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# Molecular mechanisms of cell polarity in a range of model systems and in migrating neurons

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ABSTRACT

Cell polarity is defined as the asymmetric distribution of cellular components along an axis. Most cells, from the simplest single-cell organisms to highly specialized mammalian cells, are polarized and use similar mechanisms to generate and maintain polarity. Cell polarity is important for cells to migrate, form tissues, and coordinate activities. During development of the mammalian cerebral cortex, cell polarity is essential for neurogenesis and for the migration of newborn but as-yet undifferentiated neurons. These oriented migrations include both the radial migration of excitatory projection neurons and the tangential migration of inhibitory interneurons. In this review, I will first describe the development of the cerebral cortex, as revealed at the cellular level. I will then define the core molecular mechanisms – the Par/Crb/Scrib polarity complexes, small GTPases, the actin and microtubule cytoskeletons, and phosphoinositides/PI3K signaling – that are required for asymmetric cell division, apico-basal and front-rear polarity in model systems, including *C elegans* zygote, *Drosophila* embryos and cultured mammalian cells. As I go through each core mechanism I will explain what is known about its importance in radial and tangential migration in the developing mammalian cerebral cortex.

## 1. Introduction

Most animal cells are polarized, with anisotropic distribution of membrane components, internal cytoskeletal structures, organelles and signaling machinery. Polarity is essential for unicellular animals to migrate and find prey, and for individual cells in multicellular animals to form tissues and coordinate their activities. Differentiated mature neurons are commonly cited as an example of highly polarized mammalian cells. However, before reaching this final asymmetric state, immature neurons undergo a succession of polarized events. For instance, cell polarity plays a crucial role during the development of the cerebral cortex that goes from a thin neuroepithelial sheet to a complex structure with layers composed of different types of neurons and glia (Kon et al., 2017). During this process, asymmetric division of neural stem cells is important to determine the fate of the daughter cells by imposing a differential inheritance of fate determinants that are asymmetrically distributed in the dividing mother cell. The neuroepithelium exhibits an apico-basal polarity typical of epithelia with adhesive junctions that bind the cells together and separate the apical surface from the basolateral domain. After the last cell division, newborn undifferentiated neurons migrate away from their place of birth to settle down in a distant area. During their oriented migration, neurons maintain a front-rear polarity. One prominent feature is the presence of a long leading process facing towards the direction of migration. This process contains the centrosome, working as the microtubule-organizing center (MTOC), and the Golgi apparatus. Finally, mature neurons display axon-dendrite polarity with an axon at one side of the cell and neurites at the other side. The apico-basal polarity of cortical neural stem cells and the axon-dendrite polarity of mature neurons do not change over time. On the other hand, the front-rear polarity of migrating neurons is dynamic and reacts to diverse signals from the environment along the cell's path. Current techniques allow scientists to investigate in details these cells. Neuronal oriented migration can be studied in a simplified controlled *in vitro* environment or in an *in vivo*-like organotypic tissue culture and recorded using time lapse videomicroscopy. Neuronal migration and positioning are crucial for the establishment of functional neural circuitry. Not surprisingly, defects in establishing and maintaining a correct oriented neuronal migration has deleterious effects on the formation of the cerebral cortex and are associated with human developmental brain disorders.

Here we will mainly focus on neuronal migration and more specifically the radial migration of excitatory neurons and the tangential migration of inhibitory interneurons. Fully differentiated functional cortical neurons are born in a germinal zone located at a distance from their final adult position. Intracellular molecular mechanisms come into play to make sure immature neurons gain and sustain a cell polarity,

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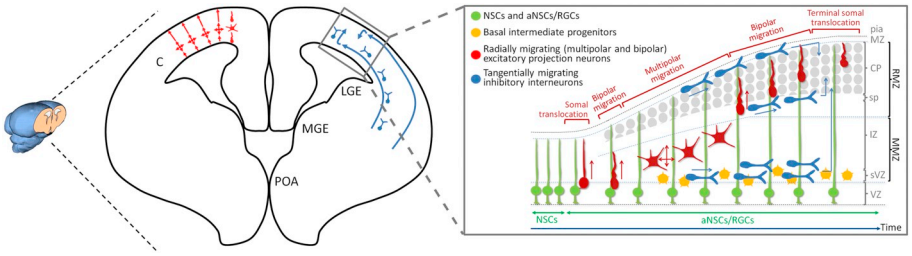


**Fig. 1.** Radial and tangential migrations in the developing neocortex

Before neurogenesis, neural stem cells (NSCs) (in green) located at the ventricular zone (VZ) self-renew then become apical neural stem cells/radial glia cells (aNSCs/RGCs) (in green) that produce glutamatergic excitatory projection (pyramidal) neurons (in red) and basal intermediate progenitors (in yellow). Basal progenitors are located at the subventricular zone (sVZ) and produces projection neurons. Projection neurons migrate radially. This radial migration comprises the glia-dependent bipolar migration and the glia-independent somal translocations and multipolar migration. Inhibitory interneurons (in blue) originate from the ventral subcortical forebrain. Interneurons migrate tangentially to reach the cerebral cortex where they will enter specific layers after switching to a radially oriented movement. Arrows show the directions of migration. C: Cerebral Cortex; LGE: lateral ganglionic eminence; MGE: medial ganglionic eminence; PA: preoptic area; MZ: marginal zone; CP: cortical plate; sp.: subplate; IZ: intermediate zone; RMZ: radial morphology zone; MMZ: multipolar morphology zone. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

necessary to move, and ensure that the orientation of migration is maintained adequately to reach the correct final destination.

In this review, I will first give an overview on the development of the cerebral cortex, including the separate origins and migration routes of excitatory neurons and interneurons, and their different modes of migration as revealed at the cellular level (Summarized in Fig. 1). Then I will describe five core molecular mechanisms, namely the Par/Crb/Scrib polarity complexes, small GTPases, the actin and microtubule cytoskeletons, and phosphoinositides/PI3 kinase signaling that govern asymmetric cell division, apico-basal and front-rear polarity in model systems such as the *C elegans* zygote, *Drosophila* embryos, epithelial sheets, and cultured mammalian astrocytes and fibroblasts. After discussing the basic principles of each of these core molecular processes, I will explain what is known about its involvement in cortical neuron migration (Summarized in Fig. 2).

## 2. Background: cerebral cortex development and neuron migrations

The vertebrate nervous system appears at the end of gastrulation when the dorsal midline ectoderm undergoes thickening to form the neural plate which curves into the neural groove bracketed by the two neural crests. The neural crests then become apposed and fuse together, thus sealing the neural groove and creating the neural tube. This process is called neurulation and occurs between embryonic days 19 and 29 in humans and between embryonic days 7 and 9 in mice (Stiles and Jernigan, 2010). The neural tube generates the central nervous system while the neural crests give rise to elements of the peripheral nervous system such as the sensory ganglia of spinal and cranial nerves, and the autonomic ganglia. The rostral part of the neural tube develops initially into 3 vesicles: primary prosencephalon, mesencephalon (midbrain) and rhombencephalon (hindbrain). As development proceeds, the primary prosencephalon divides into the diencephalon, which forms mainly the thalamus, and the secondary prosencephalon, which gives rise to the hypothalamus ventrally, the eye vesicles dorsolaterally, the telencephalic vesicles (cerebral hemispheres) dorsally, and a ventral telencephalic preoptic area (Moreno and Gonzalez, 2011).

The germinal layer of the future telencephalon is a pseudostratified neuro-epithelium primarily containing neural stem cells (NSCs) that proliferate symmetrically which increase their number and expand the tissue laterally until embryonic day 11.5 in the mouse and gestation week 5–6 in humans (Takahashi et al., 1995; Zecevic et al., 2005). These cells then transform into more fate-restricted stem cells called apical neural stem cells (aNSCs) or radial glia cells (RGCs). RGCs are able to self-renew, giving rise to two RGCs through symmetric cell division or divide asymmetrically to produce one RGC and either one neuron or one basal progenitor (also called intermediate progenitor) (Anthony et al., 2004; Miyata et al., 2004; Noctor et al., 2004). Basal progenitors do not have apical contact with the ventricular surface, are multipolar in shape and move basally away from what is now called ventricular zone (VZ). They are located basally to the VZ in the subventricular zone (sVZ) and produce neurons, increasing indirectly the neuronal production by RGCs (Haubensak et al., 2004; Sessa et al., 2008; Kowalczyk et al., 2009; Vasistha et al., 2015; Turrero Garcia and Harwell, 2017). Neurogenesis is initiated and the tissue starts to expand radially. Production of basal progenitors starts at around E12 in the mouse and at gestation week 7–8 in humans (Zecevic et al., 2005). Other proliferative cells were also identified such as the short neural precursors located in the VZ and directly produce neurons (Stancik et al., 2010; Turrero Garcia and Harwell, 2017). At the sVZ, outer RGCs are rare but present in the mouse while they are more prominent in humans resulting in the expansion of the sVZ with an outer sVZ (Fietz et al., 2010; LaMonica et al., 2012; Pollen et al., 2015). In humans, outer RGCs are RGCs that have lost their apical contact with the ventricular surface. They undergo multiple rounds of asymmetric division to self-renew and produce basal progenitors and become the predominant radial scaffold and main neuronal progenitors by 17 gestational weeks (Nowakowski et al., 2016). At the end of neurogenesis, RGCs produce oligodendrocyte and astrocyte then, finally, transform into astrocytes (Kessaris et al., 2008; Freeman and Rowitch, 2013; MuhChyi et al., 2013).

The cerebral cortex contains two major types of neurons based on neurotransmitter expressions: glutamatergic excitatory projection (pyramidal) neurons and GABAergic inhibitory interneurons (Molyneaux et al., 2007; Kumamoto and Hanashima, 2014; Mukhtar and Taylor, 2018). These cells migrate long distances from their germinative zone to their final destination within the cerebral cortex, where they integrate into common neuronal circuits. The peak of neuronal migration in the mouse takes place from E12 to E16 while in humans it occurs from gestational week 12 to 20 (Jaglin and Chelly, 2009; Turrero Garcia and Harwell, 2017). Excitatory neurons are produced within the cortex and constitute the majority of cortical neurons (Fig. 1). They migrate radially in successive waves from the VZ and sVZ to occupy progressively more superficial positions within the cortical plate (CP), moving past the neurons already installed. This results in the development of a 6-layered cortical structure with younger neurons in the outermost field of the cerebral wall and older neurons more inside. Neurons within each layer share similar properties and functions (Gaspard and Vanderhaeghen, 2011; Kumamoto and Hanashima, 2014; Mukhtar and Taylor, 2018). Inhibitory cortical interneurons travel a much larger distance compared to excitatory neurons (Fig. 1). They originate from the ventral subcortical forebrain with the medial and caudal ganglionic eminences (MGE and CGE respectively) as the primary sources and a small diverse subset of interneurons originating in the preoptic area (Gelman et al., 2009; Hansen et al., 2013; Ma et al., 2013; Chu and Anderson, 2015). Diffusible cues such as ephrin A5, netrin 1 and Slit1/2 repel migrating neurons from their germinative zone (Hamasaki et al., 2001; Marin et al., 2003; Zimmer et al., 2008) while other signaling proteins such as the chemokine stromal-derived factor 1 (SDF1), neuregulin-1 and neuregulin-3 attract them into the

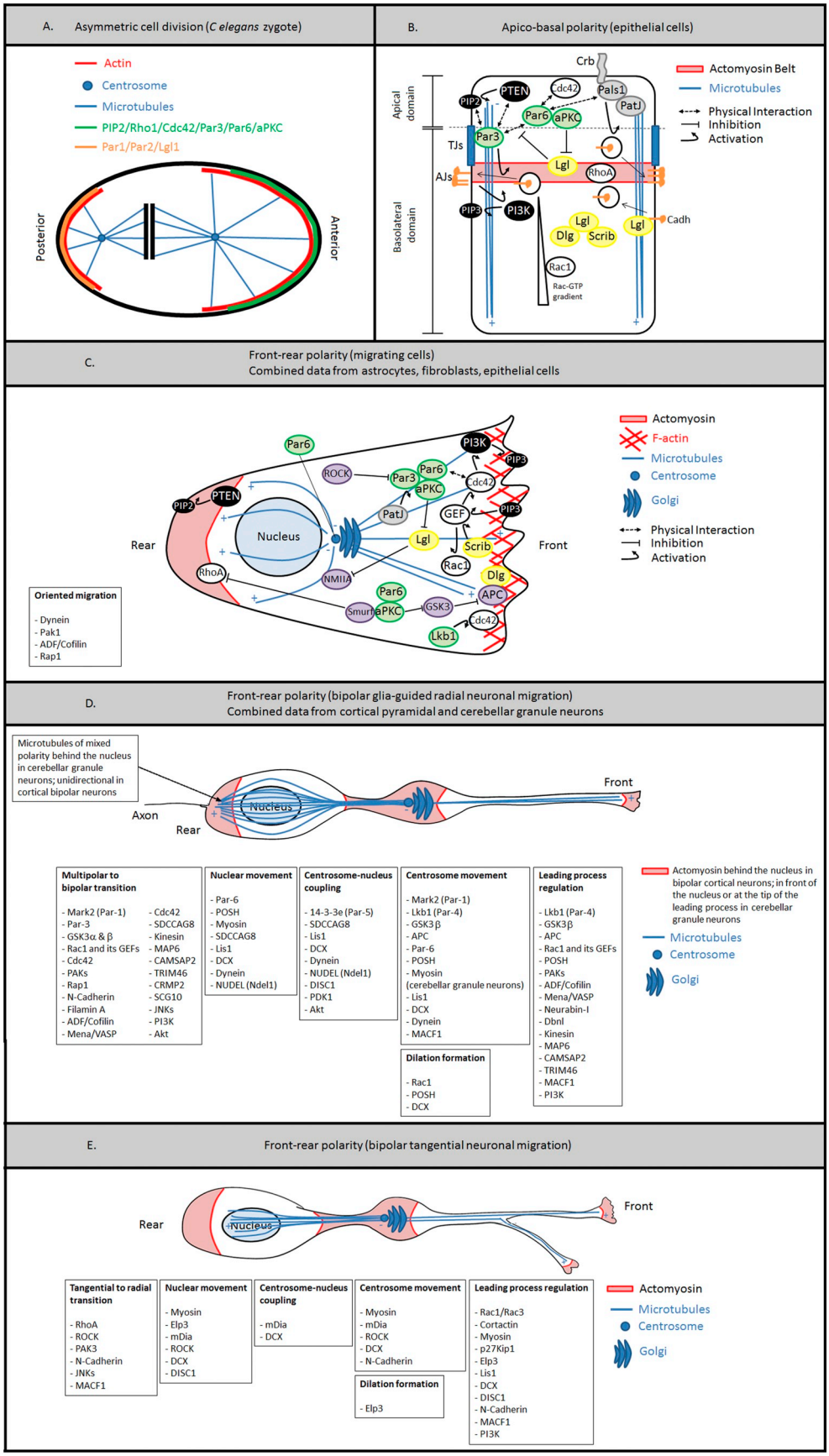


**Fig. 2.** Summary of the main polarity-defining molecules described in this review and involved in various polarity model systems.

