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Neuronal migration mechanisms in development and disease

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Neuronal migration is a fundamental process that determines the final allocation of neurons in the nervous system, establishing the basis for the subsequent wiring of neural circuitry. From cell polarization to target identification, neuronal migration integrates multiple cellular and molecular events that enable neuronal precursors to move across the brain to reach their final destination. In this review we summarize novel findings on the key processes that govern the cell biology of migrating neurons, describing recent advances in their molecular regulation in different migratory pathways of the brain, spinal cord, and peripheral nervous system. We will also review how this basic knowledge is contributing to a better understanding of the etiology and pathophysiology of multiple neurological syndromes in which neuronal migration is disrupted.

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Introduction

Instructed by extracellular cues, the activation of guidance receptors and their downstream signaling pathways enable newborn neurons to migrate through the developing nervous system until they reach their destination. The migratory cycle of neurons involves leading process dynamics, through which directional migration is achieved, and somal translocation, which involves the movement of perinuclear material and organelles as well as the nucleus. Different classes of neurons adjust and modify this basic migratory cycle depending on the specific requirements of their migratory pathway, which may also change through time. For example, pyramidal cells transit through at least three different phases during their migration toward the cortical plate [1] (Figure 1). During these stages, pyramidal cells adopt different morphologies, each of which probably involves distinct

molecular requirements and whose disruption causes specific neurological syndromes [2,3].

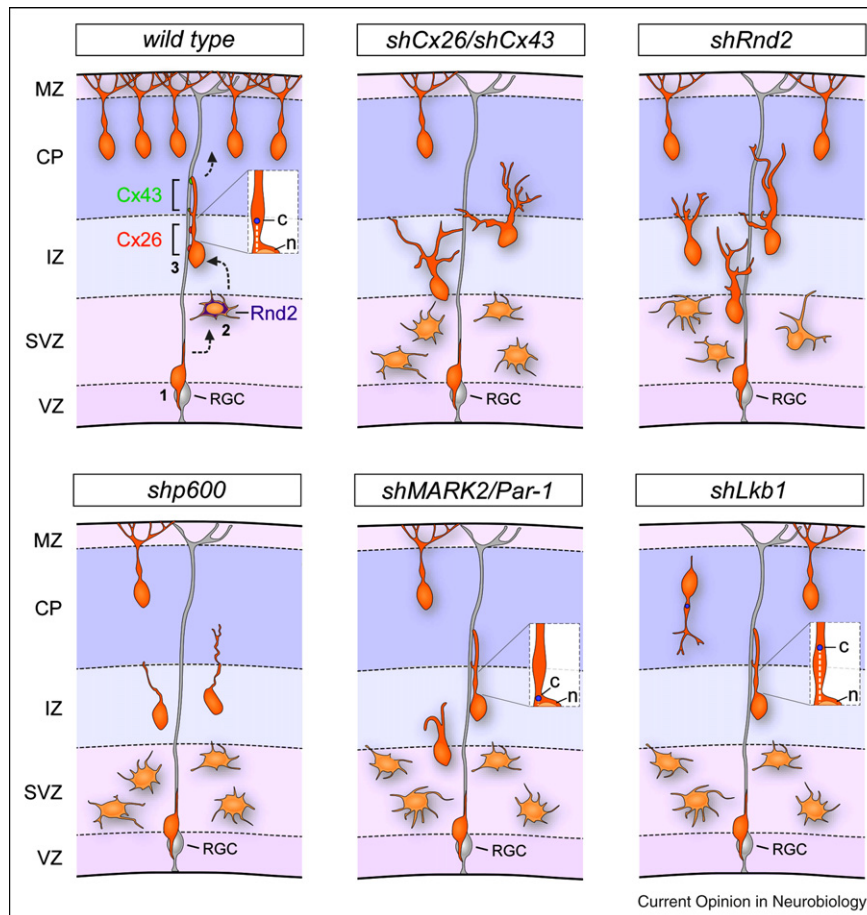
Recent work has shed light on the molecular mechanisms regulating each of the different aspects of the migratory cycle of neurons, the topic of the present review. We will also summarize recent findings illustrating how abnormal neuronal migration may cause neurological disorders. The transcriptional mechanisms regulating neuronal migration will not be addressed in this article, as it has recently been reviewed elsewhere [4,5].

Leading process dynamics

Real time imaging experiments have begun to shed light into the dynamic behavior of the leading process in migrating neurons. Somehow surprisingly, we have discovered that the leading process of migrating neurons has relatively distinct morphologies in different classes of neurons, probably reflecting their adaptation to specific microenvironments. In contrast to the simplicity of the single leading process reported for radially migrating pyramidal cells [6], tangentially migrating neurons display very elaborated leading process morphologies. This is the case, for example, of precerebellar neurons, cortical interneurons, or immature enteric neurons, all of which have branched leading processes [7–10]. In these cells, leading process branches are stabilized or retracted in binary decisions that determine the direction followed by the nucleus during nucleokinesis [11•] (Figure 2), and this process is intimately linked to their directional guidance [8,11•,12•]. Thus, guidance cues influence the frequency and orientation at which new leading process branches emerge, which allow migrating neurons to rapidly change direction without having to reorient pre-existing branches. This guidance mechanism is different from that described for growing axons, in which growth cone steering determine the direction of movement [13].

