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Neurons in motion: same principles for different shapes?

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The special conformation of the developing nervous system, in which progenitor zones are largely confined to the lumen of the neural tube, places neuronal migration as one of the most fundamental processes in brain development. Previous studies have shown that different neuronal types adopt distinct morphological modes of migration in the developing brain, indicating that neuronal migration might be a diverse process. Here, we review recent data on the molecular mechanisms underlying neuronal migration that suggest that similar signaling principles are responsible for the frequently variable morphology of different types of migrating neuron. According to this idea, the same basic molecular mechanisms found in other cell types, such as fibroblasts, might have been adapted to the special morphological needs of migrating neurons in different regions of the developing brain.

Introduction

Cell migration is a fundamental process in the biology of most living creatures, from single-celled organisms to humans. In multicellular organisms, cell migration not only has a pivotal role during embryonic morphogenesis, but also contributes to multiple processes in the adult, such as tissue repair and the immune response. The specific organization of the neural tube during embryonic development, which greatly limits the origin of new neurons to the neuroepithelium that surrounds the ventricular space, defines the nervous system as the organ in which cell migration is at its most complex. The most extreme case is the human brain, the intricate cytoarchitecture of which results from the coordinated migration of millions of neurons.

In this article, we review recent data on the cellular and molecular mechanisms that underlie neuronal migration in the developing nervous system, with the aim of providing an integrated view of this process. We suggest that similar mechanisms control the migration of different types of neurons, independently of their morphology, pattern of migration or location in the brain. Moreover, we hypothesize that many of the mechanisms that control the movement of neurons are likely to be analogous to those described in other cell types, such as fibroblasts.

Migrating neurons have diverse morphologies

The amazing diversity in the morphology adopted by migrating neurons in different regions of the brain poses a major obstacle in the search for common mechanisms in neuronal migration. Radially migrating neurons are typically described as bipolar, with opposing leading and trailing processes. By contrast, tangentially migrating neurons, which migrate perpendicularly to radial glia, appear to have a much more diverse morphology. Some tangentially migrating neurons have a short and compact leading process, as is the case for migrating neuroblasts in the rostral migratory stream. Other neurons, by contrast, have a long process that stretches for hundreds of microns ahead of the nucleus, as is the case for migrating precerebellar neurons in the pons. Tangentially migrating neurons can also have a distinctly branched leading process, as observed in migrating cortical interneurons.

Over the years, the morphological heterogeneity found in migrating neurons has been systematically considered as obvious evidence that diverse mechanisms control the migration of different types of neuron. However, there is increasing evidence that a neuron can adopt distinct morphologies at different times during its migration (Figure 1). Even cortical pyramidal cells, which have been consistently described as the prototypic bipolar migrating neurons, become transiently multipolar during an early phase of their migration towards the cortical plate [1]. Similar morphological changes also occur during the migration of cerebellar granule cells and cortical interneurons, so it seems to be a common feature for many migrating neurons. From this perspective, it is tempting to speculate that migrating neurons use a common set of signaling mechanisms to migrate, which they might then adapt to their specific morphology.

Neuronal migration consists of distinct steps

Cell migration has been comprehensively studied in fibroblasts and in other model cells. In these cells, different cellular domains seem to be responsible for carrying out specific tasks cyclically during cell migration [2]. Neuronal migration can also be described as a cyclic multi-step process that consists of interrelated but independent discrete events [3] (Figure 2). Migration is initiated by the chemotactic response, which leads to cell polarization and extension of the leading process, followed by somal translocation. The nucleus is the most prominent organelle that moves during the forward repositioning of the soma, in a process commonly referred as nucleokinesis [3]. Parallel to these events, rearrangements in adhesive elements of the plasma membrane lead to overall movement of the neuron.