A. Mitosis in the one cell stage early embryo of *C. elegans* is a well-known model for the study of asymmetric cell division. In the *C. elegans* zygote, the first division is asymmetric with regard to the partition of the cytoplasm which will give rise to two non-equivalent daughter cells. The polarity cue initiating the embryonic anterior-posterior polarity is provided by the sperm which will initiate an asymmetric positioning of the mitotic spindle and the asymmetric distribution of proteins. B. In mammalian epithelial cells, development of an apico-basal polarity allows the organization of two well defined domains separated by tight junctions. C. In slow migrating cells such as fibroblasts, astrocytes and epithelial cells, a polarized organization of intracellular molecules and structures allow the formation and maintenance of a leading edge with membrane extensions and the retraction of the rear of the cell. These regulations allow a sustained orientation of migration into the desired direction. D-E. Bipolar radial and tangential migration of cortical neurons is characterized by a saltatory movement defined by the formation of a dilation/swelling at the proximal region of the leading process, the forward migration of the centrosome and Golgi into the dilation followed by the nucleus. Polarity-defining molecules are regulating different aspects of these oriented migrations such as: nuclear movement, centrosome-nucleus coupling, centrosome movement, formation of the dilation/swelling, formation and regulation the leading process, multipolar to bipolar transition in cortical projection neurons and tangential to radial transition in interneurons. PIP2: PtdIns(4,5)P3; PIP3: PtdIns(3,4,5)P3.

cerebral cortex (Flames et al., 2004; Tiveron et al., 2006; Bartolini et al., 2017). The striatum is also a highly repulsive structure for cortical interneurons with its expression of class 3 semaphorins Sema3A and Sema3F (Marin et al., 2001). Interneurons migrate through different streams from the ganglionic eminences across the cortico-subpallial boundary and course tangentially into the cortex (Marin and Rubenstein, 2001). An early stream of interneurons migrates on top of the preplate, a later stream migrates into the cortex through the intermediate zone and some interneurons migrate through the cortical proliferative zone. Then, at later stages, streams of interneurons enter the cortex through the lower intermediate zone, the sVZ, the subplate and the marginal zone (Marin and Rubenstein, 2001). Once in the cortex, interneurons switch their direction of migration and move radially to enter the CP (Ang Jr. et al., 2003; Tanaka et al., 2006; Yokota et al., 2007). Similarly to projection neurons, the laminar positioning in the cortex shows an inside-out pattern for somatostatin+,parvalbumin+, and calbindin+ subtypes of MGE- and preoptic area-derived interneurons while CGE-derived calretinin+ interneurons do not (Ang Jr. et al., 2003; Valcanis and Tan, 2003; Rymar and Sadikot, 2007; Bartolini et al., 2013). The laminar distribution might depend on signals provided by pyramidal neurons as interneurons adopt their position after the differentiation of cortical layers and disruption of pyramidal neurons layering affects the cortical distribution of interneurons (reviewed in (Lim et al., 2018)).

## 3. Cell morphology and dynamics of migrating cortical neurons

### 3.1. Radial migration of projection neurons

During the early phase of cortical neurogenesis, the cerebral wall is thin. A short and straightforward movement is sufficient for newborn neurons to displace their cell body away from the proliferative zone. At that stage, early-born neurons inherit a basal process from the division of the mother cell (Miyata et al., 2001; Kosodo et al., 2008). The nucleus and other organelles translocate within the elongated cytoplasm while the cell detaches from the apical surface (Miyata et al., 2001; Nadarajah et al., 2001; Gupta et al., 2002). This short movement is called “somal translocation” and might not be considered as a migration *per se* (Fig. 1). The polarity seems to be directly inherited from the apicobasal polarity of the mother cell.

As the neocortex develops, the cerebral wall increases in thickness. The distances travelled by radially migrating neurons reach several hundred microns in the mouse and range from 1 to 4 mm in humans (Defelipe, 2011). The somal translocation mode of migration is gradually replaced by a radial migration subdivided into four steps: a short bipolar migration during which postmitotic cells move away from the VZ, followed by a multipolar migration. Cells then transit back to the bipolar locomotion and finish their journey with a terminal somal translocation (Fig. 1) (Nadarajah et al., 2001; Tabata and Nakajima, 2003; Noctor et al., 2004). Neurons born from intermediate basal progenitors follow the same migration steps as the ones born from RGCs but without the initial bipolar migration. Multipolar neurons exhibit several neurites that extent and retract dynamically while the cell is migrating. Multipolar neurons are still polarized cells otherwise they would not be able to migrate but their orientation is quite dynamic as they are switching direction of movement frequently in the tangential and radial directions. The net movement is however still directed towards the pial surface. During the bipolar locomotion that follows, pyramidal neurons migrate on radial glia fibers that are extensions from the RGCs and that span the entire depth of the cerebral wall (Campbell and Gotz, 2002). Locomoting neurons exhibit a single leading process with very few branches (Rakic, 1972; Nadarajah et al., 2001). Its branching increases aberrantly when its interaction with radial glia fibers is defective (Gupta et al., 2003; Elias et al., 2007). Bipolar neurons move in a saltatory manner. After extension of the leading process, the centrosome and Golgi apparatus, which are most of the time in front of the nucleus, advance into a cytoplasmic swelling or dilation of the leading process (Tsai et al., 2007). This is followed by translocation of the elongated nucleus, an event suggested being dependent on the centrosome and microtubules (see below). But occasionally, nucleokinesis occurs prior to centrosome movement, after what the centrosome positions again in front of the nucleus (Sakakibara et al., 2014). Similar overtaking of the centrosome by the nucleus has been observed in migrating cerebellar granules, another model of bipolar radial migration, and in migrating zebrafish rhombic lip-derived neurons (Umeshima et al., 2007; Distel et al., 2010). Even though the vast majority of cortical radially migrating neurons in the cortex exhibit the centrosome in front of the nucleus (Insolera et al., 2014), this is suggesting the existence of a centrosome-independent mechanism of nucleokinesis which could involve actomyosin (see below). When reaching close to the top of the CP, neurons detach from the radial fibers and perform a terminal somal translocation (Fig. 1) (Nadarajah et al., 2001; Sekine et al., 2011).

The orientation of multipolar and bipolar migration is regulated by extracellular cues. Multipolar neurons migrate towards the CP while also dispersing laterally. These movements are both under the control of Ephrins and Reelin signaling (Torii et al., 2009; Jossin and Cooper, 2011; Dimidschstein et al., 2013) (discussed in (Kon et al., 2017)). On the other hand, locomoting bipolar neurons move unidirectionally towards the pial surface, attracted by a descending gradient of semaphoring-3A across the cerebral wall (Chen et al., 2008). Tgfβ extracellular signaling is also required for bipolar migration, maybe through its activation of JNK (Yi et al., 2010; Zhang et al., 2016).

### 3.2. Tangential migration of inhibitory interneurons

During their migration from the ganglionic eminences to the cerebral cortex, tangentially migrating interneurons are bipolar and continuously extend multiple branches from their leading process in order to sense directional cues and orient their migration accordingly (Martini et al., 2009). The branching is more dynamic and extensive compared to radially migrating projection neurons. This might originate from the different substrate on which they migrate. While locomoting bipolar projection neurons move along radial fiber tracks, interneurons travel a much longer distance at a higher speed and are therefore more likely to require a constant sensing of positional cues across their path. High resolution time-lapse videomicroscopy on telencephalic slices or on a flat permissive substrate revealed that interneurons respond to chemoattractant signals by generating new leading process branches that are better aligned with the source of the gradient, and not by reorienting previously existing branches (Bellion et al., 2005; Martini et al., 2009). This is also the case during the migration of precerebellar neurons, neuroblasts in the rostral migratory stream and immature enteric neurons (Ward et al., 2005; Hao et al., 2009; Watanabe and Murakami, 2009). Once the direction is set, the centrosome and the Golgi apparatus translocate into a swelling of the leading process. In a second phase, the nucleus translocates towards the swelling and the trailing process retracts (Bellion et al., 2005). Growth and branching of the leading process stop during somal translocation. This results in a saltatory movement alternating resting phases with phases of nuclear movement which seems uncorrelated to the degree of branching of the leading process (Britto et al., 2009). Similarly to what was observed for the radial migration, translocation of the Golgi/centrosome sometimes either precedes or occurs in parallel to that of the nucleus when observed in living embryos, suggesting the possibility of independent movements (Yanagida et al., 2012).

## 4. Molecular mechanisms of cell polarity

Cell polarity can be described as an asymmetric and ordered distribution of structures and molecules along an axis resulting in intracellular gradients, asymmetric cell shape and compartmentalized

functions. Polarization is necessary for a broad range of cell functions such as asymmetric division, oriented migration, transport of molecules or nerve impulses and to perform as a barrier. Structures such as cell-surface subdomains, the cell cytoskeleton, cellular organelles and lipids, RNA or proteins are reorganized by the cell to generate, maintain or modify its polarity. Polarity starts with a break in symmetry and is commonly triggered by external, mechanical or biochemical cues. But cells may as well polarize spontaneously, albeit in an apparent stochastic manner, when an obvious external signal is absent such as in *in vitro* culture (Wedlich-Soldner and Li, 2003; Altschuler et al., 2008). This is suggesting that the role of the sum of the multiple extracellular signals received by the cell *in vivo* is to activate an intrinsic symmetry-breaking pathway in a desired fashion. The changes in polarity can be very dynamic and short-lived such as the front-rear polarity of migrating cells that varies with their direction of movement. While in other system such as epithelial cells, the apico-basal polarity is quite stable and maintained for a long period of time, helped by reinforcing mechanisms. Polarization can be seen as a succession of important steps: It generally starts with an initial symmetry-breaking cue from an external signal or the unequal distribution of cytoplasmic factors. Then, intracellular signaling pathways amplify the initial cue resulting in the generation of distinct subcellular domains. The cytoskeleton is also involved in these events and its rearrangements settle morphological changes.

Below I describe the function of polarity protein complexes, small GTPases, actin and microtubule cytoskeletons and phosphoinositides/PI3K signaling during several physiological processes. These processes include asymmetric cell division, epithelial apico-basal polarity, and the front-rear polarity in migrating cells. For each of these molecules and associated proteins, I explain their involvement in the radial and tangential neuronal migrations during embryonic development of the cerebral cortex (Summarized in Fig. 2).

### 4.1. Polarity complexes

Three major groups of polarity proteins are commonly involved in different signaling pathways, depending on the polarity context, and act together to generate and maintain polarity: The Par complex including the Partitioning defective proteins (Par proteins) and atypical protein kinase C (aPKC); the Scribble (Scrib) complex ((Scrib, Disc Large (Dlg) and Lethal giant larvae (Lgl)); and the Crumbs (Crb) complex formed by Crb, proteins associated with Lin-7 1 (PALS1) and Pals1 associated tight junction protein (PATJ). They are highly conserved in multicellular organisms and evidence from studies in multiple organisms and cell types suggest a conserved molecular mechanism for polarity initiation and maintenance.

#### 4.1.1. The Par-aPKC complex

The Par-aPKC complex makes reference to two scaffold proteins, PAR6 and PAR3 and an atypical protein kinase C (aPKC). In mammals three PAR6 proteins encoded by three different genes have been identified: PAR6A, PAR6B and PAR6G encoding PAR6α, PAR6β and PAR6γ, respectively (Joberty et al., 2000; Gao and Macara, 2004). They all contain a Phox/Bem 1 (PB1) domain, a Cdc42/Rac interaction binding (CRIB) motif and a PDZ domain. Mammalian PAR3 proteins contain three PDZ domains and a C-terminal aPKC-binding region and are encoded by two genes *Pard3* and *Pard3b*. There are two aPKC homologs in mammals (aPKCι/λ and aPKCζ) encoded by two different genes (Ono et al., 1989; Selbie et al., 1993).