It has been suggested that leading process branching represents a general, default strategy for neuronal migration, which might be suppressed under certain circumstances, for example, during glial-guided radial migration [14]. Consistent with this view, the leading process of pyramidal cells become progressively unipolar as neurons transit from the progenitor region toward the intermediate zone (Figure 1), where they start actively interacting with radial glial fibers [1,3]. Moreover, preventing the normal interaction of pyramidal cells with radial glial fibers increases the number of leading process branches in these cells [15••] (Figure 1). One of the proteins that may regulate this process is the small GTP-binding protein Rnd2 [16••]. *Rnd2* silencing

Figure 1



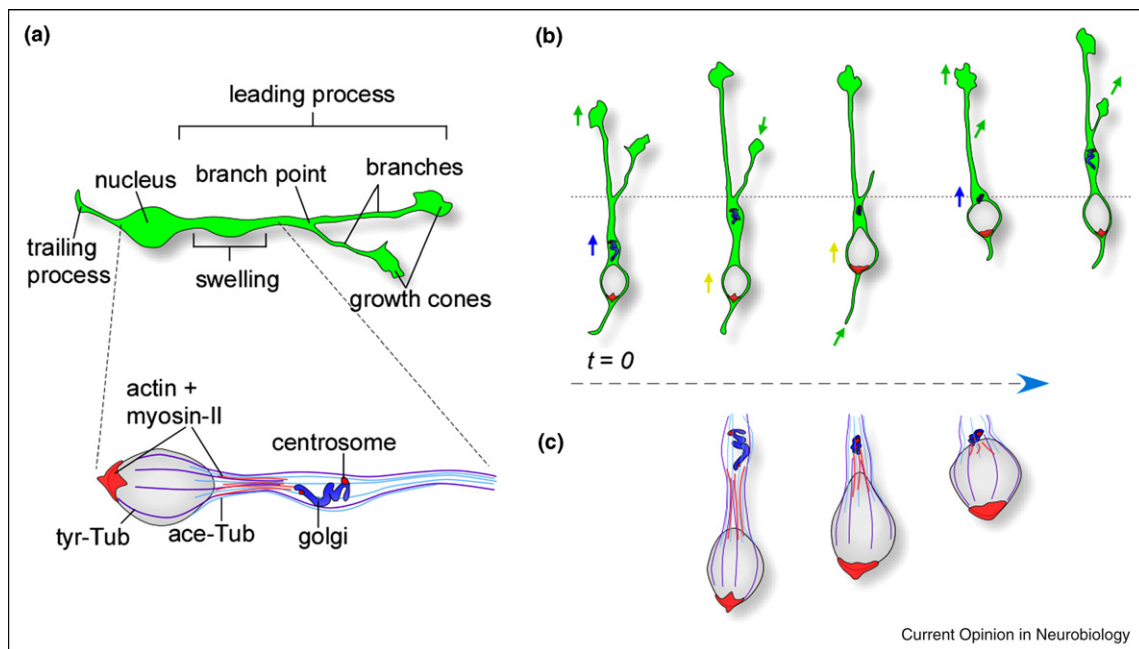
Regulators of cell morphology during glial-guided migration. Radial glia cells present in the ventricular zone (VZ) are the progenitors of cortical projection neurons and extend a long basal process that ends in the pial basement membrane over the marginal zone (MZ). Newborn neurons polarize and begin their migration close to the progenitor radial glia cell (1). At the subventricular zone (SVZ), however, migrating neurons halt their progression toward the cortical plate (CP) and modify their morphology (2), becoming multipolar cells. Cells at this state are characterized by the generation of multiple processes all around the cell and can make small tangential displacements. Eventually, cells polarize again, acquire a clear bipolar morphology (3), and restart their migration through the intermediate zone (IZ) and into the CP. During this later phase, projection neurons migrate closely attached to the basal process of radial glia cells. Interaction with the cellular scaffold of radial glia is mediated, among other molecules, by connexins Cx26 and Cx43. The coupling of the nucleus (n) and the centrosome (c) is also schematically depicted in these drawings. The distance between the nucleus and centrosome (white dashed line) changes during migration owing to the forward displacement of the centrosome and the saltatory movement of the nucleus. Knockdown of several regulators of the morphology of pyramidal cells impairs their migration. For example, RNAi against Cx43 or Cx26 disrupts the progression of projection neurons from the multipolar stage, probably owing to a failure in their ability to interact with radial glial fibers. Of note, cells that manage to progress toward the CP develop a leading process with multiple branches. *Rnd2* knockdown causes a similar phenotype, although it is presently unclear how this small GTP-binding protein (expressed by cells in the SVZ/IZ transition) controls this process. Other proteins that regulate the stability of microtubules (e.g., p600, MARK2/Par-1, and Lkb1) are essential for the progression of neurons from the multipolar stage into glial-guided migration. Loss of p600 leads to abnormal development of the leading process, which becomes thin and wavy. Reduction in the levels of MARK2/Par-1 or Lkb1 causes different defects in centrosome–nucleus coupling. Axons of migrating and positioned neurons were not drawn for simplicity. For axonal phenotypes see corresponding references.

perturbs the transition of pyramidal cells from the multipolar stage to the unipolar stage, and even those cells that manage to polarize in the absence of *Rnd2* have many more leading process branches than normal cells (Figure 1).