In migrating neurons, the leading process is formed by a palm-like lamellipodium built on a meshwork of actin and

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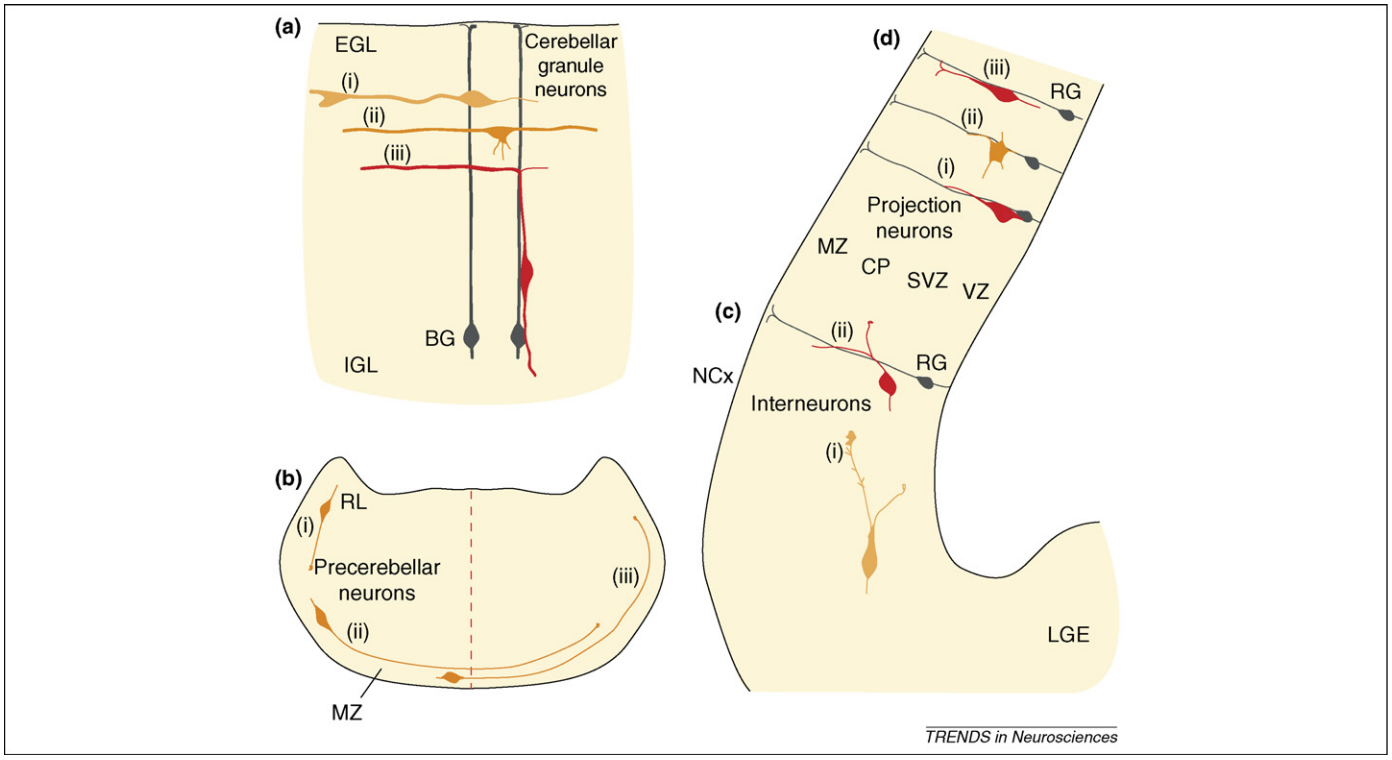