*4.1.1.1. The Par-aPKC complex in asymmetric cell division.* The *Par* genes were discovered in genetic screens for regulators of cytoplasmic partitioning necessary to establish anterior/posterior polarity during mitosis in the one cell stage early embryo of *C. elegans*. *C. elegans* embryo is the best studied example of asymmetric cell division due to its large cell size, simplicity, transparency of the animal and strictly defined hierarchy of cell divisions. In total six *Par* genes were identified and named Par1 to 6 (Kemphues et al., 1988). Par1 and Par4 are serine/threonine protein kinases (Morton et al., 1992; Guo and Kemphues, 1995), Par2 is a putative E3 ubiquitin ligase with its RING finger domain (Levitan et al., 1994), the PDZ domain-containing Par3 and Par6 are scaffolding proteins (Etemad-Moghadam et al., 1995; Watts et al., 1996), and Par5 is a member of the 14–3-3 protein family that binds to phosphorylated serines and threonines (Morton et al., 2002). PKC3, an ortholog of mammalian aPKC, is a serine/threonine kinase that co-localizes in a co-dependent manner with PAR3 and PAR6 and has a similar loss of function phenotype in *C elegans* (Tabuse et al., 1998). In the one cell stage early embryo of *C. elegans* most of the Par proteins are required for the asymmetric positioning of the mitotic spindle (important for asymmetric division) and for the asymmetric distribution of proteins and RNAs (important for cell fate decision). The first division is asymmetric with regard to the partition of the cytoplasm. The daughter cell that becomes the anterior region of the adult is significantly larger than the other daughter cell that becomes the posterior region. In Par mutant embryos, the division appeared symmetric and the fate of the daughter cells is altered. The polarity cue initiating the embryonic anterior-posterior polarity is provided by the sperm. Before symmetry breaking, newly fertilized *C. elegans* zygotes have no predetermined anterior/posterior polarity. PAR3, PAR6 and PKC3 are uniformly distributed at the cell cortex, and keep PAR1 and PAR2 in the cytoplasm. During symmetry breaking, the sperm centrosome contacts the cortex, eliciting the recruitment of PAR1 and PAR2 to the cortex nearest to the MTOC on the posterior periphery of the zygote and enrichment of PAR3, PAR6 and PKC3 at the anterior periphery (Fig. 2a). PAR4 and PAR5 remain symmetrically localized through this period, and are both cortical and cytoplasmic (St Johnston and Ahringer, 2010; Motegi and Seydoux, 2013). After the establishment of polarity, a maintenance phase takes place. PAR2 sustains anterior-posterior polarity by excluding the PAR3/PAR6/PKC3 complex from the posterior cortex (Cuenca et al., 2003). In the anterior cortex, PKC3 phosphorylation of PAR2 prevents its cortical association (Hao et al., 2006).

Similarly, the mammalian Par complex regulates asymmetric division and fate determination. During mammalian oocyte maturation, PAR3 becomes asymmetrically localized during meiosis and plays a role in defining the future site of polar body emission (Duncan et al., 2005). Par complex components are expressed at the apical surface of the murine cortical neuro-epithelium (Costa et al., 2008). During neurogenesis, aNSCs either divide symmetrically to self-renew or asymmetrically to produce another aNSC and either a neuron or a basal progenitor (See references in (Kon et al., 2017)). Pard3 is enriched at the lateral domain in the ventricular end-feet of aNSCs during interphase but shows asymmetric segregation as the cell cycle progresses (Bultje et al., 2009). The daughter cell that accumulates Pard3 will become the aNSC while the other one will differentiate. Pard3 loss of function during early neurogenesis leads to increased aNSCs symmetric proliferative division resulting in an overproduction of aNSCs while its deletion during late neurogenic phases results in increased symmetric neurogenic division resulting in a depletion of aNSCs (Costa et al., 2008; Bultje et al., 2009; Liu et al., 2018). It was suggested that Pard3 regulates the balance between proliferation and differentiation through the temporal regulation of the Hippo and Notch pathways (Liu et al., 2018). In epithelial cells, Par6α seems to regulate protein transport to the centrosome (Kodani et al., 2010). Its depletion causes the mislocalization of centrosomal components critical for microtubule anchoring at the centrosome which results in blockade of cell division. In the adult *Drosophila* midgut, asymmetric division of intestinal stem cells depends on the unequal distribution of Par3, Par6 and aPKC into the apical daughter cell driving its differentiation, as a consequence of an aPKC-induced enhanced Delta/Notch signaling (Goulas et al., 2012).

Par proteins are also important in *C elegans*, *D melanogaster* and mammalian cells in polarized events such as the apico-basal polarity of

epithelial cells and the front-rear axis of polarized migrating cells (Izumi et al., 1998; Joberty et al., 2000; Etienne-Manneville and Hall, 2001; Nance et al., 2003; Welchman et al., 2007) as discussed below.

*4.1.1.2. The Par-aPKC complex in apico-basal epithelial polarity*. In MDCK epithelial cells, PAR3 is recruited to the plasma membrane by its interaction with the cytoplasmic tails of Nectins 1 and 3 through its PDZ domain (Ooshio et al., 2007). This association promotes the recruitment of Afadin and Cadherins to further the development of adhesive junctions. In epithelial cells, homodimerization of Par3 seems important to bind to the junctional protein JAM (Junctional adhesion molecule) at cell-cell contacts *via* Par3 first PDZ domain during polarization and formation of an apical domain (Ebnet et al., 2001; Itoh et al., 2001; Mizuno et al., 2003). Once located at these sites, Par3 acts as a scaffold protein and interacts with Par6 and aPKC (Fig. 2b) (Joberty et al., 2000; Suzuki et al., 2001). The recruitment of the Par6-aPKC complex to Par3 enables aPKC-mediated phosphorylation of specific substrates (Nagai-Tamai et al., 2002; Horikoshi et al., 2009). Suppression of Par3 expression by RNA interference or disturbance of Par3-Par6 interaction causes a dramatic disruption of tight junction assembly (Joberty et al., 2000; Chen and Macara, 2005). Liver kinase B1 (LKB1, also known as serine/threonine kinase 11 (STK11)) is a serine/threonine kinase homologous to the Par4 polarity genes in *C. elegans* and *D. melanogaster*. Activation of Lkb1 induces apico-basal polarization of intestinal epithelial cells even in the absence of intercellular contacts, challenging the current view that cell-cell contact is important for apico-basal polarization (Baas et al., 2004). Conditional deletion of Lkb1 in the mammary gland compromises epithelial integrity revealed by mislocalization of cell polarity markers and lateralization of tight junctions (Partanen et al., 2012).

*4.1.1.3. The Par-aPKC complex in front-rear polarity of migrating cells*. Wound induced directed migration of astrocytes and fibroblasts are two models extensively used to study front-rear polarity *in vitro*. It can be delineated by the extension of a protrusion with adhesion at the front of cell migration, the orientation of the centrosome (or MTOC) and Golgi apparatus towards the direction of migration, the forward movement of the nucleus, and the involvement of a set of intracellular regulatory proteins. The function of the centrosome positioning is to polarize the microtubule network towards the leading edge while positioning of the Golgi apparatus favors the transport of cytoplasmic and membrane elements to the front of migration (Prigozhina and Waterman-Storer, 2004).

In migrating astrocytes and fibroblasts, the Par complex is located at the leading edge and mediates directionality of migration along with the orientation of the centrosome with respect to the direction of movement (Fig. 2c) (Etienne-Manneville and Hall, 2001; Plant et al., 2003; Etienne-Manneville et al., 2005; Gomes et al., 2005). Interestingly, the Par6-aPKC complex is not required for protrusion formation and establishment of a front-rear polarity but is necessary for the correct and sustained orientation of the protrusion and centrosome in order to avoid random cell migration. In migrating MDCK epithelial cells, Par complex proteins also concentrate at the leading edge (Shin et al., 2007) while in hTERT-RPE-1 epithelial cells, Par6γ localizes at the centrosome and controls centrosomal protein composition through a Par6α-dependent pathway (Dormoy et al., 2013). Its depletion prevented centrosome reorientation during migration in an *in vitro* wound assay. Inhibition or over-activation of the Par4 homolog LKB1 also disturbs polarization and centrosome reorientation of astrocytes (Forcet et al., 2005). LKB1 was shown to regulate polarity of other cells such as lung cancer cell by mediating Cdc42 recruitment and activity at the leading edge (Zhang et al., 2008).

The Par-aPKC complex is essential during border cell migration in the *Drosophila* ovary (Pinheiro and Montell, 2004). During collective migration of *Drosophila* border cells, where cells migrate together as a synchronized sheet, the cell cluster adopts a front-rear polarity. The leading cell extends lamellipodial protrusions while border cells at the side and back only show a few small protrusions. Par3 and Par6 localize at the leading edge of the cluster and their inhibition by RNAi resulted in disorganization of the border cell cluster and impaired migration.

*4.1.2. The Crb complex*

Crb was one of the first polarity protein identified in *D melanogaster*. The fly Crumbs is an EGF-like transmembrane protein (Tepass et al., 1990) that has three homologs in mammals (Crb1, Crb2 and Crb3) (den Hollander et al., 1999; Makarova et al., 2003; Katoh, 2004). Crb1 and Crb2 extracellular domains consist of EGF-like domains and Laminin A/G domains while Crb3 has only a very short extracellular domain (den Hollander et al., 1999; Medina et al., 2002; Katoh, 2004). On the intracellular side, interactions with multiple partners is mediated *via* two distinct domains namely a FERM-binding domain and a PDZ-binding domain (Klebes and Knust, 2000; Bulgakova and Knust, 2009). Crb3 is the most widely expressed member in mammalian epithelial cells, and is localized at the apical region of polarized epithelial cells (Makarova et al., 2003; Lemmers et al., 2004). Pals1 (also named MPP5 for membrane-associated palmitoylated protein 5) is the mammalian protein homolog of *Drosophila* Stardust that encodes a membrane-associated guanylate kinase (MAGUK) protein containing a single PDZ domain, a Src homology region 3 (SH3) domain and a GUK (homologous to the known guanylate kinases without enzymatic activity) domain (Hong et al., 2000; Bachmann et al., 2001). There are two mammalian homologs of the *Drosophila* Dpatj named PatJ and MUPP1 (multi-PDZ domain protein 1) both of which can be linked to the Crb complex (Roh et al., 2002).

*4.1.2.1. The Crb complex in apico-basal epithelial polarity*. The loss of Crb in *Drosophila* embryos leads to a loss in the organization of primary epithelial tissues leading to their degeneration. As a result, the epidermis is disrupted and abnormal “crumbs” of cuticle are secreted (Jurgens et al., 1984). The Crb complex consists of Crb, Pals1 and PATJ and they all localize to the apico-lateral membrane boundary of epithelial cells (Fig. 2b) (Wodarz et al., 1993). Loss of these proteins or expression of mutant proteins that interfere with the Crb complex disrupts the polarization of epithelial cells in *Drosophila* and in mammals while absence of the three Crb homologs in *C elegans* does not affect epithelial polarity (Muller and Wieschaus, 1996; Hurd et al., 2003; Roh et al., 2003; Waaijers et al., 2015). Conditional deletion of Crb2 in the mammalian cerebral cortex results in defective localization of apical complex proteins and adherens junction formation, leading to a disorganization of the tissue and precocious neuronal differentiation (Dudok et al., 2016). Mammalian Pals1 is an adaptor protein that mediates the interaction between Crbs and PatJ while PatJ links the Crb/Pals1 complex to tight junctions in epithelial cells (Straight et al., 2004). Pals1 is involved in adherens junction maintenance by mediating E-cadherin delivery to the cell surface (Wang et al., 2007). Conditional removal of Pals1 in the mouse cerebral cortex or in the cerebellum disrupts the localization of apical complex proteins followed by adherens junction defects and a premature neuronal differentiation (Kim et al., 2010; Park et al., 2016).

*4.1.2.2. The Crb complex in front-rear polarity of migrating cells*. This complex might also play some role during oriented migration (Shin et al., 2007; Du et al., 2010). Those studies showed that in a wound healing assay, PATJ controls directional migration of MDCK cells. Its disruption leads to a disorganization of the microtubule network and a defective orientation of the MTOC. During collective migration of *Drosophila* border cells, inhibition of Crb polarity proteins results in a migration defect with cells exhibiting a reduction in polarized distribution of F-actin at the front and ectopic dynamic protrusions at the side and back of the cluster (Wang et al., 2018).

#### 4.1.3. The Scrib complex

Another group of polarity proteins identified in *D melanogaster* and present in *C elegans* and vertebrate includes Scrib, Lgl and Dlg. They are large proteins rich in protein-protein interaction domains. Scrib is a member of the LAP (LRR and PDZ) family and contains LRR (Leucin Rich repeat) and PDZ (PSD-95/Dlg/ZO-1 homology) domains (Santoni et al., 2002). There is only one Scrb homolog described so far in mammals. Dlg is a MAGUK protein and contains PDZ, SH3 and GUK domains. There are 4 Dlg homologs (Dlg1, Dlg2, Dlg3 and Dlg4) in mammals with Dlg1 being the closest to the *Drosophila* homolog and the most studied (Humbert et al., 2008). Mammals have two Lgl homologs (Llgl1 and Llgl2) encoded by two different genes that contains WD40 repeats involved in protein-protein interactions. Unlike the components of the apical complexes, only a few physical interactions among the Scribble module have been published. Lgl2 has been shown to directly interact with Dlg and Scrb in mammalian cells (Kallay et al., 2006; Zhu et al., 2014), while Dlg indirectly associate with Scrib through the GUK-holder (Gukh) protein at neuronal synapses and epithelial tissues in *Drosophila* (Mathew et al., 2002; Caria et al., 2018).

*4.1.3.1. The Scrib complex in asymmetric cell division.* In *C elegans*, LGL-1 localizes asymmetrically to the posterior of the early embryo and functions redundantly with Par2 to maintain polarity by preventing the accumulation of myosin in the posterior cortex (Fig. 2a) (Beatty et al., 2010). In *D melanogaster*, neural stem cells, called neuroblasts, are formed during the embryonic stages then delaminate from the neuroepithelium and start dividing asymmetrically. This gives rise to a large apical neuroblast and a small basal ganglion mother cell, which divides once to produce neurons and glial cells. During *D melanogaster* neuroblast division, Scrb, Dlg and Lgl show apical cortical enrichment at prophase/metaphase and regulate the alignment of the mitotic spindle along the apico-basal axis which is important for the asymmetric division (Albertson and Doe, 2003). In addition, Dlg and Lgl promote actomyosin-dependent basal segregation of fate determinant such as Numb (Peng et al., 2000). Mammalian Scrb has also a function in asymmetric division in the immune system and hematopoietic stem cell maintenance (Pham et al., 2015; Mohr et al., 2018).