Leading process stability depends on a system of longitudinal microtubules that links the leading edge of the cell with the soma. This system not only provides struc-

tural support to the leading process, but also allows the flow of vesicles required for intracellular communication. This process seems to be directly regulated by p600 (also known as Ubr4), a novel microtubule associated protein (MAP) that interacts with the endoplasmic reticulum (ER). Knockdown of p600 in pyramidal cells leads to a prominent reduction in acetylated tubulin and an almost complete loss of the ER in the leading process, which acquires a wavy appearance (Figure 1) and disrupts

Figure 2



The cell biology of neuronal migration. **(A)** Schematic drawing of representative structures in a migrating interneuron. A high magnification of the nucleus and associated cytoskeleton and organelles is also depicted. Note that actin and Myosin II are enriched at the rear part of the nucleus and at the proximal aspect of the leading process. **(B)** Schematic of the migratory cycle of cortical interneurons. The cycle starts with the extension of a branch of the leading process (green arrow) and the forward movement of the perinuclear dilatation or swelling, containing the Golgi apparatus and the centrosome (blue arrow). Extension and retraction of different branches of the leading process coexist until one of them is selected. At this time, the nucleus moves forward until the branch point (yellow arrow), which represents the main static point for the cell in the entire cycle. Non-selected processes retract while a new process starts to grow, and the cycle is repeated. **(C)** A high magnification schema of nucleus and cytoskeleton during nucleokinesis. tyr-Tub, tyrosinated tubulin; ace-tub, acetylated tubulin; and t , time.

migration [17]. These experiments reinforce the notion that microtubule stability and membrane trafficking are required for leading process maintenance.

The signaling mechanisms that control leading process branching are presently unknown, although recent work in cerebellar granule cells suggests that this process is modulated by intracellular Ca^{2+} and cAMP levels. Thus, experimentally increasing the concentration of intracellular Ca^{2+} from extracellular sources or internal organelle deposits or stimulating the adenylyl cyclase promotes leading process branching, while reducing the intracellular Ca^{2+} concentration or inhibiting PKA decreases its frequency [12^{*}]. These results suggest that guidance cues regulating intracellular Ca^{2+} and cAMP levels are likely regulators of leading process branching during neuronal migration.

Molecular regulation of nucleokinesis

While the leading process determines the direction in which the neuron moves, effective neuronal migration is only achieved by the subsequent translocation of the cell soma, including the small organelles and the nucleus. Soma translocation occurs in two consecutive phases in most neurons studied so far, as initially described in

cerebellar granule cells [18]. First, a cytoplasmic dilatation or swelling appears in the proximal part of the leading process, toward which the centrosome and the Golgi apparatus moves. Second, the nucleus advances forward and invades the cytoplasmic dilatation (Figure 2).

The movement of centrosome and nucleus is highly dependent on the integrity of a rich network of microtubules with different post-transcriptional modifications that extends between both [18,19^{**},20,21^{*},22]. Most microtubules surrounding the nucleus are tyrosinated, which makes them highly dynamic. By contrast, microtubules at the anterior pole of the nucleus, near the centrosome, are acetylated and therefore more stable. Although the function of these two types of microtubules is not completely understood, they seem to play different roles in somal translocation [20,21^{*}].

It has been hypothesized that the microtubule network surrounding the nucleus is connected with the centrosome, which is the main microtubule-organizing center (MTOC) in these cells. Consequently, it was suggested that the microtubule-dependent pulling forces on the nucleus converge at the centrosome [18,23,24]. Recent experiments, however, have put this hypothesis into

question [21[•]]. Analysis of migrating granule cells in organotypic slices, a preparation that resembles the microenvironment found *in vivo*, suggests that most perinuclear microtubules are not anchored to the centrosome but rather extend into the leading process. In addition, the authors frequently observed that the nucleus in these cells advance forward pass the centrosome, which would argue against a role of this structure in pulling the nucleus. Further experiments would be needed to elucidate whether these observations represent a specialization of granule cells or indeed define a general principle for migrating neurons.

MAPs and related motor proteins are important regulators of the movement of organelles. RNAi experiments have shown that Lissencephaly 1 (Lis1) and the related motor protein dynein are both independently required during centrosome progression and nucleokinesis [19^{••}]. In addition, several proteins involved in cell polarity have been described to play important roles in coordinating the movement of the centrosome and the nucleus in each migratory cycle. Par6 α , for instance, localizes to the centrosome and is required for its forward movement [18]. Similarly, loss of MARK2 (microtubule affinity-regulating kinase 2, also known as Par-1) perturbs centrosome dynamics and blocks the transition of radially migrating pyramidal cells through the multipolar stage (Figure 1) [25[•]]. MARK2 levels are inversely related to the stability of microtubules, and so loss of MARK2 function may impair migration owing to excessive microtubule stabilization. Interestingly, the lissencephaly-associated gene Doublecortin (DCX) is a substrate of MARK2, and loss of DCX function increases microtubule dynamics [26[•]]. Another polarity protein, LKB1 (a Ser/Thr kinase related to Par-4), may also be involved in regulating the transition of migrating neurons through the multipolar stage (Figure 1) [27[•]]. Knockdown of LKB1 in migrating neurons impairs neuronal migration, probably owing to interfering with centrosome–nucleus coupling [27[•]]. It should be noted, however, that genetic loss of *Lkb1* function does not lead to layering defects in the cerebral cortex [28], and so the precise involvement of this protein in neuron migration requires further examination. Nevertheless, disruption of *Lkb1* leads to exuberant leading process branching, which is likely to perturb neuronal migration [27[•],28,29].