Figure 1. Migrating neurons adopt multiple morphologies. **(a)** Migration of cerebellar granule neurons during postnatal development [mouse postnatal day (P) 0–10]. Granule neurons first move tangentially through the external granule layer (EGL) (i); they then extend a process perpendicular to the surface (ii) and move radially towards the internal granule layer (IGL) (iii), in close contact with Bergmann glia (BG). Simultaneously, parallel fibers left behind by the migrating cell continue growing in the EGL. **(b)** Migration of precerebellar neurons during embryonic development [mouse embryonic day (E) 13–17]. Neurons move from the caudal rhombic lip (RL) to the most superficial region of the brainstem marginal zone (MZ) (i), and then they travel tangentially towards the midline (red broken line) as they extend a long leading process that into the contralateral side (ii). During most of the migration, the moving soma is far from the tip of the leading process (iii); the leading process eventually becomes the axon, which begins to elongate even before the cell soma reaches its final position [56]. (c,d) Migration of cortical neurons during embryonic development (E13–18). **(c)** Interneurons migrate from the subpallium tangentially towards the neocortex (NCx) (i). After reaching their appropriate position in the cortex, they move radially along radial glia (RG) to their corresponding cortical layer, where they differentiate (ii). **(d)** Projection neurons first migrate radially from the ventricular zone (VZ) to the subventricular zone (SVZ) (i), where they become transiently multipolar (ii). After a few hours, they reinitiate their movement towards the cortical plate (CP) using radial glia processes as guides (iii). Additional abbreviation: LGE, lateral ganglionic eminence.

finger-like filopodia made of actin bundles. Despite the close resemblance of such leading processes – especially long leading processes – to growing axons, analysis of molecular markers suggests that these two structures differ molecularly to a large extent, bearing strong similarity only at their distant tips (growth cones) [4]. During extension of the leading process, actin polymerization exerts protrusion forces; these are the net result of continuous remodeling by extension and retraction linked to the exploratory activity of the growth cone. Microtubules also grow during the elongation of the leading process. In addition, extension of the leading process requires the establishment of adhesion complexes that link the extracellular substrate to the actin cytoskeleton. Adhesive cell–substrate interactions of neurons that migrate along radial glia seem to be mediated by integrins [5], but little is known about the nature of interactions between other migrating neurons and their substrates.

The translocation of the soma and its organelles into the leading process, which is the most characteristic feature of neuronal migration, involves two consecutive steps. The first step is the appearance of a cytoplasmic dilatation in the leading process, immediately ahead of the nucleus. This swelling is prominent in several types of tangentially migrating neuron [6,7], but has also been observed in neurons that migrate radially [8]. In migrating interneurons, this transient compartment is occupied by the centrosome, which comprises the main microtubule organizing centre (MTOC), the Golgi apparatus, the mitochondria and the rough endoplasmic reticulum. During the movement of the swelling ahead of the nucleus, the centrosome splits and the Golgi apparatus acquires a linear conformation [6]. Despite the distance between the nucleus and the centrosome (1.5–15.0 μm, depending on the neuron type), the centrosome seems to remain constantly attached to the nucleus as it moves forwards through a net of microtubules – also described as a fork-like structure – that enwraps the nucleus in a cage-like fashion in cerebellar granule cells [9,10] and radially migrating cortical neurons [11]. Because the distance between the nucleus and the centrosome varies during migration, and because microtubules do not support strong stretching or compressing forces, it is likely that the microtubule network between the nucleus and the centrosome is restructured in distinct phases of the migratory cycle by the elongation or shortening of microtubules.

The second step in somal translocation is nucleokinesis, which relocates the nucleus forwards into the cytoplasmic dilatation previously occupied by the MTOC and other organelles [6,7]. As in other cell types, nucleokinesis occurs as a distinct step during neuronal migration, although it is not equally apparent in all migrating neurons. Thus,