*4.1.3.2. The Scrib complex in apico-basal epithelial polarity.* In epithelia, Scrib, Lgl and Dlg associate with the lateral membrane, beneath the adherens junctions (Fig. 2b) (Bilder et al., 2000; Bilder and Perrimon, 2000; Musch et al., 2002; Navarro et al., 2005). The Scrb complex is required for restricting the localization of apical proteins to the apical domain (Bilder and Perrimon, 2000; Qin et al., 2005; Fletcher et al., 2012). Defect in the expression of any of these proteins results in a failure of the formation of adherens junctions and the spreading of apical markers towards the basal surface. Scrib is essential for epithelial polarity in *Drosophila* and *C elegans* but its role in mammalian apico-basal polarity seems to be limited due to the compensatory function of two other LAP proteins, Erbin and Lano (Bonello and Peifer, 2019; Choi et al., 2019). Deletion of Llgl1 in mice, results in loss of cell polarity in aNSCs that fail to divide asymmetrically, exit the cell cycle and differentiate (Klezovitch et al., 2004). These mice exhibit severe brain disorganization with Nestin-positive rosette formation and hemorrhagic hydrocephalus leading to neonatal death. On the other hand, mice with conditional deletion of Llgl1 specifically in the cerebral cortex at a later time point at the beginning of neurogenesis survive and show symptoms of epilepsy (Beattie et al., 2017; Jossin et al., 2017). Their brains display severe periventricular heterotopias caused by disruption of apical junctional complexes. Llgl1 was found to maintain adherens junction integrity by inducing a polarized distribution of N-cadherin at the membrane of aNSCs (Jossin et al., 2017).

*4.1.3.3. The Scrib complex in front-rear polarity of migrating cells.* In many types of migrating cells, basolateral components Scrib, Dlg and Lgl are found at the leading edge and are required for orienting the direction of migration (Fig. 2c) (Plant et al., 2003; Etienne-Manneville et al., 2005; Osmani et al., 2006; Dahan et al., 2012; Dahan et al., 2014). In astrocytes, Scrib recruits β-PIX, a Rac1/Cdc42 guanine nucleotide exchange factor (GEF), to the leading edge to facilitate localized Cdc42 activity (Osmani et al., 2006). In an *in vitro* wound closure assay, Scrib depletion induces random migration without reduction in velocity in MCF10A cells that fail to recruit Rac1 and Cdc42 at the leading edge, suggesting its function in cell orientation but not motility *per se* (Dow et al., 2007). In several cancer cell lines and dendritic cells, interaction of the transmembrane receptor SemaA4 with Scrib reduces Scrib interaction with β-PIX to modulate the polarized activity of Rac and Cdc42 and regulate cell migration (Sun et al., 2017). Scrib promotes directed migration of endothelial cells by regulating the turnover of integrin α5 at focal adhesions (Michaelis et al., 2013). Inhibition of Lgl in migrating fibroblast leads to aberrant oriented migration that could be due to mislocalization of myosin in the lamellipodium (Dahan et al., 2012). Similarly, loss of Dlg1 in astrocytes does not perturb front-rear polarity formation but only affects the orientation of migration (Etienne-Manneville et al., 2005). Dlg1 seems to regulate microtubule interaction with the plasma membrane at the front of migration.

#### 4.1.4. Crosstalk between polarity complexes

Proteins belonging to these three groups directly interact with and regulate each other. During asymmetric cell division of *Drosophila* neuroblasts, the phosphorylation of Dlg by aPKC disrupts a Dlg intramolecular autoinhibition to align the mitotic spindle to the polarity axis (Golub et al., 2017).

In epithelial cells, the Scrib complex inhibits the Par complex functions and promotes the expansion of the basolateral domain (Bilder and Perrimon, 2000; Tanentzapf and Tepass, 2003). Lgl inhibits aPKC activity by binding to Par6 in the aPKC-Par6 complex and competing with the binding of Par3, as well as preventing membrane accessibility of the Par6-aPKC complex (Fig. 2b) (Yamanaka et al., 2003; Yamanaka et al., 2006). The antagonistic effect is reciprocal and once Lgl is interacting with the active Par6-aPKC complex, it is phosphorylated by aPKC, excluding Lgl from the plasma membrane (Plant et al., 2003; Hutterer et al., 2004; Betschinger et al., 2005).

On the other hand, there is a positive feedback loop between the Par complex and the Crb complex. Par and Crb complexes can associate with one another through a direct interaction between Crb3 and Par6 or Pals1 and Par6 (Hurd et al., 2003; Lemmers et al., 2004). In epithelial cells, Crb3 recruits Par6/aPKC to the apical membrane through Pals1 and this is regulated by Cdc42 which may induce a conformational change in Par6 that increases binding to Pals1. The localization of the two polarity complexes is co-dependent. aPKC phosphorylates Crb at the apico-lateral surface and prevents Crb endocytosis while Lgl inhibits this positive feedback loop at the basolateral domain (Fletcher et al., 2012). Par3 is required for the recruitment of Par6/aPKC and Crb to the apical membrane while Crb maintains the Par6/aPKC apically (Nunes de Almeida et al., 2019).

One hallmark of epithelial polarity is the localization of Cadherins to Adherens Junctions. Par3 and Lgl seem to collaborate in this process by removing non-junctional cadherins from the lateral membrane and recycling them to Adherens Junctions. In one hand, Par3 binds Exo7 to recruit the exocyst to the junctional domain of epithelial cells, an event important for trafficking E-cadherin to the plasma membrane (Ahmed and Macara, 2017). On the other hand, in the neuroepithelium of the developing cerebral cortex, Llgl1 binds to N-cadherin and promotes its internalization at the basolateral membrane domain (Jossin et al., 2017). This is inhibited by the phosphorylation of Llgl1 by aPKC at the apicolateral membrane domain. The resulting polarized distribution of N-cadherin is essential for the integrity of the neuroepithelium.

In a wound-induced migration assay, PATJ controls the directional migration of MDCK cells by regulating the localization of aPKC and

Par3 to the leading edge (Fig. 2c) (Shin et al., 2007). In a similar assay, phosphorylation of Lgl by the Par6-aPKC complex is important for embryonic fibroblasts to polarize correctly (Plant et al., 2003; Dahan et al., 2014). In migrating astrocytes, activation of the Par6-PKCζ complex by Cdc42 promotes the interaction of membrane-associated Dlg1 with adenomatous polyposis coli (APC) at the leading edge (Etienne-Manneville et al., 2005). This interaction is required for polarization of the microtubule cytoskeleton and orientation of the centrosome. Dlg1 also interacts with dynein at the front of migrating astrocytes *via* the scaffolding protein guanylate kinase-associated protein (GKAP) to control microtubule dynamics and organization and promote centrosome positioning in front of the nucleus (Manneville et al., 2010).

#### 4.1.5. Polarity complexes & cortical neuronal migration

While Par Polarity proteins are involved in the oriented migration of cortical neurons, implication of the other groups of polarity proteins has not been revealed yet. The mammalian orthologs of the polarity protein Par1 are also known as microtubule affinity-regulating kinase (MARK) gene family (Tassan and Le Goff, 2004). An investigation using *in utero* electroporation approach found that the downregulation of Mark2 results in a defect in the multipolar to bipolar transition and in a reduction in the speed of bipolar migration associated with a reduced speed of centrosomal movement (Fig. 2d) (Sapir et al., 2008b). One of the microtubule-associated proteins (MAPs) phosphorylated by Mark2 is Doublecortin (DCX) and knockdown of DCX enhance centrosomal movement in both forward and backward orientations, leading however in reduced net processivity resulting in a defective cortical neuron migration (Sapir et al., 2008a). These defects might be caused by the consequent increase or decrease in microtubule stability when Mark2 or DCX are inhibited respectively.

Knockdown of Par3 disrupts the multipolar to bipolar transition and migration of cortical projection neurons (Funahashi et al., 2013). Par3 is also important for the radial migration of cerebellar granule neurons in order to exit the germinal zone (Famulski et al., 2010). Here, Par3 localizes at the leading process and promotes adhesive interaction between the migrating cell and the glial fibers through the recruitment of JAM-C to the neuronal cell surface. The authors found that JAM-C is necessary and sufficient to initiate radial migration even though migrating neurons lack the classical tight junctions of an epithelial cell.

Other kinases belonging to the MARK family are SAD-A and SAD-B. They are regulated by LKB1 (the closest homolog of Par4). In some studies, inhibition of SAD kinases or LKB1 had no effect on the migration of cortical excitatory neurons even though the specification of the axon was defective (Barnes et al., 2007). The importance of LKB1 in cortical radial migration is not clear as another study showed that its downregulation using specific shRNAs induces an arrest of cells just beneath the subplate (Asada et al., 2007). Their data suggest that the migration defect is due to a disruption of microtubule stabilization in the leading process resulting in an abnormally long leading process and a defective centrosomal movement (Asada and Sanada, 2010). They found that LKB1 phosphorylates and inactivates Glycogen synthase kinase 3 β (GSK3β) which would allow APC to bind microtubules plus-ends at the tip of the leading process. The consequent microtubule capture and stabilization would contribute to pulling the centrosome within the leading process. Inhibition of both Gsk3α and β in post-mitotic neurons resultes in a delay in the multipolar to bipolar transition and later, an arrest of bipolar neurons in the lower part of the CP while these cells differentiates properly and axons and dendrites are formed (Morgan-Smith et al., 2014). LKB1 also regulates neuronal migration in the developing cerebellum (Kuwako and Okano, 2018). Differentiating granule cells deleted for LKB1 fail to migrate radially down from the external granular layer to the internal granular layer along the fibers of Bergmann glia.

14-3-3ε belongs to the group of 14-3-3 proteins, which bind to phosphorylated sites, and is equivalent to the polarity protein Par5. Knockout of 14-3-3ε results in neuronal migration retardation in the mouse, and its deletion is associated with more severe lissencephalies caused by Lissencephaly 1 (Lis1) mutations in humans (Toyo-oka et al., 2003). They found that 14-3-3ε interacts with and prevents dephosphorylation of the Lis1-binding protein NUDEL (also named Ndel1), involved in the coupling of nucleus and centrosome movements (Shu et al., 2004).

In cerebellar neurons migrating *in vitro*, Par6 localizes with aPKC to the centrosome (Solecki et al., 2004). Modulating Par6 levels disrupts the perinuclear microtubule cage and nuclear movement. It also inhibits centrosomal motion and neuronal migration through the modulation of Myosin II phosphorylation and activity in the leading process (Solecki et al., 2004; Solecki et al., 2009).

### 4.2. Small GTPases and polarity

Small GTPases of the Ras superfamily are molecular switches that cycle between active (GTP-bound) and inactive (GDP-bound) conformations under the control of guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs) and guanine dissociation inhibitors (GDIs) (Van Aelst and D'Souza-Schorey, 1997; Cherfils and Zeghouf, 2013). The most studied are the RhoA family members RhoA, Rac1 and Cdc42. They are best known for their function in the organization of the actin cytoskeleton. Rac1 and Cdc42 establish actin modules at the cell periphery to generate lamellipodia and filopodia respectively, whereas RhoA controls the generation of contractile forces through the regulation of actin-myosin filament assembly (Nobes and Hall, 1995). Rho GTPases are intimately involved in the establishment and maintenance of polarity (Etienne-Manneville, 2004). In mammalian and non-mammalian cells, multiple GEFs have been involved in polarizing events (Liu et al., 2006; Osmani et al., 2006; Otani et al., 2006; Guillemot et al., 2008; Vicente-Manzanares et al., 2011; Zihni et al., 2014). Experimental evidences showed that small GTPases are mutually dependent with the polarity network for their effects. I also discuss the small GTPase Rap1 (Ras-related protein 1) as several findings point to a role of this enzyme in polarity regulation.

#### 4.2.1. Small GTPases in asymmetric cell division

A critical event during asymmetric cell division in the *C elegans* embryo is the inactivation of Rho1 in the vicinity of the sperm-donated centrosome at the delivery point of the sperm, named the posterior site. The establishment of contractile polarity necessary for Par proteins segregation is achieved by the asymmetric distribution of Rho GEFs and Rho GAPs and the subsequent asymmetric activity of Rho1 at the anterior cortex (Fig. 2a) (Cowan and Hyman, 2007; Schonegg et al., 2007). The small GTPase Cdc42 plays an important role in the activation of the Par-aPKC complex and is in fact considered to be part of the Par-aPKC polarity group. The interaction between Par6 and aPKC is constitutive and the complex is inactive until Cdc42-GTP interacts with the complex and induces a conformational change in Par6 allowing aPKC phosphorylation and activation (Joberty et al., 2000; Lin et al., 2000; Noda et al., 2001; Yamanaka et al., 2001; Garrard et al., 2003). A recent model has been suggested during asymmetric division of the *C elegans* one-cell embryo: Par3 recruits aPKC-Par6 at the anterior but keep aPKC inactive then Cdc42 interacts with the aPKC-Par6 complex in which aPKC becomes active but the complex becomes poorly segregated (Rodriguez et al., 2017). This cycling between the two types of complexes would ensure a robust establishment of polarity. Similarly in *Drosophila*, Cdc42 is enriched at the apical cortex of asymmetrically dividing neuroblasts and acts downstream of Bazooka (Baz/Par3) to direct Par6-aPKC localization. Cdc42 relieves Par6 suppression of aPKC kinase activity (Atwood et al., 2007).