Independently of the precise function of MAPs and associated motor proteins in somal translocation, it is unlikely that they alone provide the forces required for the movement of these structures. Several studies have shown that the motor protein Myosin II is enriched behind the nucleus of migrating neurons and that pharmacological blocking its ATPase activity inhibits nucleokinesis, suggesting that rear contraction of actomyosin fibers propels the nucleus [30,31]. Recent work suggests that F-actin and Myosin II motors are also

enriched in the proximal region of the leading process of migrating cerebellar granule cells [32[•]]. Rapid F-actin turnover powered by Myosin II in this region appears to contribute to the forward movement of the centrosome, which in turn facilitates the subsequent displacement of the nucleus [32[•]]. These results are nevertheless controversial, because previous experiments in pyramidal cells led to the suggestion that centrosome movement is independent of Myosin II function [19^{••}].

Recent studies suggest that signals emanating from the cell surface influence centrosome–nucleus coupling, and therefore somal translocation. During cerebellar development, *Sema6A* is expressed in the deep aspect of the external granule layer, where it promotes the inward migration of granule cells through its PlexinA2 receptor [33^{••}]. Interestingly, disruption of *Sema6A*/PlexinA2 signaling impairs centrosome–nucleus coupling, which leads to defective migration [33^{••}]. Although the precise mechanisms linking PlexinA2 activation with the cytoskeleton are currently unknown, these results nicely illustrate that guidance and somal displacement are probably coordinated downstream of surface receptors during neuronal migration.

Adhesion during neuronal migration

Cell migration requires the dynamic regulation of adhesion complexes between migrating cells and surrounding extracellular matrix (ECM) proteins. In many cell types, this process involves integrin-mediated adhesion [34], but the function of this signaling system in neuronal migration has remained controversial. In the CNS, cell adhesion dynamics have been best characterized during glial-guided migration in developing cortical structures [35]. Early *in vitro* studies emphasized a role for neuronal $\alpha3\beta1$ integrin receptors in mediating the interaction of migrating pyramidal neurons with radial glial cells [36]. Subsequent analyses of mouse mutants have in turn focused the attention to radial glial cells, as these cells and their endfeet anchorage to the meningeal basement membrane are dramatically affected in the absence of $\beta1$ integrin signaling [37–39]. According to this later view, integrin function is only indirectly required for migrating neurons, which would otherwise migrate normally in the absence of integrin-mediated adhesion. As migration on two-dimensional substrates naturally overemphasizes the role of adhesion, it is very likely that *in vivo* studies may offer a much more precise idea of the contribution of integrin signaling during neuronal migration. Nevertheless, mouse genetic analyses may have overlooked subtle defects in the motility of integrin mutant neurons [40], which may only cause a minor delay in migration and not a major disruption of cortical layering. Consistent with this notion, two recent studies suggest that integrin signaling cell-autonomously influence neuronal migration. Conditional deletion of neuronal laminin $\gamma1$, a component of the ECM deposited

around migrating neurons and radial glial fibers that binds integrin receptors, disrupts the migration of pyramidal neurons [41]. In addition, specific removal of $\alpha 3$ integrins from tangentially migrating interneurons perturbs their normal distribution as they invade the embryonic cortex, suggesting that these receptors are required to recognize specific guidance cues present in the migratory route of interneurons [42].

Recent studies have provided a new perspective to the role of cell–cell adhesions during radial migration. The Gap junction proteins Connexin 26 and 43 are expressed at the contact points between radial glial fibers and migrating neurons during glial-guided migration [15^{••},43] (Figure 1). Gap junctions are best known for their channel capabilities, which allow the electrical and chemical coupling of cells or the release of small molecules to the extracellular space. During radial migration, however, Gap junctions provide dynamic adhesive contacts between neurons and radial glial fibers that enable the stabilization of the leading process of migrating neurons along radial glial processes [15^{••}]. Very little is known about the mechanisms regulating Gap adhesion dynamics during radial migration, but recent work suggests that the C-terminal tail of connexins is required in this process [44^{*}]. This domain has been shown to regulate mobility in other cell types, and it is known to interact with several cytoskeleton proteins, such as zona occludens-1 (ZO-1) and N-cadherin.

News from the Reelin front

Reelin is crucial for the lamination of cortical structures [45], but the molecular mechanisms underlying its action remain unclear [46]. Genetic studies have positioned Reelin, ApoER2, Vldlr and Dab1 into a common signaling pathway that leads to the phosphorylation of Dab1 in migrating neurons (Figure 3), an event that is required for normal layering of the cortex [47,48]. ApoER2 and Vldlr are the canonical Reelin receptors, but their relative contribution to neuronal migration is controversial. Recent experiments suggest that the neuronal positioning of late-born pyramidal neurons is largely attributable to ApoER2. On the contrary, lack of Vldlr causes ectopic accumulation of pyramidal neurons into layer I, which suggest that both phenotypes (layering and invasion) are molecularly distinguishable [49^{*}] (Figure 3).