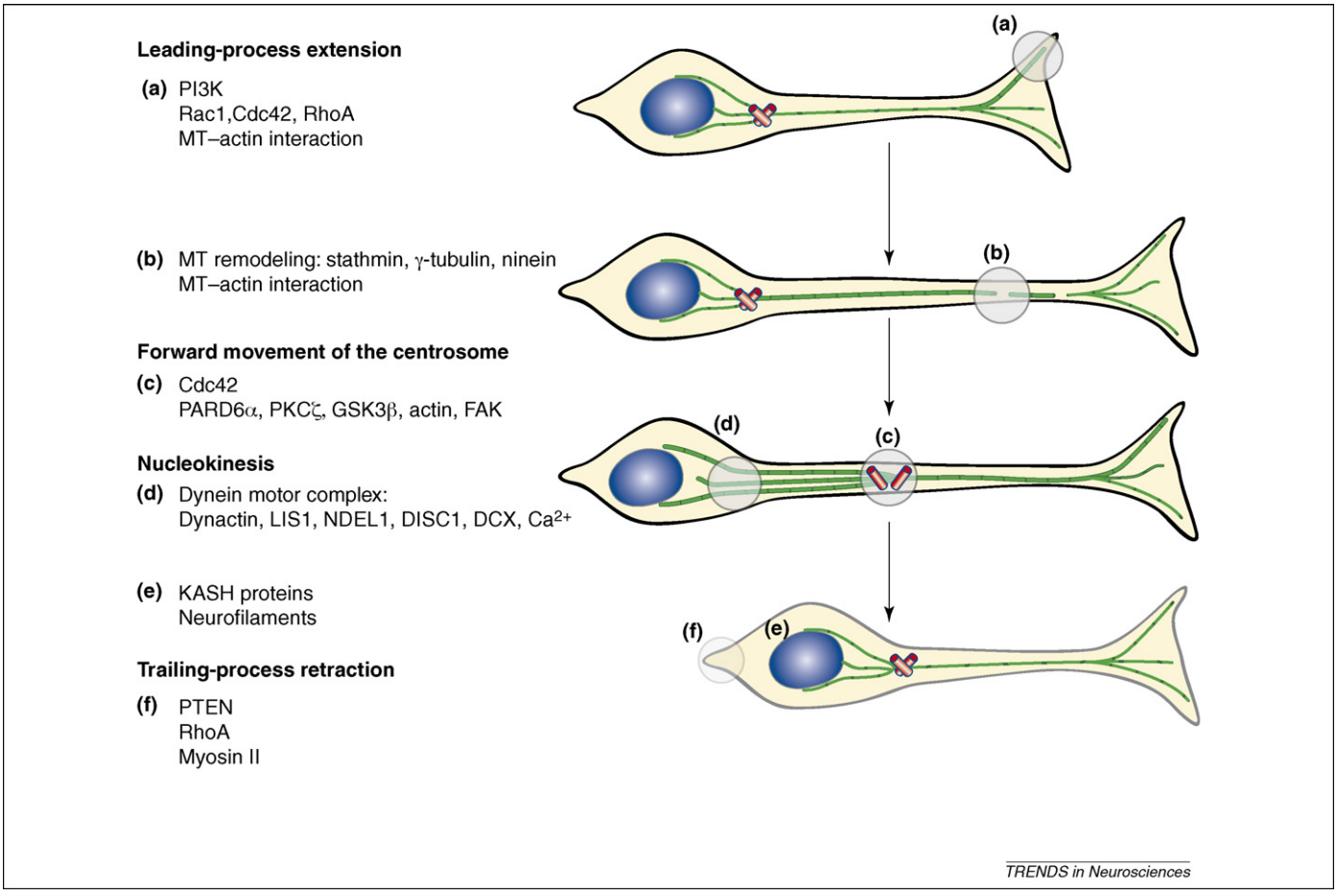

Figure 2. Steps in neuronal migration and molecules involved. (a,b) Polarized extension of the leading process. **(a)** PI3K signaling at the front of the cell regulates the balance of activation of the Rho GTPases Cdc42, Rac1 and RhoA. Inhibition of RhoA enhances leading-process outgrowth, whereas inhibition of Rac1 and Cdc42 impairs neurite outgrowth. Microtubule plus ends are recruited to the cortical actin meshwork. **(b)** In the intermediate segment of the leading process, microtubules (MT, green) are loosely organized, probably owing to the destabilizing activity of stathmin. γ-Tubulin and the microtubule-related protein ninein show a wide distribution in migrating neurons. **(c)** Forward movement of the centrosome. Cdc42 is found mainly in the perinuclear region. Forward movement of the centrosome (red rods) involves PARD6α and its associated kinase PKCζ; reorientation of the centrosome requires the activity of GSK3β, PKCζ and the actin cytoskeleton. Focal-adhesion kinase (FAK) also contributes to centrosomal dynamics. Both centrioles split during the advance of the soma. (d,e) Movement of the nucleus (blue oval) towards the centrosome (nucleokinesis). **(d)** Nucleokinesis requires a microtubule motor complex based on dynein; proteins interacting within this include dynactin, LIS1, NDEL1, DISC1 and DCX. DCX molecules are found attached to microtubules that extend from the centrosome to the perinuclear 'cage'. Ca^{2+} signaling might also operate at this stage. **(e)** Various components of the KASH family of proteins anchor the nucleus to the centrosome and cell membrane. Neurofilaments might contribute to connecting the nucleus to the cell cortex. **(f)** Trailing-process retraction. PTEN signaling at the back regulates RhoA. Actomyosin contraction has a role in driving the nucleus towards the centrosome.

nuclear movement in migrating neurons is most evident when it occurs without net advance of the leading process (the somal translocation mode of migration [12]), or in neurons that have multiple branches (e.g. cortical interneurons) or a long leading process (e.g. precerebellar neurons). By contrast, the discrete movement of the nucleus is difficult to detect when the front of the migrating cell is also moving, as during glia-guided radial migration of neurons (the 'locomotion' mode of migration [12]). However, the fact that nucleokinesis cannot be easily distinguished as a distinct event in some migrating neurons, as is the case in migrating fibroblasts, does not necessarily mean that neurons can move their leading process, soma and trailing process simultaneously.

Independently of the rate of nuclear displacement, nuclear movement seems to involve the participation of microtubules [10,13]. Actomyosin activity at the rear of the nucleus also contributes to the nucleokinesis by providing a pushing force that squeezes the nucleus forward [6,7]. This process can occur concurrently with the rupture of cell adhesions at the back of the cell and the concomitant retraction of the trailing process, which leads to the end of the migratory cycle.