Another small GTPase, Rap1, also plays a critical role in polarity. In *D melanogaster* neuroblasts, Rap1 is enriched at the apical pole during metaphase/anaphase and is found in a complex with aPKC and Par6 (Carmena et al., 2011). Here, Rap1 is required for the mitotic axis orientation, apical protein localization and asymmetric division. They

found that Rap1 regulates asymmetric division of neuroblasts through the Ral guanine nucleotide exchange factor Rgl, Ral, and Canoe (AF-6/Afadin in vertebrates).

#### 4.2.2. Small GTPases in apico-basal epithelial polarity

The establishment of epithelial cells apico-basal polarity is subsequent to the formation of cadherin-mediated adhesions (Ebnet, 2008). The clustering of cadherins leads to the activation of Rac1 and Cdc42 (Kim et al., 2000; Nakagawa et al., 2001). Rac1 and Cdc42 interact and activate the Par6-aPKC complex leading to the maturation of the first contacts into adherens junctions and tight junctions and the formation and maintenance of the apico-basal polarity (Takaishi et al., 1997; Yamanaka et al., 2001; Chen and Macara, 2005; Mertens et al., 2005). Localization of tight junction molecules such as JAM at the nascent cell-cell adhesion is important for the recruitment of polarity proteins such as Par3 and activations of Rho GTPases to initiate signaling cascades (Fig. 2b) (Kim et al., 2000; Ebnet et al., 2001; Itoh et al., 2001; Nakagawa et al., 2001; Kawakatsu et al., 2002). While Rac activity is important for the promotion of tight junctions and adherens junctions, Par3 inhibits Rac1 activity through inhibition of the Rac activator Tiam1 (T-cell lymphoma invasion and metastasis 1) (Chen and Macara, 2005; Mertens et al., 2005; Guillemot et al., 2008). It was suggested that β2-syntrophin and Par3 fine tune Rac activity along areas of cell-cell junctions and create a Rac activity gradient controlling tight junction assembly (Mack et al., 2012). Cdc42 localizes and recruits aPKC and Par6 to the apical domain of MDCK cells grown in 3D (Martin-Belmonte et al., 2007). This is required for the establishment of the apical domain and lumen formation. In another system of epithelial polarization such as morphogenesis of the *Drosophila* pupal photoreceptor, Cdc42 defines apical identity through the recruitment of Baz/Par3, Par6, aPKC and Crb (Nunes de Almeida et al., 2019). They propose a model where the Par6-aPKC complex is recruited at the developing apical membrane through its direct interaction with Cdc42 or Baz/Par3 but its retention at the apical domain depends on its interaction with Crb which is promoted by the binding of Par6 to Cdc42. Par6 binding to Crb promotes the accumulation of this membrane protein, mutually reinforcing each other. Cdc42 is also important in the neuroepithelium of the developing mouse cerebral cortex. Conditional deletion of Cdc42 results in loss of apico-basal polarity reflected by the loss of apical localization of Par complex and depletion of adherens junctions leading to a decrease in symmetrical self-renewing division of aNSCs and an increase in the generation of basal progenitors (Cappello et al., 2006). On the other hand, conditional deletion of Rac1 in the cerebral cortex did not affect the polarity of aNSCs (Leone et al., 2010).

RhoA also plays a central role during epithelial polarization. It mediates actomyosin contractility and generates the cortical actomyosin ring during polarization of epithelial sheets (Vaezi et al., 2002; Ivanov et al., 2005). RhoA activity is important, along with its downstream effector mammalian Diaphanous-related formin1 (mDia1), for the formation and maintenance of adherens junctions in the neuroepithelium of the future cerebral cortex (Katayama et al., 2011; Thumkeo et al., 2011; Cappello et al., 2012). In addition, Rho-associated protein kinase 2 (ROCK2), another downstream RhoA effector that also promotes actin stress fiber formation, maintains neuro-epithelial apico-basal polarity and adherens junctions in the medaka fish (Herder et al., 2013).

In the *Drosophila* embryo, Rap1 is essential for epithelial cells apico-basal polarity establishment as both Baz/Par3 and adherens junctions are mispositioned in its absence (Choi et al., 2013). Similarly, vertebrate cadherin-based epithelial and neuroepithelial cells adhesion depends on Rap1 (Price et al., 2004; Maeta et al., 2016; Shah et al., 2016). Inhibition of Rap1 generates immature adherens junctions, whereas activation of Rap1 tightens cell-cell junctions. Rap1 GEFs are linked to junctional proteins and there is a positive activation feedback loop between adherens junction formation and Rap1 activation.

#### 4.2.3. Small GTPases in front-rear polarity of migrating cells

During migration of cells such as astrocytes, fibroblasts, epithelial cells and circulating T lymphocytes, Cdc42 and Rac1 mediate the expansion of cytoskeleton-dependent cell protrusions in the direction of migration while RhoA is involved in the retraction of membranes and adhesion proteins at the rear of the cell (Fig. 2c) (D'Souza-Schorey et al., 1998; Etienne-Manneville and Hall, 2001; Lee et al., 2004; Cau and Hall, 2005). This front-rear polarity depends on a crosstalk between small GTPases and polarity complex proteins (Etienne-Manneville and Hall, 2001; Etienne-Manneville et al., 2005; Osmani et al., 2006; Dow et al., 2007; Shin et al., 2007). During fibroblasts and astrocytes migration, the localized activation of Cdc42 at the front of migration stimulates a pathway involving the Par6-aPKC complex to correctly orient the microtubule network (Etienne-Manneville and Hall, 2001; Watanabe et al., 2005). Par3 associates with Dynein to regulate the Cdc42-dependent polarized localization of the centrosome during fibroblasts and astrocytes oriented migration (Etienne-Manneville and Hall, 2001; Palazzo et al., 2001; Schmoranzer et al., 2009). Par6 recruits Smurf1 (Smad ubiquitination regulatory factor-1) to promote RhoA degradation at the leading edge and might therefore contribute to front-rear polarity by polarizing RhoA activity and cell contraction (Wang et al., 2003). The RhoA effector ROCK phosphorylates Par3 at Thr833 and disrupts its interaction with aPKC and Par6 (Nakayama et al., 2008). This phosphorylation occurs mainly at the rear and the central region of migrating cells thus controlling front-rear polarity and directional migration. Quite surprisingly, while astrocytes from mice conditionally deleted for Cdc42 exhibit an oriented migration defect in an *in vitro* wound assay, they seem to polarize correctly *in vivo* towards the lesion after stab wound injury in the somatosensory cortex (Robel et al., 2011). The number of astrocytes recruited to the lesion site was however significantly reduced. This could be explained by the presence of other signals that could compensate for the absence of Cdc42 *in vivo*. Small GTPases are also important during T cells oriented migration. For instance, Cdc42 regulates the polarization of both actin and MTOC towards antigen presenting cells (Stowers et al., 1995).

p21-activated kinase 1 (Pak1) is activated by, and serves as an effector for both Rac and Cdc42 (Bokoch, 2003). It either promotes or suppresses actomyosin contractility *via* phosphorylation of myosin light chain or of myosin light chain kinase respectively (Chew et al., 1998; Sanders et al., 1999). Pak1 can also activate the LIM-kinase-mediated modulation of the actin severing and depolymerizing function of ADF/cofilin (Edwards et al., 1999). In migrating fibroblasts, PAK1 activity maintains a polarized persistent oriented migration by spatially restricting Rac-dependent actin polymerization to the leading edge of migrating cells (Sells et al., 1999; Cau and Hall, 2005). Pak1 and aPKC were recently shown to phosphorylate a similar set of polarity proteins and found to act semi-redundantly to maintain apical membrane identity in *Drosophila* and mammalian epithelia (Aguilar-Aragon et al., 2018). It would be interesting to investigate whether Pak1 and aPKC also act redundantly during oriented migration.

In migrating lymphocytes, Rap1 induces a polarized phenotype and is important for chemokine-induced directed migration (Shimonaka et al., 2003). Activated Rap1 co-localizes with Par3, aPKC and Cdc42 at the leading front after chemokine stimulation (Gerard et al., 2007). The Rac activator Tiam1 associates with both Rap1 and Par3, and may function to connect the Par polarity complex to Rap1. During *Drosophila* border cell collective migration, Rap1 regulates the proper distribution of E-cadherin, maintains proper cell shape and controls the extension of polarized, front-directed protrusions (Sawant et al., 2018).

#### 4.2.4. Small GTPases, polarity and cortical neuronal migration

*4.2.4.1. Small GTPases, polarity and radial migration.* Conditional knockout or perturbation of Rac1 activity or of its GEFs STEF/Tiam1 or P-Rex1 in cortical projection neurons results in a migration defect with cells accumulating at the multipolar zone with a round morphology and shorter processes (Fig. 2d) (Kawauchi et al., 2003;

Yoshizawa et al., 2005; Chen et al., 2007; Leone et al., 2010; Jossin and Cooper, 2011; Li et al., 2019). Failure to form a leading process suggests that Rac1 activity is required for morphological polarization and migration of cortical neurons. Another study found that the Rac1-interacting scaffolding protein POSH (plenty of SH3s) controls the formation of the cytoplasmic dilation of cortical projection neurons leading process, centrosome translocation and nucleokinesis through the regulation of F-actin assembly (Yang et al., 2012). Conditional deletion of Rac1 in the cerebral cortex only delays, but does not prevent, radial migration of pyramidal neurons (Chen et al., 2007). This could be due to compensatory mechanisms that overcome the loss of Rac1. For instance, Rac3 has been suggested to regulate the lateral orientation of multipolar migration (Dimidschstein et al., 2013). Cerebellar granule neurons also undergo radial neuronal migration. Rac1 was also found to be important for the migration of these cells, through the Wiskott–Aldrich syndrome protein (WASP) family verprolin-homologous Protein (WAVE) actin regulating complex (Tahirovic et al., 2010). In culture, Rac1-deleted cerebellar granule cells exhibit impaired actin dynamics, mislocalization of WAVE and absence of lamellipodia at the tip of the leading process.

Cdc42 is also required for a correct migration of glutamatergic neurons in the mammalian cortex or for the migration of cerebellar granule neurons (Konno et al., 2005; Kholmanskikh et al., 2006; Jossin and Cooper, 2011). Inhibition of Cdc42 specifically in radially migrating neurons results in a defect in migration and an accumulation of multipolar cells in the developing cerebral cortex and cerebellum (Jossin and Cooper, 2011; Govek et al., 2018). The defect is associated with a function of Cdc42 in the regulation of N-cadherin in cortical neurons and in the regulation of adhesion to radial fibers in the cerebellum.

p21-activated kinases (PAK), effectors for Rac and Cdc42, have been implicated in the migration of chicken cerebellar neurons (Sakakibara and Horwitz, 2006). The authors found that the kinase activity of PAK is important for the stabilization of protrusion direction but not for the extension of the process itself. Inhibition of Pak1 in the mouse telencephalon by *in utero* electroporation affects the migration of cortical projection neurons that fail to enter the CP (Causeret et al., 2009). Multipolar neurons display broad lamellipodial protrusions surrounding the soma and bipolar neurons exhibit a shorter leading process.

RhoA is highly expressed in aNSCs of the cortex and its expression decreases in postmitotic neurons. On the other hand, RhoB has a low expression in aNSCs while it has a higher expression in postmitotic neurons. RhoC is barely detected within the whole cerebral wall during development (Olenik et al., 1999). Deletion of RhoA in the developing cerebral cortex causes subcortical band heterotopias meaning a prominent tissue mass underneath an apparently layered but thinner cerebral cortex (Katayama et al., 2011; Cappello et al., 2012). Alterations in the radial glia scaffold are the cause of this migration defect. Indeed, RhoA−/− neurons seem to migrate normally when transplanted into wild-type cerebral cortex, suggesting that RhoA is dispensable for cell-autonomous neuronal migration. However, overexpression of a dominant negative form of RhoA by *in utero* electroporation accelerates radial migration (Ge et al., 2006).

In migrating cortical projection neurons, the small GTPase Rap1 regulates the orientation of multipolar migration towards the pial surface without affecting the speed of migration by maintaining N-cadherin on the neuron surface (Jossin and Cooper, 2011). The function of N-cadherin however does not depend on its homophilic adhesive properties, but rather it physically interacts with FGF receptors (FGFRs) and prevents FGFRs from being ubiquitinated and degraded through the lysosome (Kon et al., 2019). Inhibition of FGFRs affects the orientation of multipolar migrating neurons but has no effect on their morphology. How the N-cadherin/FGFRs complex orients migration is still unknown but might involve the prolonged activation of Erk1/2. In this pathway, Rap1, N-cadherin, FGFRs and Erk/2 are regulated by Reelin, an extracellular matrix protein secreted by Cajal-Retzius cells located at the marginal zone. Reelin is processed by metalloproteinases to allow the active central fragment to diffuse and reach multipolar migrating neurons (Jossin et al., 2004; Jossin et al., 2007; Jossin, 2011; Kon et al., 2019). During the terminal somal translocation near the top of the CP, Rap1 is also involved but this time it regulates integrin receptors instead (Sekine et al., 2012). The F-box protein Fbxo45 is secreted by an unconventional mechanism by cortical neurons and interacts with the extracellular domain of N-cadherin (Na et al., 2020). This interaction seems to be important for N-cadherin functions during multipolar migration but the mechanism of action is still unclear. The glia-independent somal translocation of early-born neurons is also regulated by Reelin and depends on an interaction between the leading process of translocating neurons and Cajal-Retzius cells (Franco et al., 2011; Gil-Sanz et al., 2013). The authors suggest a model where nectin1 on Cajal-Retzius cells and nectin3 on the leading process mediate an initial heterophilic interaction which is then stabilized by N-cadherin homophilic contacts induced by Reelin, facilitating the translocation of the nucleus. However, inhibition of this interaction did not affect cell polarization (localization of the Golgi apparatus ahead of the nucleus) and leading process extension.

