show a remarkable malformation called ''double cortex''. The females by definition represent a mosaic state, since brain cells in the female normally inactivate one or the other X chromosome during development. It is natural to assume that the normal cortex contains cells that express genes from the normal X chromosome, and that the abnormal band contains cells expressing the mutant X chromosome, but this has not been directly shown.

DCX encodes a protein, called doublecortin, without known enzymatic activity. *DCX* is expressed intensely in all migrating neurons in the developing brain, and is persistently expressed only in those few regions of the adult brain that undergo continuing migration, such as the olfactory bulb [Francis et al., 1999; Gleeson et al., 1999]. *DCX* appears to localize in the soma of migrating neurons, forming a meshwork in the cytoplasm of the soma that resembles the ''cages'' of microtubules previously described by Hatten and co-workers [Gregory et al., 1988; Rivas and Hatten, 1995; Gleeson et al., 1999]. Like *PAFAH1B1*, *DCX* can be precipitated with microtubules from brain. Moreover, *DCX* dramatically stimulates microtubule polymerization in a dose-dependent fashion [Francis et al., 1999; Gleeson et al., 1999]. The interaction of both *DCX* and *PAFAH1B1* with microtubules suggests that the very similar phenotype caused by mutations in these two genes reflects a common or linked mode of action on microtubule dynamics.

The amino acid sequence of doublecortin suggests a potential biochemical connection between human lissencephalies and the mouse neuronal migration disorders. Doublecortin shows a consensus substrate site for c-Abl [des Portes et al., 1998; Gleeson et al., 1998], which is intriguing given the known ability of c-Abl to regulate actin dynamics and axon outgrowth [Wills et al., 1999a, 1999b], and also the potential connection between *DCX* and mDab1 through an Abl-dependent signaling pathway. While c-Abl or some Abl-like tyrosine kinase represents a possible biochemical link between mDab1 and doublecortin, it remains to be demonstrated that these proteins physically interact or function in concert.

Periventricular Heterotopia: A Common Downstream Target Molecule?

Whereas lissencephalies, as well as mouse mutations in Reelin, *mdab1*, *cdk5*, and *p35*, show some preserved migration (and instead are characterized by misdirected or incomplete migration), periventricular heterotopia reflects the complete failure of migration of some cell types and results in persistent accumulations of neurons (''heterotopias'') in the periventricular region into adulthood. The nodules in periventricular heterotopia represent remarkably mature-appearing neurons of multiple size classes and showing well-developed dendrites [Eksioglu et al., 1996]. The most common cause of periventricular heterotopia appears to be an X-linked gene that is dominant in females and lethal to most males, and the periventricular heterotopia gene has recently been identified as *filamin 1* (*FLN1*) [Fox et al., 1998]. *FLN1* encodes a protein that has been critically implicated in control of cell shape, migration, filopodia formation, and chemotaxis [Hartwig and Stossel, 1975; Hartwig et al., 1980; Gorlin et al., 1990]. Since *filamin 1* directly interacts with both receptors and actin itself [Hartwig, 1992; Matsudaira, 1994; Marti et al., 1997], it forms a potential focus upon which the signaling molecules required for the guidance of migration may assemble [Fox and Walsh, 1999].

CONCLUSIONS

Molecular genetics has allowed the identification of several genes that are critical to neuronal migration but the roles that they play are still being investigated. Since many of the genes involved in migration encode predicted proteins that appear to lack intrinsic enzymatic activity, their cellular mechanism of action presumably involves interactions with other signaling molecules. The genes identified so far may be part of a common signal transduction pathway carrying signals from the plasma membrane to the cytoskeleton, or may represent several pathways. Disorders of signal transduction may be a common denominator in the human and mouse disorders of neuronal migration.

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