Molecular basis of polarization and leading-process advance

Knowledge of the molecular mechanisms that direct the initial polarization of migrating neurons is still fragmentary. As in other cell types, the chemotactic response that initiates neuronal migration requires the amplification of small differences in extracellular chemical gradients generating steeper intracellular gradients. In many cell types, this involves polarized distribution of phosphoinositides [e.g. PtdIns(4,5)P_2 (PIP_2) and PtdIns(3,4,5)P_3 (PIP_3)]; this is mediated by localized accumulation at the front of the cell of phosphoinositide-3-kinase (PI3K), which generates PIP_3, and by restricted localization and activation at the rear of the cell of the phosphatase and tensin homolog (PTEN), which transforms PIP_3 into PIP_2 [14]. Similarly, the initial response of postmitotic neurons to motogenic

and/or chemotactic factors frequently involves activation of the PI3K–Akt pathway [15–17], and experimental disruption of PI3K or PTEN function perturbs both radial and tangential migration [8,16,18].

PI3K signaling regulates the activity of the cytoskeleton by modulating the balance of activation of the Rho GTPases Cdc42, Rac1 and Rho [19]. In other cell types, Cdc42 is active towards the front of migrating cells during chemotactic responses and contributes to polarization by localizing the MTOC ahead of the nucleus. Similarly, Rac1 is also polarized to the front of migrating cells and is involved in promoting directional extension of protrusions through a signaling loop that also involves Cdc42 and PI3K. In radially migrating cortical neurons, Rac1 is present in the plasma membrane, where it might be required for the formation of leading processes and/or their adhesion to radial glia; in these cells, Cdc42 is mainly perinuclear, and it might contribute to polarization of this region. Inhibition of Rac1 or Cdc42 activity prevents the polarization of cortical neurons, suggesting that the regulated activity of these small GTPases is essential for the polarization of migrating neurons in response to guiding molecules [8]. In agreement with this notion, Cdc42 is inactivated during chemorepulsion induced by Slit proteins in neurons derived from the anterior portion of the subventricular zone (SVZa) [20]. In contrast to Rac1 and Cdc42, RhoA activity has been linked to cytoskeleton dynamics at the back of the cell [2]. Thus, the initial polarization of cortical projection neurons seems to require the transient inactivation of RhoA, as suggested by recent experiments in which the migration phenotype of cortical pyramidal neurons that lack the transcription factor neurogenin-2 is partly rescued by expression of a dominant-negative form of RhoA [21].