*4.2.4.2. Small GTPases, polarity and tangential migration.* While conditional deletion of RhoA, Rac1 or Cdc42 in the VZ of ganglionic eminences affects tangential migration, their conditional deletion in more restricted progenitors of the sVZ using Dlx5/6-Cre mice does not cause any obvious defect in cortical interneurons migration (Chen et al., 2007; Katayama et al., 2013). This suggests that these small GTPases are important in ventral cortex progenitors to induce acquisition of migration competency during differentiation while they are not critical for cellular polarity or motility *per se*. The lack of effect on tangential migration could however be due to compensatory effects by other small GTPases as suggested for Rac1 and Rac3 (Fig. 2d) (Tivodar et al., 2015). Indeed, Rac1/Rac3-deficient interneurons exhibit a reduced length of their leading process that could be rescued by a treatment *in vitro* with taxol, a microtubule stabilizing agent. This suggests that the role of Rac1 and Rac3 during interneurons migration is to regulate microtubule dynamics.

After completing their tangential migration, GABAergic interneurons colonize the CP, switching to a radially-oriented migration. Inhibition of RhoA/ROCK signaling results in leading-process elongation, reduced branching, and impaired tangential-to-radial transition (Martini et al., 2009). Similarly, overactivation of PAK3 in Dlx1/2-mutant interneurons contributes to decreased branching, excessive leading process extension, and defect in the tangential-to-radial migration transition (Cobos et al., 2007). This neuronal reorientation from tangential migratory streams towards the CP is also regulated by the primary cilium that maintains the centrosome to the plasma membrane and transduces local Sonic hedgehog signal (Baudoin et al., 2012).

### *4.3. Actin and microtubule cytoskeletons and polarity*

Actin filaments (also called F-actin) are composed of linear polymers of actin subunits. The filaments are polarized and the elongation of one filament end is coupled with shrinkage at the other. They also act as tracks for the movement of myosin motor molecules. Both actin polymerization and myosin motor movement along F-actin can generate forces to move cellular organelles, or the cell itself, relative to its surroundings. In addition, actin filaments cross-link into bundles regulated by different families of actin binding proteins (Blanchoin et al., 2014).

Microtubules are dynamic polymers with an intrinsic polarity as they are built from α-tubulin and β-tubulin heterodimers in a head to tail fashion. This results in two distinct ends: the plus end, terminating with β-tubulin and assembling faster *in vitro* than the minus end, terminating with α-tubulin. *In vivo*, the minus end seems to never grow

and is often anchored to a MTOC, such as the centrosome and the Golgi complex (Akhmanova and Hoogenraad, 2015). This uniform orientation of microtubules allows molecular motors to move directionally along them.

Actin and microtubule cytoskeleton are important for cell polarity establishment and maintenance. Not only, their structure is intrinsically polarized but they also interact closely with the polarity complexes. After the initial polarizing signal, a reciprocal interaction between the cytoskeleton and polarity proteins takes place to consolidate cell polarity.

#### 4.3.1. Cytoskeleton in asymmetric cell division

Following fertilization, the initially uniform actomyosin network of the one-cell *C elegans* embryo becomes concentrated at the anterior pole, generating a polarized contractility (Fig. 2a). The actomyosin cytoskeleton appears to play a direct role in localizing the PAR3 complex and disruption of cortical F-actin prevents cortical association of PAR3 (Severson and Bowerman, 2003; Munro et al., 2004). Reciprocally, PAR3 positively regulates the speed of anterior cortical movement and *Par* mutants show disrupted actin distribution (Cheeks et al., 2004; Munro et al., 2004).

During asymmetric cell division in the *C elegans* embryo, polarity is marked by the anterior-posterior gradient of cortical microtubules and the asymmetric spindle is dependent on microtubule-mediated forces regulated by the Par proteins (Grill et al., 2001). And even though studies suggested that microtubules are not essential to establish the anterior-posterior polarity, it seems they contribute in strengthening the polarity process and the polarized distribution of Par proteins (Wallenfang and Seydoux, 2000; Cowan and Hyman, 2004; Tsai and Ahringer, 2007; Motegi et al., 2011). A recent study found that PAR3 directly interacts with dynein. They showed that microtubules and the dynein motor, in connection with vesicular trafficking, are required for PAR3 transport on vesicles towards the anterior cortex (Jouette et al., 2019).

#### 4.3.2. Cytoskeleton in apico-basal epithelial polarity

Acquisition of epithelial apico–basal polarity requires an intricate reorganization of the actin cytoskeleton. F-actin concentrates at perijunctional regions and the organization of actin at the lateral membrane is determined to a large extent by cadherins and associated catenins (Fig. 2b) (Drees et al., 2005). Reciprocally, the formation and maintenance of adherens junctions and tight junctions depends on actin dynamics (Niessen et al., 2011). The formation of an actomyosin ring during apico-basal polarization mediates recruitment and maintenance of adherens junctions and tight junction proteins at intercellular contacts (Ivanov et al., 2005). Par3 interacts with the Rac GEF TIAM1 and LIMK2 which phosphorylates and inactivates cofilin, a key regulator of actin dynamics, to regulate tight junction formation (Chen and Macara, 2005, 2006). Loss of Par3 causes an increase in Rac activity and in the phosphorylated pool of cofilin, which results in a disorganization of actin filaments at the cell cortex and a defect in tight junction assembly. The Arp2/3 complex is a seven-subunit protein complex that nucleates branched actin networks. Its conditional deletion in the murine cerebral cortex leads to loss of aNSCs polarity, defective organization of adherens junctions at the ventricular surface and retards basal process outgrowth (Wang et al., 2016).

The establishment of epithelial apico-basal polarity is also tightly linked to the reorganization of microtubules from a radial array to a vertical alignment of non-centrosomal microtubule bundles along the lateral membrane with their minus ends towards the apical surface, and a meshwork under the apical and basal membranes (Musch, 2004). The mammalian polarity protein PAR1b (also known as MARK2), is indispensable for establishment of the microtubule assembly at the lateral membrane of MDCK cells (Cohen et al., 2004). In *C. elegans* intestinal epithelial cells, Par3 contributes to this reassignment of microtubules to a non-centrosomal MTOC (Feldman and Priess, 2012).

#### 4.3.3. Cytoskeleton in front-rear polarity of migrating cells

During cell migration, F-actin is enriched at the migrating front and actin-mediated forces sequentially promote the formation of lamellipodia and filopodia, adhesion, contraction, and retraction (Fig. 2c). At the rear of the migrating cell, actin is reorganized into stable actomyosin cables. Both centrosome and Golgi apparatus orient to the front of migration but are separately controlled in fibroblasts with the relocation of the centrosome being independent of actin but inhibited by disruption of microtubules, whereas Golgi polarity is dependent of actin and independent of microtubules (Magdalena et al., 2003a). Some function of actin however might vary depending on the cell type. For instance, Golgi reorientation in a scratch-wound assay is actin-independent in astrocytes (Magdalena et al., 2003b). Myosin II controls the distance and position of the nucleus with respect to the centrosome under the control of Cdc42 and MRCK and contributes to retraction and adhesion disassembly at the rear under the control of RhoA (Gomes et al., 2005; Vicente-Manzanares et al., 2011). The actin binding protein Cofilin participates in the orientation of migration (Ghosh et al., 2004). Using photoactivatable analog of Cofilin, they showed that intracellular Cofilin activity generates free barbed ends, polymerizes actin, induces protrusion, and sets the direction of cell migration. Arp2/3 nucleates the formation of the dendritic actin network at the leading edge of motile cells. Its inhibition in migrating fibroblasts results in a defect in persistent directional migration correlated with a lack of coordination of the protrusive activities at the leading edge (Suraneni et al., 2012). Similarly, neural stem cell-derived oligodendrocyte precursors inhibited for Arp2/3 are no longer orienting their migration towards the cathode in electric fields (Li et al., 2015).

Microtubules extend in radial arrays from the centrosome towards the cell periphery (Fig. 2c). During cell migration, microtubules accumulate preferentially at the front of the cell resulting from a longer lifetime compared to the rear of the cell (Gundersen and Bulinski, 1988). Microtubules provide a network for the transport of signaling molecules, membrane vesicles, cytoskeletal components or RNAs through motor proteins such as kinesins and dyneins to maintain persistent oriented migration. They provide pushing forces that maintain membrane protrusions and pulling forces to move the nucleus and centrosome (Kaverina and Straube, 2011; Letort et al., 2016).

Polarity proteins influence the cytoskeleton. In migrating fibroblasts, Lgl1 facilitates actin polymerization at the leading edge through its interaction with non-muscle myosin II isoform A (NMII-A) (Dahan et al., 2012; Dahan et al., 2014). Directional migration of myeloid cells in wounded medaka fish larvae depends on the regulation of the actin cytoskeleton and MTOC repositioning by the PAR3-Par6-aPKC complex (Crespo et al., 2014). In freely migrating keratinocytes, Par3-aPKC complex interacts with Tiam1 to control persistent migration by stabilizing microtubule-dependent front-rear polarity (Pegtel et al., 2007).

The mammalian Cdc42-Par6-aPKC complex plays a role in the microtubule-mediated reorientation of the centrosome during astrocyte and fibroblast migration in a scratch wound assay *in vitro* and in endothelial cell polarization induced by sheer-stress (Etienne-Manneville and Hall, 2001; Tzima et al., 2003; Cau and Hall, 2005). The Par6-aPKC complex induces the phosphorylation of GSK3β at the leading edge of migrating cells and triggers the interaction of APC protein with the plus ends of microtubules (Etienne-Manneville and Hall, 2003). Control of Cdc42 localization and activity by Scrib and interaction of the polarity protein Dlg1 with APC and dynein are required for polarization of the microtubule cytoskeleton to promote cell orientation during astrocyte migration (Etienne-Manneville et al., 2005; Osmani et al., 2006; Manneville et al., 2010). The Dlg1-APC interaction induces the capture of microtubule plus ends at the cell cortex while the position of dynein at the front edge may provide pulling force along microtubules to bring the centrosome in front of the nucleus. However, an alternative explanation is that the nucleus is pulled to the rear of migrating astrocytes by N-cadherin-dependent signals from cell-cell contacts (Dupin et al., 2009). Similarly, in kidney epithelial cells, rearward movement of the

nucleus may depend on E-cadherin mediated signals from cell-cell contacts (Desai et al., 2009). In fibroblasts, dynein localizes with Par3 at cell-cell contacts and not at the wound-front edge (Schmoranzer et al., 2009). In these cells, centrosome reorientation occurs by a myosin-dependent rearward movement of the nucleus, while the Par complex and dynein hold the centrosome in place (Gomes et al., 2005; Schmoranzer et al., 2009). Overall, these results show that the actin and microtubule cytoskeletons might be used differently in diverse cell types for regulating the orientation of migration.

The microtubule plus-end–tracking protein cytoplasmic linker-associated proteins (CLASP) contribute to the asymmetry of the microtubule network by stabilizing them at the leading edge of migrating cells *via* linkages to the cell cortex and actin filaments. They also localize at the trans-Golgi network for the nucleation of Golgi-derived microtubules and for the formation of the Golgi ribbon. These functions regulate directional trafficking from the Golgi apparatus allowing polarization of the cell (Drabek et al., 2006; Miller et al., 2009; Myer and Myers, 2017). Interestingly, CLASP2 interacts with the Par complex and is phosphorylated by aPKC to regulate Golgi organization and could be involved in the generation of cell polarity (Matsui et al., 2015).

#### *4.3.4. Cytoskeleton, polarity and neuronal migration*

Actin and microtubule cytoskeletons play a critical role in neuronal migration and polarity. Mutations in genes coding for proteins that regulate the cytoskeleton lead to brain malformations that are induced, at least in part, by a defective oriented neuronal migration.

*4.3.4.1. Cytoskeleton in radial migration.* In radially migrating neurons, actin accumulates at the leading process and at the rear of the nucleus (Fig. 2d) (Solecki et al., 2009). Cytochalasin B, which inhibits assembly of actin subunits, reversibly prevents gliophilic migration (Rivas and Hatten, 1995) and mutations in actin genes result in pachygyria and lissencephaly (Di Donato et al., 2016).

Human mutations in the actin binding protein Filamin A (FLNA) lead to periventricular heterotopia (Fox et al., 1998; Fox and Walsh, 1999). Filamin-A is a very large (280 kD) cytoplasmic protein responsible for cross-linking actin filaments into orthogonal networks but can actually interact with many other proteins with diverse functions (Feng and Walsh, 2004; Popowicz et al., 2006). Filamin A inhibition in embryonic mouse brains using a dominant negative form results in less motile and rounded cells while its overexpression or the downregulation of the Filamin A degradation-inducing protein FILIP promotes a radially-oriented bipolar shape in cortical neurons located in the multipolar migration zone (Nagano et al., 2004).

Another actin regulating protein involved in neuronal migration is Cofilin. Cofilin is part of a family of actin-binding proteins which disassembles actin filaments (Kanellos and Frame, 2016). Complete deletion of Cofilin in the mouse impairs neural crest cell migration, neural tube closure and leads to embryonic lethality (Gurniak et al., 2005). Conditional knockout in the cerebral cortex results in premature cell cycle exit and a defective neuronal migration with increased multipolar neurons leading to a defect in cortical layering (Bellenchi et al., 2007). Deletion of the other member of the family, ADF, affects neither the development of the nervous system, nor the formation of neurites while deletion of both proteins shows cortical ectopias and a defect in multipolar migration with neurons exhibiting very short or no neurites (Flynn et al., 2012). In addition, it has been suggested that Reelin signaling increases phosphorylation of cofilin through LIM kinase 1 in neurons approaching the marginal zone, inhibiting cofilin activity and stabilizing the leading process which result in a stop of migration (Chai et al., 2009; Chai et al., 2016).