The mechanisms underlying Reelin function in neuronal migration are only beginning to be elucidated. Recent experiments have shown that Dab1 tyrosine phosphorylation sites have distinct signaling properties *in vivo* [50] (Figure 3). Two of the putative tyrosine phosphorylation sites, named *ab* sites (Y185 and Y198), are sufficient for the recruitment of Src-family kinases (SFKs), phosphorylation of Dab1 at these sites, stimulation of Akt/PI3K signaling, and targeting activated Dab1 for degradation. The *ab* sites seem also important for the subsequent

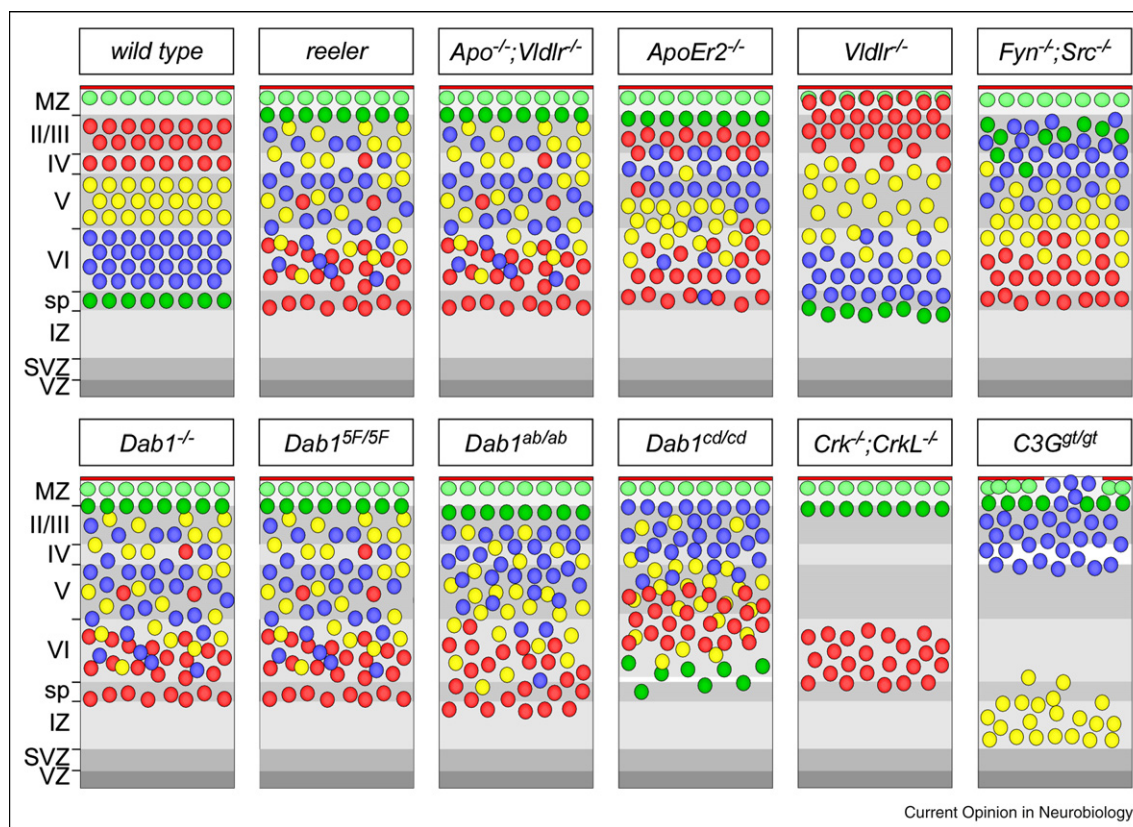
phosphorylation of another two tyrosine residues, the *cd* sites (Y220 and Y232). Previous work has shown that phosphorylation of the *cd* tyrosines is necessary to terminate glial-guided migration, because neurons expressing non-phosphorylatable forms of these residues (Y220F and Y232F mutants, respectively) fail to downregulate the expression of $\alpha 3$ integrin in the cortical plate, and consequently remain attached to the radial glia [51]. This function might be mediated by other elements in the signaling cascade, such as the adaptor proteins Crk and Crk-like (CrkL) and the Ras family guanine nucleotide exchange factor C3G, because their recruitment to the Dab1 complex also requires intact *cd* sites [50]. Moreover, loss of these proteins causes phenotypes that are similar to those described in *reeler* [52^{*},53] (Figure 3). In sum, Dab1 seems to operate both as an activator and scaffold protein through the phosphorylation of the *ab* and *cd* domains, respectively, and both functions are required for normal cortical development *in vivo*.