Several proteins, including GDP-dissociation inhibitors, guanine-nucleotide exchange factors and GTPase-activating proteins, spatially and temporally regulate the activity of small Rho GTPases. At least two of these activators, T-cell lymphoma invasion and metastasis 2 (TIAM, also known as STEF) and SET-domain-containing 6 (SETD6, also known as P-REX1), have been shown to regulate radial migration [22,23]. In addition, several other proteins involved in neuronal migration seem to control cell polarization, at least in part, through the regulation of small Rho GTPases. For example, the product of the gene lissencephaly 1 (LIS1, also known as platelet-activating factor acetylhydrolase isoform 1b or PAFAH1B1) has been frequently linked to nuclear translocation (see the following section), and it promotes actin polymerization in migrating neurons by indirectly regulating RhoA activity [24].

Regulation of the cytoskeleton by Rho GTPases is the final mechanism that mediates extension of migrating cells in a specific direction. Several effectors downstream of Rho GTPases directly influence actin dynamics in migrating neurons; these include enabled vasodilator-stimulated phosphoprotein (Evl, also known as Ena and VASP), neuronal Wiskott–Aldrich syndrome protein (WAS, or N-WASP), destrin (DSTN, also known as the actin-depolymerizing factor ADF), non-muscle cofilin (CFL1) and the actin-related protein 2/3 (ARPC2/3) complex. Ena/VASP proteins, which are concentrated at filopodial tips, regulate the assembly of long actin filaments in response to chemotactic signals [25], and are thereby fundamental for the normal positioning of cortical pyramidal neurons [26]. CFL1, which depolymerizes actin branches in older parts of the actin meshwork, is also essential for normal polarization of migrating neurons, as shown by analysis of neural crest cell migration in CFL1 mutant mice [27].

In addition to Rho GTPases, other molecules have a prominent role in neuronal migration through their interaction with the cytoskeleton. For example, the mouse protein disabled homologue 1 (DAB1) might activate WAS directly and induce actin polymerization through the ARPC2/3 complex [28]. Moreover, inhibition of cyclin-dependent kinase inhibitor 1B (CDKN1B, also known as p27), which is regulated by cyclin-dependent kinase 5 (CDK5), results in decreased F-actin levels in neuronal processes and perturbed radial migration [29], a phenotype that can be rescued by inactivation of the RhoA GTPase [30].

The contributions of the microtubule cytoskeleton to neuronal polarization and motility are incompletely understood. Although the microtubules ensure the stabilization and advance of the leading front, the more proximal parts of the leading process, which must accommodate the advance of the nucleus, most probably require a microtubule destabilizing activity that maintains microtubules in a loosely organized state. Stathmin, a microtubule-destabilizing protein that is expressed at high levels in migratory pathways in the developing brain, might have such a role [31]. Even the centrosome, which represents the fixed centroid in stationary cells, is a mobile structure in migrating neurons, when the two centrioles split from one another during the advance of the soma. Consistently, γ-tubulin [32] and the microtubule-related protein ninein [6,33], which are associated with the centrosome in stationary cells, are more widely distributed in migrating neurons, suggesting that microtubules reconfigure continuously in the proximal parts of the leading process during migration. Remarkably, reorientation of the centrosome in migrating neurons derived from the SVZa requires the activity of glycogen synthase kinase 3β (GSK3β), protein kinase Cζ (PKCζ) and the actin cytoskeleton, but not that of microtubules [34].