Mena/VASP proteins bind to barbed ends of actin filament and compete with capping proteins, allowing for longer filament elongation. Neurites from multipolar cells are rich in actin and inhibition of Mena/VASP decreases the number of these neurites (Yoshinaga et al., 2012). Inhibition of Mena/VASP in mice results in aberrant neuronal positioning to superficial regions of the cortex due to a migration defect (Goh et al., 2002; Kwiatkowski et al., 2007). Inhibition of Neurabin-I, a neuronal-specific F-actin-binding protein, affects neuronal morphology and radial migration of differentiating cortical neurons (Causeret et al., 2007). Multipolar neurons inhibited for Neurabin-I display thinner neurites while bipolar neurons have a shorter, branched leading process. Downregulation of the actin interaction adaptor protein Drebrin-like (Dbnl) using shRNA and *in utero* electroporation in mouse embryonic cerebral cortex induces a defect in oriented migration and in the formation of processes in multipolar neurons (Inoue et al., 2019).

Non-muscle myosin II is an actin-binding protein that has actin cross-linking and contractile properties. Myosin IIB, a RhoA downstream effector, is the predominant myosin II in the cortex and is regulated by phosphorylation of its light and heavy chains. Inhibition of Myosin IIB in bipolar migrating cortical neurons blocks nuclear but not centrosomal movement (Tsai et al., 2007). They propose that Myosin II located at the rear of the cell might push the nucleus forward as suggested for the migration of interneurons (see below). On the other hand, myosin II regulates nuclear and centrosomal movement of bipolar cerebellar granule neuron migrating on radial fibers *in vitro* (Solecki et al., 2009). Here, active myosin is located near the centrosome in the dilation at the proximal part of the leading process, in front of the nucleus, and actomyosin contraction provides a pulling force for nuclear forward movement. This suggests that the two types of glia-guided migration might have different mechanisms of regulation. However differences might also stem from the experimental approach and the type and strength of adhesion used to migrate. Indeed, when granule neurons migrate on a mix of poly-D-lysine and laminin, myosin II activity is not at the proximal dilation but is located at the tip of the leading process (He et al., 2010).

Microtubules are concentrated at the leading process and around the nuclei (called either microtubule cages in granule neurons or forks in cortical neurons) of migrating bipolar neurons (Rivas and Hatten, 1995; Xie et al., 2003). Studies in cerebellar granule neurons revealed that microtubules emanate from the centrosome and form longitudinal arrays oriented parallel to the direction of movement (Schaar and McConnell, 2005). In the leading process they are polarized with their newly assembled positive ends in the leading process uniformly facing the tip and their negative ends facing the nucleus (Rakic et al., 1996). In the trailing process, by contrast, microtubule arrays are of mixed polarity. On the other hand, cortical bipolar neurons migrating in brain slices and expressing EB3 and centrin2 fused to fluorescent proteins display microtubules emanating as an astral array from the centrosome but both microtubules in the leading process and in the trailing axon are arranged unidirectionally and parallel (Tsai et al., 2007).

The disruption of microtubule structure results in the collapse of the migrating neuron cell body and cessation of nuclear translocation. Mutations in α- and β-tubulin cause abnormal neuronal migration in mice and lissencephaly or polymicrogyra in humans (Keays et al., 2007; Jaglin et al., 2009; Kumar et al., 2010; Ngo et al., 2014). Knockdown of Tubb5 results in shorter processes in migrating multipolar cortical neurons (Ngo et al., 2014). γ-tubulins are mostly found at centrosomes and Tubg1 downregulation in mice leads to a migration arrest in the subventricular and intermediate zones (Poirier et al., 2013). shRNA-mediated downregulation of the centrosomal protein SDCCAG8 (Serologically defined colon cancer antigen 8) impairs centrosomal recruitment of γ-tubulin and pericentrin that are essential for microtubule nucleation and anchorage. The knockdown of SDCCAG8 also interferes with microtubule organization, decouples the centrosome and the nucleus, disrupts bipolar neuronal migration and delays the multipolar to bipolar transition (Insolera et al., 2014).

Dynamic elongation and shortening of microtubules is important for neuronal migration. This remodeling depends on MAPs that either stabilize or destabilize microtubules. Lissencephaly 1 (Lis1, also known as PAFHA1b1) and Doublecortin (DCX) are two microtubule-stabilizing proteins produced by gene mutated in human lissencephaly or double

cortex syndrome (also called subcortical band heterotopia) (Kerjan and Gleeson, 2007). Those malformations are caused in part by defects in cortical projection neuron migration and lead to epilepsy and cognitive impairment. DCX and Lis1 coimmunoprecipitate from brain lysate, and purified DCX and Lis1 bind cooperatively to and stabilize microtubules (Sapir et al., 1997; Caspi et al., 2000; Moores et al., 2006). Cortical lamination is intact in DCX and Dclk (doublecortin-like kinase, a protein with the highest reported homology to DCX) knockout mice while inactivation of both Dclk and DCX is associated with disordered cortical lamination suggesting redundant activities (Koizumi et al., 2006a). Homozygous Lis1 knockout mice die perinatally while Lis1-null heterozygous mice display severe cortical layer disorganization and cognitive deficits (Hirotsune et al., 1998; Youn et al., 2009). Lis1 predominantly localizes to the centrosome and cooperates with DCX and dynein to mediate coupling of the nucleus to the centrosome during the radial migration of cerebellar granule neurons *in vitro* (Tanaka et al., 2004) and during the bipolar migration of cortical neurons (Tsai et al., 2007). Here, they observed a pronounced accumulation of dynein in the migratory process swellings, which correlated with the onset of centrosomal movement, and a subsequent enrichment in the cell body. Dyneins are minus-end directed motor proteins that move along microtubules and are targeted to the plus-end of microtubules *via* Lis1 and Ndel1 (Li et al., 2005; Youn et al., 2009). It is suggested that dynein pulls on the microtubule network from the swelling and that the nucleus is transported along the microtubules by dynein. The nucleus connects to the dynein complex on microtubules through the outer nuclear envelope proteins Syne1/2, themselves interacting with the inner nuclear envelope proteins SUN1/2 (Zhang et al., 2009; Wu et al., 2018). Disrupted-In-Schizophrenia-1 (DISC1), a susceptibility gene for major psychiatric disorders, is a component of the dynein and Lis1 protein complex and has an essential role in stabilizing the complex at the centrosome (Kamiya et al., 2005). Loss of DISC1 inhibits the rate of radial neuronal migration in the developing neocortex, increases the distance between the centrosome and the nucleus, and impairs the orientation, polarity and degree of dendritic arborization of those neurons that manage to migrate into position. While we have just discussed a collaborative function of DCX with Lis1 and dynein for nuclear and centrosomal movements, it seems that DCX is also involved in the formation of the dilation without any obvious implication of Lis1 and dynein (Tsai et al., 2007; Nishimura et al., 2014). How DCX carries this function is unclear.

Mutations in microtubule-dependent kinesin motor proteins cause lissencephaly in humans (Poirier et al., 2013). In the mouse, knockout of Kif2a, a member of the kinesin 13 family and a plus-end molecular motor, leads to abnormal lamination of projection neurons (Homma et al., 2003). Kinesin-6 is enriched in the proximal region of the leading process. Its depletion prevents the formation of a clear leading process and disturbs the multipolar to bipolar transition of cortical neurons *in vivo* and *in vitro* while it affects the directionality but not migration *per se* of cerebellar granule neurons migrating *in vitro* (Falnikar et al., 2013). The knockdown of kinesin-5 (also named Kif11) in cerebellar granule neurons migrating *in vitro* results in faster but more random migration with a shorter leading process (Falnikar et al., 2011). They suggest a model in which kinesin-5 acts as a brake to the sliding of microtubules along each other.

MAP1B is another microtubule associated protein important for neuronal migration (Takei et al., 2000; Teng et al., 2001). Its function could lie in its interaction with LIS1, affecting the interaction of LIS1 with cytoplasmic dynein (Jimenez-Mateos et al., 2005). MAP6, a protein important for microtubule stabilization and organelle trafficking, calmodulin-regulated spectrin-associated protein 2 (CAMSAP2), a protein that binds and stabilizes free microtubule minus ends, and the tripartite motif containing protein TRIM46, another microtubule binding protein, regulate cortical neuron migration (Yau et al., 2014; van Beuningen et al., 2015; Tortosa et al., 2017). Their depletion results in fewer bipolar migrating neurons that display shorter leading process and absence of a specified axon. Microtubule-actin crosslinking factor 1 (MACF1) is a microtubule plus-end tracking protein. Neurons depleted for this protein also show a shorter leading process along with a decreased movement of their centrosome (Moffat et al., 2017). Collapsin response mediator protein 2 (CRMP2) interacts with tubulin dimers and microtubules and promotes microtubule polymerization (Fukata et al., 2002; Niwa et al., 2017). Inhibition of CRMP2 suppresses axon formation *in vitro* and the multipolar to bipolar transition of migrating cortical mammalian neurons *in vivo* (Inagaki et al., 2001; Sun et al., 2010).

The knockdown of SCG10 (also known as stathmin-2), a member of the stathmin family of microtubule destabilizing proteins, in the mouse cerebral cortex increases both the frequency of exit from the multipolar stage and the locomotion rate (Westerlund et al., 2011). They found that SCG10 is regulated through its phosphorylation by c-Jun N-terminal kinase 1 (JNK1, also named Mapk8) and regulates microtubules stability in migrating neurons. Mice lacking JNK1 or specific inhibition of cytoplasmic JNKs (the three members of the family JNK1, 2 and 3) also show an increased rate of radial migration while inhibition of nuclear JNKs or simultaneous depletion of cytoplasmic and nuclear JNKs has the opposite effect (Kawauchi et al., 2003; Westerlund et al., 2011). This suggests that regulations of microtubules and gene expression by JNKs have opposite effects on cortical projection neuron migration.

A recent study found that the knockdown of the microtubule plus-end tracking protein CLASP2 (cytoplasmic linker associated proteins 2) using shRNAs results in a small positional shift of the electroporated neurons deeper in the CP compared to control cells (Dillon et al., 2017). Time lapse videomicroscopy showed that the radial bipolar migration speed and orientation were not affected, suggesting that the inhibition of CLASP2 might affect the terminal somal translocation at the end of bipolar migration. Indeed, when observing electroporated neurons at the top of the CP, they found a defect in the orientation of the leading process and in the localization of the centrosome and Golgi apparatus.

Overall, these data demonstrate the importance of the regulation of microtubule dynamics during the different phases of radial migration.

*4.3.4.2. Cytoskeleton in tangential migration*. Regulation of the actin cytoskeleton plays an important role in cortical interneurons migration. F-actin is enriched at the tip of the leading process throughout migration while it condenses ahead of the nucleus and moves towards the leading process prior to nuclear translocation (Fig. 2e). In addition, F-actin transiently accumulates behind the nucleus during nuclear movement (Shinohara et al., 2012). Cortactin promotes polymerization and rearrangement of the actin cytoskeleton and localizes at the tips of most leading process branches, the bulge and behind the nucleus of migrating interneurons. Its activity regulates actin protrusion at the leading process tip and regulates leading process branching (Lysko et al., 2014).

Active myosin localizes to the central region of the leading process and at the rear of neurons undergoing somal translocation to control the forward movement of the nucleus (Bellion et al., 2005; Schaar and McConnell, 2005; Martini and Valdeolmillos, 2010). Myosin activity was also observed at the tip of the leading process and it might be fine-tuned by p27 Kip1 to regulate leading process branching (Godin et al., 2012). Somal and growth cone distribution of actomyosin is regulated by the Elongator complex as observed after conditional knockout of its Elp3 subunit in cortical interneurons (Tielens et al., 2016). Loss of Elp3 impairs nucleokinesis, reduces velocity, directional persistence, the dynamic branching of the leading process and reduces the percentage of neurons with a swelling ahead of the nucleus. N-cadherin also regulates myosin activity and promotes the directional migration of MGE interneurons to the embryonic cortex and their radial migration in the developing CP (Luccardini et al., 2013). *In vitro*, inhibition of N-cadherin-dependent adhesion affects the polarization of myosin activity at the rear of the cell, induces a shorter leading process and a mislocalization

of the centrosome behind the nucleus.

In humans, tangential migration defects are observed in cases of Miller-Dieker syndrome, which result from reduced amount of LIS1 due to heterozygous deletion (Pancoast et al., 2005). Interneurons from heterozygous Lis1 mutant mice exhibit a slower tangential migration and a defect in the stability of new branches in the leading process (McManus et al., 2004; Gopal et al., 2010). While deletion in mice of the actin nucleators mammalian diaphanous homolog 1 (mDia1, also known as Diap1) and mDia3 (also named Diap2) does not affect radial migration of excitatory neurons or cortical layer formation, it impairs tangential migration of interneurons (Shinohara et al., 2012). mDia-deficient interneurons exhibit a reduced separation of the centrosome from the nucleus due to reduced velocity of the centrosome and delayed nuclear translocation. F-actin movement and condensation at the cellular rear is impaired while the formation of the cytoplasmic dilation is not affected. In an *in vitro* model for tangential migration, mDia controls nuclear translocation and F-actin dynamics. The same group used an inhibitor of ROCK in an *in vitro* migration assay and found that ROCK inhibition slowed down the movements of the nucleus and the centrosome but did not affect nucleus-centrosome separation.