Recent work has revealed additional elements in the signaling cascade downstream of Dab1. Biochemical experiments suggest that activated Dab1 prevents the degradation of the intracellular, active form of Notch in migrating pyramidal neurons [54^{••}]. It is presently unclear how this process works, since Reelin signaling also promotes the degradation of Dab1 as part of a feedback loop that exists in the pathway [55,56,57^{••}]. In any case, Notch-ICD is cell-autonomously required for the normal positioning of neurons both in the neocortex and in the dentate gyrus [54^{••},58^{*}], suggesting that one of the possible functions of Reelin signaling in cortical development would be to modulate Notch signaling (Figure 4). This would be consistent with the hypothesis that Reelin functions as a signal that incites migrating neurons to adapt their cytoskeleton during glial-guided migration [59]. In *Drosophila* growth cones, for instance, Notch controls actin cytoskeletal dynamics through its interaction with Abl [60]. Consistently, pyramidal cells lacking Notch display abnormal leading processes [54^{••}].

Halting migrations

Upon arrival to their final destination, neurons cancel their migratory program and continue their differentiation into mature neurons. Understanding the mechanisms through which neurons perceive that they have reached their target position has been a puzzling question for a long time, but recent studies have begun to elucidate this issue [61,62]. It has been suggested that early patterns of activity generated in the target region may influence this process. Migrating interneurons, for example, sense ambient GABA and glutamate in their way to the cortex using GABA_A and AMPA/NMDA receptors [63]. At early stages of cortical development, both neurotransmitters seem to depolarize migrating cells, inducing intracellular Ca²⁺ transients that promote cell movement. Upon arrival to the cortex, interneurons upregulate the expression of the

Figure 3



The genetics of Reelin signaling. Schematic drawings of the distribution of cortical pyramidal cells in wild type mice and in different mouse mutants related to the Reelin signaling pathway. In wild type mice, early born pyramidal cells split the preplate in two layers, the marginal zone (MZ, light green circles) and the subplate (sp, dark green circles), to form the cortical plate. Here, subsequent cohorts of pyramidal cells are organized according to an inside-out sequence to progressively form layers VI to II (blue, yellow and red circles). The absence of Reelin (*reeler* mice), both Reelin receptors (ApoER2 and *Vldlr*) or the intracellular adaptor protein *Dab1* all cause the same phenotype: the preplate does not split and the layering pattern is grossly inverted. Mouse mutants for individual Reelin receptors have milder phenotypes than double mutants and reveal specific differences in their function. Loss of ApoER2 leads to a phenotype that is similar to that found in the double receptor mutant, although milder. On the contrary, the absence of *Vldlr* primarily affects the late-born pyramidal cells, which end up migrating all the way to the basement membrane in the MZ. Although layering has been investigated in these mice, the preplate state was not specifically addressed; the schema thus depicts the most likely situation. The function of *Dab1* involves tyrosine phosphorylation by the Src-family kinases *Fyn* and *Src*. Mice with point mutations in all tyrosine residues phosphorylated in *Dab1* upon Reelin activation (*Dab1^{S5F/S5F}*) or with simultaneous loss of both kinases (*Fyn^{-/-}; Src^{-/-}*) reproduce the phenotype found in *reeler* or *Dab1* mutants (scramble, *yotari* or *Dab1^{-/-}* mice). When point mutations only affect the so-called *ab* residues (Y185, Y198), the phenotype is very similar to complete loss of *Dab1*. By contrast, point mutation of the *cd* residues (Y220, Y232) does not impair preplate splitting and causes a relatively milder layering phenotype than that found in *Dab1* mutants. Biochemical experiments suggest that *Crk*, *Crk*-like (*CrkL*) and *C3G* are downstream effectors of the Reelin signaling pathway, whose activation is dependent on *Dab1* phosphorylation at the *cd* residues. Mice that are homozygous for *C3G* hypomorphic alleles (*C3G^{gt/gt}*) fail to split the preplate and have inverted layering, but in addition show disruption of the basal lamina (red line) and many neurons fail to migrate altogether. Conditional deletion of both *Crk* and *CrkL* using a *Nestin-Cre* mouse line leads prominent cortical defects, with preplate splitting failure and roughly inverted layering. It should be noted that the layering defects in both *C3G^{gt/gt}* and *Crk^{-/-}; CrkL^{-/-}* double mutants requires a more detailed examination. *Apo*, *ApoER2*; IZ, intermediate zone; SVZ, subventricular zone; VI, *Vldlr*; and VZ, ventricular zone.