Regulation of the centrosome and nuclear movement

As described earlier, somal translocation takes place in two phases: an initial phase that involves the movement of the centrosome and of the Golgi apparatus; and a second phase during which the movement of the nucleus takes place. The alternation of these two phases produces the appearance of the saltatory movement that has often been described in migrating neurons. During this saltatory movement, the centrosome and the nucleus alternate their anchoring and release from other cell structures to coordinate their movement within the cell. Thus, disruption of the mechanisms responsible for their anchoring or movement both lead to impaired nucleokinesis. Experimental interventions that uncouple the movements of the centrosome and the nucleus are becoming extremely useful for elucidating

the specific processes in which a particular molecule is preferentially involved.

Movement of the centrosome during somal translocation seems to involve partitioning-defective 6α (PARD6α), which participates in acquisition of polarity and in orientation of the mitotic spindle in various cell types. PARD6α and its associated kinase, PKCζ, localize to the centrosome in radially migrating neurons. Overexpression of PARD6α in migrating cerebellar cells disrupts the perinuclear tubulin cage, re-targets PKCζ and γ-tubulin away from the centrosome, and inhibits centrosomal motion, which leads to decreased distance between centrosome and nucleus and to impaired migration [10]. Movement of the centrosome also seems to involve Cdc42, which is present in the pericentrosomal region of migrating neurons [8] and activates the PARD6α–PKCζ complex [35] and GSK3β [34] in other cell types. Focal-adhesion kinase is also present in this region and seems to contribute to centrosomal dynamics during somal translocation [11].

Nuclear movements require a microtubule motor complex that is based on dynein and includes dynactin, LIS1/PAFAH1B1, NudE-like protein (NDEL1, formerly known as NUDEL) and disrupted in schizophrenia 1 (DISC1). Dynein, a minus-end microtubule motor, can be anchored to plasma membrane sites in the neuronal leading process or at the nuclear membrane [36], and might therefore mediate movement of the centrosome and Golgi apparatus and also movement of the nucleus [3]. Uncoupling of these movements during neuronal migration has been observed both in *LIS1*$^{+/-}$ neurons and in wild-type neurons after disruption of dynein function, which leads to a net increase in the distance between nucleus and centrosome. Interestingly, the centrosome–nucleus uncoupling in *LIS1*$^{+/-}$ neurons or after dynein inhibition can be rescued by overexpression of doublecortin (DCX), a microtubule-associated protein that is located along the microtubules that extend from the centrosome to the perinuclear 'cage' [13]. These results suggest that LIS1 and DCX function with dynein to mediate the movement of the nucleus towards the centrosome. Similarly, NDEL1, the mammalian homolog of yeast NudE, also enhances dynein activity and contributes to the centrosome–nucleus coupling by facilitating the interaction between LIS1 and dynein [37]. Finally, *DISC1*, mutation of which is associated with major psychiatric illness [38], interacts with NDEL1 to anchor the dynein complex to the centrosome during nucleokinesis [39]. Together, current evidence suggests that the cortical lamination defects observed in loss-of-function experiments involving LIS1, dynactin, NDEL1, DCX, doublecortin and Ca^{2+}/calmodulin-dependent protein kinase-like 1 (DCAMKL1 or DCLK) or DISC1 are due, at least in part, to uncoupling of the centrosome and the nucleus during nucleokinesis, so that the distance between them increases [37,40–46]. Thus, the function of this protein complex seems to be crucial in the second phase of soma translocation: the nuclear movement. Notably, although most of the current evidence is based on the analysis of radially migrating neurons, this multi-protein complex seems to have the same role in tangentially migrating neurons [47,48].

As described earlier in this review, current evidence suggests a model of nucleokinesis in migrating neurons in which the PARD6α–PKCζ complex participates in forward movement of the centrosome into the leading process, and the dynein motor complex participates in translocation of the nucleus towards the centrosome. Interestingly, in migrating wound-edge fibroblasts, in which polarity is acquired by retrograde movement of the nucleus while the centrosome remains stationary [49], dynein, PARD6α and PKCζ are also needed to maintain the centrosome at the cell centroid, and the movement of the nucleus is coupled with an actin retrograde flow regulated by a pathway that involves Cdc42, MRCK-type Cdc42-binding proteins, myosin and actin. Thus, despite the extreme morphological differences, similar mechanisms might contribute to the regulation of the coordinated movement of the nucleus and the centrosome in both fibroblasts and neurons.

Translocation of the nucleus in migrating neurons also requires fine coordination between the movements directed by the microtubule-based motor complex and the actin cytoskeleton. Inhibition of non-muscle myosin II, which accumulates at the rear of migrating cortical interneurons, blocks the forward movement of the nucleus [6]. So actomyosin contraction probably also has a role driving the nucleus towards the centrosome. In addition to the microtubule and actomyosin components of the cytoskeleton, other elements are likely to be required in coordinating the movement of the centrosome and nucleus. Klarschit, a member of the KASH family of proteins that links the nucleus to the centrosome by interacting with the microtubule cytoskeleton, is needed for nuclear positioning during development of photoreceptors in *Drosophila* [50]. Other members of this family of proteins, including synaptic nuclear envelope 1 (SYNE1, also known as ANC-1, MSP-300 and nesprin-1) and SYNE2 (nesprin-2), link the nucleus to the actin cytoskeleton. SYNE1 participates in the migration of myonuclei and their anchoring at the postsynaptic apparatus. Finally, nesprin-3 binds to plectin, which could connect the nucleus to the cell cortex through the intermediate-filament cytoskeleton [51]. The function of these proteins in migrating neurons in vertebrates remains to be elucidated.

Signaling nucleokinesis

Rho GTPases have been implicated in the control of nucleokinesis during neuronal migration. Because these proteins are also involved in other steps in neuronal migration, their function in nuclear translocation has been unequivocally established only in precerebellar neurons, in which the length of the leading process enables the dissociation of growth-cone dynamics and nuclear movement. In these cells, inhibition of Rho enhances leading-process outgrowth but prevents migration of the nucleus, whereas inhibition of Rac1 and Cdc42 impairs neurite outgrowth without affecting nucleokinesis [52].

Intracellular Ca^{2+} signaling is also involved in nuclear translocation, although evidence for this is still fragmentary. The amplitude and frequency of Ca^{2+} fluctuations correlate positively with the rate of cerebellar granule cell movement in culture, although tonic elevation of

intracellular Ca^{2+} ($[Ca^{2+}]_i$) arrests cell movement [53]. $[Ca^{2+}]_i$ polarization has been correlated with the active phase of nucleokinesis in migrating cortical interneurons [32], suggesting that changes in $[Ca^{2+}]_i$ associated with translocation of the soma are spatially and temporarily regulated to trigger nucleokinesis efficiently. In agreement with this notion, changes in the direction of movement induced by chemorepulsive signals are preceded by changes in $[Ca^{2+}]_i$ gradients [54].

Ca^{2+} influx might also enhance neuronal motility through LIS1-dependent regulation of Rho GTPases [55]. Specifically, LIS1 promotes Cdc42 activation through interaction with the Ca^{2+}-sensitive GTPase scaffolding protein IQGAP1, maintaining its perimembrane localization and so recruiting microtubule plus ends at the cortical actin meshwork, as previously demonstrated in fibroblasts.

Towards an integrated view of neuronal migration

Despite the intricate and diverse morphology adopted by neurons during migration, the different types of neuron seem to share common principles in their migratory program. Moreover, because cell migration is fundamental not only to vertebrate development, but also to the development of plants and single-celled organisms, it seems reasonable that many of the basic elements underlying the process of migration should be common to many cell types, including neurons. Our understanding of the molecular basis of neuronal migration has progressed significantly over the past few years. In our opinion, this knowledge is starting to modify current views of this fascinating process, which uniquely influences brain development in both health and disease.

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