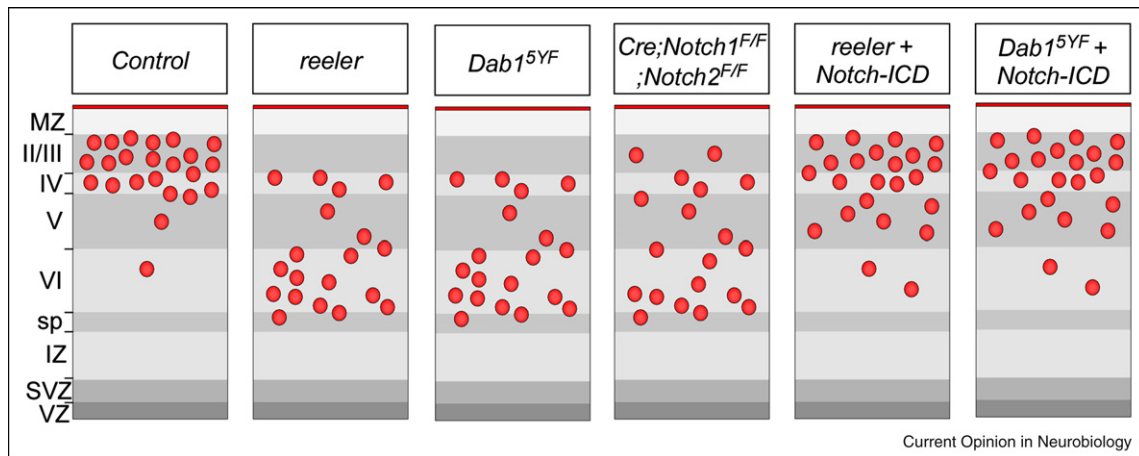
potassium/chloride (K^+/Cl^-) exchanger *KCC2*, which modifies their response to GABA from depolarizing to hyperpolarizing. This later event leads to a reduction in the Ca^{2+} influx, and since this is ultimately needed for movement, the net result is that neurons end up halting their migration [64**]. According to this model, *KCC2* expression determines the end of the migratory period for cortical interneurons, although the underlying mechanisms remain to be clarified. To this end, it would be

important to understand the dynamics of *KCC2* expression in interneurons, as these cells tend to invade the cortex in different waves according to their birth date [65].

Migration and disease

Neurological syndromes caused by disruption of neuronal migration are among the most devastating human disorders (Table 1). They typically arise during mid-embryonic stages and are mostly due to genetic causes

Figure 4



Notch signaling meets Reelin. The schemas depict the analysis of the laminar allocation of neurons born at E14.5 in the embryonic mouse cortex, which are normally allocated to supragranular layers. In *reeler* or *Dab1* mutants (in this particular case *Dab1*^{5YF/5F} mice, which carry point mutations in all tyrosine residues phosphorylated in Dab1 upon Reelin activation), many neurons born at E14.5 end up located in deep layers of the cortex. A very similar phenotype is observed when Notch is inactivated in migrating pyramidal cells (*Cre;Notch1*^{F/F};*Notch2*^{F/F}). Remarkably, reintroduction of the activated intracellular domain of Notch (Notch-ICD) in pyramidal cells rescue the layering phenotype in both *reeler* and *Dab1*^{5YF/5F} mice, suggesting that Notch-ICD is downstream of Dab1 in the Reelin signaling pathway.

(for an extensive review see, for example, Refs. [2,66]). Recent studies have shown that *de novo* mutations in α and β tubulin genes cause lissencephaly, pachygyria, and polymicrogyria syndromes in humans [67*,68*]. Analysis of orthologous mutations in mice revealed that they also disrupt cortical neuronal migration, probably owing to impaired formation of tubulin heterodimers. These results reinforce the view that disruption of microtubule-based processes underlies a large spectrum of neuronal migration disorders.

Migration disorders are considered untreatable, but recent findings have opened new venues for therapeutic intervention [69**]. Double cortex syndrome or subcortical band heterotopia (SBH) is caused by mutations in the X-linked gene *DCX*. It is characterized by periventricular accumulation of a large population of neurons, which fail to migrate during embryonic development. Remarkably, postnatal re-induction of the *Dcx* gene in the cortex of a rat model of SBH (generated by *in utero* RNAi against the *Dcx*) restores the ability of arrested cells

Table 1

Genes implicated in migration leading to human neurological syndromes

Gene	Migratory defect	Molecular defect	Syndrome	Ref.
<i>Tuba3a</i>	Abnormal lamination of hippocampus and cortex	Tubulin polymerization defects	Lissencephaly, pachygyria	[67*]
<i>Tubb2b</i>	Accumulation of late-born neurons in deep cortical layers (SVZ/IZ)	Tubulin polymerization defects	Polymicrogyria	[68*]
<i>Gpr56</i>	Basal lamina disruption in neocortex and cerebellum	Defective interaction glial endfeet-pial membrane	Polymicrogyria (BFPP)	[70,71]
<i>Drd1</i> and <i>Drd2</i>	Disrupted tangential migration of cortical interneurons	Unknown	Fetal cocaine syndrome	[73]
<i>Slc6a4</i>	Disrupted tangential migration of cortical interneurons	Unknown	Depression related to polymorphism 5-HTTLP in <i>SLC6A4</i>	[74]
<i>Nrg1/ErbB4</i>	Disrupted tangential migration of cortical interneurons	Decreased PI3K recruitment and activation	Schizophrenia	[75,76]
<i>Disc1</i>	Accumulation of late-born neurons in deep cortical layers (SVZ/IZ). Abnormal migration in hippocampus	Abnormal dynein function. Disrupted Disc1–NDEL1 interaction	Schizophrenia, depression, bipolar disorder	[77–79]
<i>App</i>	Accumulation of late-born neurons in deep cortical layers (SVZ/IZ)	Abnormal Dab1 activation	Alzheimer's disease ^a	[80]

^a APP dysfunction in Alzheimer's disease does not seem to involve neurodevelopmental mechanisms, but recent work suggests that APP might also be implicated in the regulation of neuronal migration during development.

to migrate into their proper layers in the cortex. Moreover, this intervention rescues the phenotypic deficits linked to this model of SBH, including the epilepsy that is also associated to the human disorder [69**].

Mutations in GPR56, an orphan G-protein-coupled receptor (GPCR), cause another type of polymicrogyria (BFPP), a severe disorder characterized by mental retardation and seizures. Analysis of the cerebellum of GPR56 mouse mutants has revealed major morphological abnormalities [70], reminiscent of those described in human patients. Intriguingly, GPR56 seems to be responsible for the regulation of adhesion to the basal lamina both in the cerebral cortex and cerebellum [70,71], suggesting a crucial role in the maintenance of the pial basement membrane and morphogenesis.

Multiple lines of evidence suggest that a loss of excitatory/inhibitory balance in specific brain circuitries may be responsible for some of the symptoms observed in several psychiatric disorders, such as schizophrenia, anxiety, or depression [72]. Defects in the migration of cortical interneurons are a likely source of abnormal inhibitory tone in the developing cortex, and several neurotransmitters linked to human pathologies have been shown to influence this process. For example, dopamine receptor activation influences interneuron migration [73]. Similarly, mouse mutants for the serotonin transporter gene *Slc6a4*, which in humans has been associated with an increased risk of depression, have defects in the distribution of cortical interneurons. These mice have high levels of extracellular serotonin, and experimental evidence suggests that serotonin activation of 5-HT₆ receptors in cortical interneurons decreased their migration [74].

Conclusions

Our knowledge of the mechanisms underlying the cell biology of migration is rapidly expanding, in particular in relation to nucleokinesis. There are, however, important questions that remain to be addressed. For example, we know very little about the mechanisms coordinating the guidance of the leading process with the movement of the nucleus. We also ignore the mechanisms that allow the coordinated allocation of different classes of neurons to the same region of the brain, as it is the case for the cerebral cortex. Finally, several genes linked to important neurological and neuropsychiatric disorders, such as *NRG1* [75,76], *DISC1* [77–79], or the β -amyloid precursor protein *APP* [80], are required for neuronal migration, but we still ignore the relevance of these findings in the disease process. Detailed analysis of all these questions should expand our knowledge of this central process in the development of the nervous system.

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In this manuscript, the authors demonstrate that tangentially migrating interneurons (and probably many other cell types throughout the nervous system) continuously branch their leading processes as part of their migratory cycle. They also show that interneurons use binary choices of leading process branches instead of leading process steering to achieve directional migration.

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- This study shows that intrinsic programs may dictate the behavior of migrating neurons in the absence of external cues, and that the later influence migration by modulating Ca²⁺ influx and cAMP levels.

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This paper reveals that the adhesive properties of Gap junctions mediate the dynamic interaction between pyramidal neurons and radial glial fibers during glial-guided migration. RNAi experiments suggest that both Cx26 and Cx43 seem to be required for pyramidal cell migration. The precise

mechanisms through which connexins interact with the cytoskeleton remain to be elucidated, although the authors suggest that signaling through the carboxy-terminal domains of connexins is not required in this process. This later result is in conflict with reports from a different laboratory (see annotation in Ref. [44*]).

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Besides providing the first example of the transcriptional regulation of the spatio-temporal expression of a small GTP-binding protein, this paper demonstrates that *Rnd2* is required for the radial migration of cortical pyramidal cells.

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The authors provide evidence that LIS1 and dynein are both required for the movement of the centrosome and the nucleus, and that their function in both processes is independent. Their experiments also suggest that myosin contributes to nuclear movement, but is dispensable for centrosome migration. This later finding is in conflict with recent experiments from the Hatten laboratory (see annotation in Ref. [32*]).

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This manuscript dissociates microtubule pulling forces from the centrosome, by arguing that most microtubules that form the perinuclear cage do not converge at the centrosome but rather extend into the leading process.

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The authors show that reducing or increasing MARK2 levels disrupts multipolar to bipolar transition of migrating pyramidal neurons in a kinase-independent manner, probably owing to altered microtubule dynamics. MARK2 kinase function is subsequently required for the proper migration of pyramidal cells into the cortical plate.

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This paper suggests that MARK2 and DCX have opposite functions in regulating microtubule stability. Thus, while MARK2 function seems to destabilize microtubules, DCX reduces microtubule dynamics. Knock-down of both proteins have different effects in centrosome movement: while loss of MARK2 prevents centrosome motility, reduction of DCX levels leads to rapid, disorganized movement of this structure.

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Using RNAi experiments, the authors show that LKB1 is required for the radial migration of pyramidal neurons. Thus, besides its role in establish-

ing cell polarity in these cells (see Ref. [28] for an elegant analysis of the function of LKB1 in this context), LKB1 seem to participate in the molecular machinery required for centrosome-nucleus coupling during migration.

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This elegant paper presents evidence that links the Reeling signaling pathway with Notch signaling in migrating pyramidal cells. The authors demonstrate that Notch-ICD is cell-autonomously required by pyramidal cells for radial migration. Moreover, Notch-ICD levels are reduced in *reeler*, and re-expression of Notch-ICD in *reeler* mutant neurons rescue the migration phenotype. It is suggested that phosphorylated Dab1 blocks the degradation of Notch-ICD, although at this point it is unclear how regulation of Dab1 (whose degradation is also induced by Reelin, see Ref. [57**]) influences this process.

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