In tangentially migrating interneurons, a centrosomal microtubule array is reminiscent of the perinuclear cages described in radially migrating neurons. Microtubules seem to be important for the control of cell morphology and cell directionality but not motility (Baudoin et al., 2008). They showed that partial depolymerization of microtubules using nocodazole impaires leading process morphology and cell directionality but has no effect on the speed of migration of MGE neurons migrating *in vitro*. However, it was more recently found that the centrosome and nuclear translocation occur along extra-centrosomal microtubules (Baudoin et al., 2012). Accordingly, deficiencies in microtubule-interacting proteins affect tangential migration. Tangential migration of interneurons derived from the medial ganglionic eminence and of neuroblasts in the rostral migratory stream requires DCX (Kappeler et al., 2006; Koizumi et al., 2006b). Migrating interneurons derived from DCX knockout mice show more numerous but less stable leading process branches and shorter movements of the nucleus (Kappeler et al., 2006). The leading process swelling containing the centrosome moves abnormally backward towards the nucleus showing abnormal orientation of organelles movement in those cells. While the migration speed and distance is not changed in DCX knockout interneurons, shRNA-mediated knockdown of DCX or Dclk1 induces a slower tangential migration of interneurons from the ganglionic eminences (Friocourt et al., 2007). DCX bundles and stabilizes microtubules at the leading process to reduce its branching (Lysko et al., 2014). In humans, a reduced number of interneurons has been observed in some cortical areas of post-mortem lissencephalic DCX-deficient fetuses, resembling a DCX KO mouse model (Francis et al., 2006). DISC1 knockdown by RNA interference results in a migration defect of MGE-derived cortical interneurons (Steinecke et al., 2014). Their migration is slower due to a reduction of somal translocations and a longer and less-branched leading process. DISC1 co-localizes with F-actin behind the nucleus and at the tip of the leading process and controls the level of F-actin at the leading tip through the regulation of the phosphorylation of the F-actin cross-linking protein Girdin. In contrast, DISC1 regulates the acetylation of microtubules in the leading processes but not its polymerization. Inhibition of JNKs or ablation of JNK1 and JNK2 in cortical interneurons results in aberrant migratory trajectories during tangential migration and leads to premature switch from tangential to radial migration and entry into the CP (Myers et al., 2014; Myers et al., 2020). The pathway downstream of JNKs is not known but it could involve regulation of microtubules as they do during radial migration (Kawauchi et al., 2003; Westerlund et al., 2011). Depletion of the microtubule plus-end tracking protein MACF1 in tangentially migrating interneurons slows their speed and induces an aberrant orientation of movement, probably due to an abnormal leading process (Moffat et al., 2017). In addition MACF1 regulates the transition from tangential to radial movement when interneurons enter the CP.

### 4.4. Phosphoinositides/PI3K signaling and cell polarity

Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes capable of phosphorylating the hydroxyl group on 3-position of the inositol ring of phosphatidylinositol. The PI3K family is divided into three different classes (class I, II, and III), based on their substrate specificity and molecular structure (Vanhaesebroeck et al., 2012). Phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P3) is the major product of class I PI3Ks and a key mediator in diverse intracellular signaling pathways including cell proliferation, survival, differentiation, migration and polarity (Cantley, 2002). Signaling is in part mediated by the recruitment of proteins with pleckstrin-homology (PH) domains that accumulate at sites of PI3K activation by directly binding to PtdIns(3,4,5)P3. PI3K functions are controlled by inositol phosphatases such as PTEN (Phosphatase and tensin homolog deleted on chromosome 10) and SHIP (Src homology 2 (SH2) domain containing inositol polyphosphate 5-phosphatase 1) that dephosphorylate PI3K products into PtdIns(4,5)P2 and PtdIns(3,4)P2 respectively (Lee et al., 1999; Backers et al., 2003). The localized accumulation of PtdIns(3,4,5)P3 likely represents the first spatial landmark that establishes polarization of the cell. PI3K signaling influences the activity of small GTPases, the cytoskeleton and the relocalization of polarity proteins.

#### 4.4.1. Phosphoinositides/PI3K signaling in asymmetric cell division

PI3K plays an important role during asymmetric division of activated lymphocytes that self-renew while producing differentiated progeny. The asymmetric activity of PI3K establishes fate disparity between sibling lymphocytes (Lin et al., 2015; Chen et al., 2018). The cell with high PI3K activity differentiates while its PI3K-attenuated sibling self-renews. In *C elegans*, PtdIns(4,5)P2 was recently found to be enriched on the anterior side of the single cell early embryo and modulates actin organization and Par cortical domains (Fig. 2a) (Scholze et al., 2018).

#### 4.4.2. Phosphoinositides/PI3K signaling in apico-basal epithelial polarity

During apico-basal polarization of cultured MDCK cells, basolateral and apical membrane specification depends on a relocalization of PtdIns(3,4,5)P3 and PtdIns(3,4)P2 to the basolateral membrane and concentration of PtdIns(4,5)P2 at the apical surface in a PI3K, PTEN and SHIP2 dependent manner (Fig. 2b) (Gassama-Diagne et al., 2006; Martin-Belmonte et al., 2007; Awad et al., 2013). Furthermore, E-cadherin-mediated PI3K activation following cell-cell contact formation provides a significant source of PtdIns(3,4,5)P3 during initial polarization (Yap and Kovacs, 2003). This could in turn activate small GTPases such as Rac1 through the recruitment and activation of GEFs, modify the cytoskeleton and recruit polarity complexes, reinforcing the identity of the respective membrane domains. Crosstalk with the polarity complexes has been shown. PTEN regulates the apical localization of Par3, Par6 and Cdc42 (Martin-Belmonte et al., 2007). In MDCK cells, PTEN-dependent enrichment of PtdIns(4,5)P2 at the apical domain recruits Annexin 2 which in turn recruits Cdc42. Membrane targeting of Par3 depends on its interaction with PtdIns(4,5)P2 *via* its second PDZ domain (Wu et al., 2007; Krahn et al., 2010). PTEN can be apically recruited through its interaction with junctional proteins such as the MAGUK protein MAGI-2 (Wu et al., 2000). In addition, its interaction with the third PDZ domain of Par-3 is also important for its localization to junctional membrane of MDCK cells and apical cortex of *Drosophila* epithelia (von Stein et al., 2005; Feng et al., 2008). Par3 therefore contributes in a positive loop with PTEN to the apical PtdIns(4,5)P2 concentration. In the *Drosophila* embryo epithelium, Crb antagonizes PI3K activity at the apical domain while PI3K represses Crb-dependent apical membrane growth (Chartier et al., 2011).

#### 4.4.3. Phosphoinositides/PI3K signaling in front-rear polarity of migrating cells

In migrating cells, front-rear polarization depends on the recruitment and activation of PI3K by several parallel signals at the front (Fig. 2c). In contrast, PTEN and SHIP, recruited to the cell rear, contribute to the generation of a PtdIns(3,4,5)P3 front-to-rear gradient which induces the activation of Rac and Cdc42 at the leading front through the regulation of GEFs (Welch et al., 2003). The most used models to study the role of PtdIns(3,4,5)P3 during chemotaxis are *Dictyostelium discoideum* cells and neutrophils (Kolsch et al., 2008; Weiger and Parent, 2012). These cells establish a front-rear polarity in response to a gradient of chemoattractant by establishing domains of PtdIns(3,4,5)P3 at the leading edge of the cell and PtdIns(4,5)P2 at the rear in a PI3K and PTEN dependent manner (Funamoto et al., 2002; Merlot and Firtel, 2003). One of the mechanisms involved in the creation of this PtdIns domains is a mutual inhibition between PTEN and PtdIns(3,4,5)P3 (Matsuoka and Ueda, 2018). PtdIns(3,4,5)P3 generated at the leading edge by PI3K suppresses the PTEN binding site required for stable PTEN membrane binding while PTEN dephosphorylates PtdIns(3,4,5)P3 at the rear.

A positive feedback loop can take place with other polarity molecules as shown for instance in neutrophils where Rac-induced actin polymerization is required to stabilize PI3K and reinforce the local accumulation of PtdIns(3,4,5)P3 at the cell front (Weiner et al., 2002). In migrating MDCK cells during a cell wound assay, occludin, a transmembrane protein, recruits PI3K to the leading edge *via* association with its C-terminal SH2 domain (Du et al., 2010). Downregulation of occludin attenuates the activation of PI3K, resulting in a disorganization of the actin cytoskeleton and reduced cell protrusions. Phosphoinositides are also involved in gradient sensing and oriented migration in fibroblasts (Haugh et al., 2000).

#### 4.4.4. Phosphoinositides/PI3K signaling, polarity and neuronal migration

Inhibition or hyper activation of PI3K inhibits the migration of cortical projection neurons in mice (Fig. 2d) (Konno et al., 2005; Jossin and Goffinet, 2007). In humans, mosaic activating mutations in PIK3CA result in focal cortical dysplasia, supporting a potential role of the PI3K pathway in neuronal migration (Jansen et al., 2015). Class I PI3Ks form a functional heterodimer composed of a p110 catalytic and a p85 regulatory units. In mice, overexpression of the regulatory subunit p85β results in many neurons arrested at the multipolar morphology zone and a shorter leading process with more branches in bipolar migrating neurons (Cheng et al., 2018). The p85α subunit interacts with the intracellular adaptor Dab1 in a manner dependent to Reelin, an extracellular matrix protein that regulates the architectonic of the cerebral cortex partly through the regulation of the oriented migration of multipolar cortical neurons (Bock et al., 2003; Jossin and Goffinet, 2007; Jossin, 2011; Jossin and Cooper, 2011). Inhibition of the PI3K downstream effectors PDK1 and Akt reduces the speed of locomoting cortical neurons and perturbes the coordinated movement of the nucleus and centrosome, possibly through the regulation of microtubule structure and MAP binding and/or the regulation of the cytoplasmic dynein/dynactin complex (Itoh et al., 2016). A polarized Akt activation might also contribute to the oriented migration of multipolar neurons towards the CP (Jossin and Cooper, 2011; Itoh et al., 2016). Inhibition of insulin like growth factor-1 receptor (IGF-1R) using shRNA also induces a defect in the orientation of multipolar migrating neurons and this phenotype is rescued by the co-expression of a constitutively active form of PI3K (Nieto Guil et al., 2017). This suggests that several pathways regulate PI3K to orient the migration of cortical projection neurons. On the other hand neuronal deletion of PTEN using Nex1Cre conditional deletion in mice did not induce any major defect in migration or positioning (Kazdoba et al., 2012).

Neurotrophins activate PI3K in tangentially migrating cortical interneurons and inhibition of PI3K dramatically inhibits their migration (Fig. 2e) (Polleux et al., 2002). PI3K activity regulates interneuron polarity, directionality and leading process morphology at the pallial/subpallial border (Rakic et al., 2015).

## 5. Concluding remarks

Great progress has been made in the understanding of the regulation of cell polarity. It is clear that common mechanisms are employed during different aspect of cell polarization in very diverse organisms. However proteins involved in polarity may function differently in distinct cell types and polarization events. Particular functions may require other cell specific components. In this review, I focused on the radial and tangential migrations of cortical neurons. While the regulation of their oriented migration share similarities with the migration of other slow moving cells such as fibroblasts and astrocytes as discussed here, they also exhibit differences, even when comparing radial *versus* tangential migrations.

Despite the accumulation over the years of knowledge about the molecular and cellular mechanisms driving the development of the cerebral cortex, we are still far from fully grasping the complexity of the highly coordinated process of cortical morphogenesis. Oriented neuronal migration is critical for the correct cell positioning that shapes the tridimensional organization of the cortex and is important for allowing appropriate long range and short range cell communication in the form of synaptic connectivity and diffusible cues. Neuronal migration defects are causative of human brain malformations such as lissencephalies, heterotopias and neurological and psychiatric disorders such as epilepsy, dyslexia, autism, schizophrenia and mental retardation (Francis et al., 2006; Wegiel et al., 2010; Manzini and Walsh, 2011; Adler et al., 2013; Cusmai et al., 2014; Muraki and Tanigaki, 2015; Ishii et al., 2016). The symptoms vary according to the abnormality, the extent of this abnormality and the area affected. Unfortunately, current treatment is symptomatic and a significant number of patients with these disorders is still lacking a diagnosis. It is thus crucial to identify further causes of disease and understand their mechanism of action. A better understanding of how the brain develops in normal conditions and in disease will provide new concepts for therapeutic approaches to improve diagnosis and to treat and prevent neurodevelopmental disorders. Oriented neuronal migration is regulated by the extracellular environment including surrounding cells, the extracellular matrix and diffusible cues. Understanding how all these signals are integrated by neurons to correctly polarize and migrate is one of the complex question currently facing the field.

The mouse is largely used as a model to investigate these mechanisms and has already revealed many molecular and cellular aspects of human neuronal migration disorders. However, even though many aspects of cortical development are similar between the mouse and the human neocortex, several key features differ such as the size of the brain, the presence of folding in the human cortex, and small dissimilarities in the cellular and extracellular matrix content and in gene expression profiles (Nowakowski et al., 2016; Del Toro et al., 2017; Miller et al., 2019). In some cases such as for DCX, Flna and Tuba1a, the mouse models did not reproduce the human phenotype (Koizumi et al., 2006a; Liu, 2011; Carabalona et al., 2012). Species-specific differences have therefore to be taken into account. New strategies, with their own strengths and limitations, are emerging to tackle these issues. Among those are: the use of other animal models, such as the ferret or non-human primates, that share additional specific features with the human brain; the development of human self-organized organoid models; or the transplantation of human cells into the mouse brain (Espuny-Camacho et al., 2013; Suzuki and Vanderhaeghen, 2015; Zhu et al., 2016; Pasca, 2018; Klaus et al., 2019).

Cortical malformations caused by defects in neuronal migration arise during the embryonic development making it difficult to rectify in humans. However, it was demonstrated that correction of a defective molecular pathway at early postnatal stage is possible in rodents (Manent et al., 2009). They were able to attenuate the symptoms even

when the malformation is already established, suggesting that therapeutic manipulation of the cerebral cortex during the early months after birth might one day be possible in humans.

Finally, a better understanding of the mechanisms regulating oriented migration is also of interest with regard to transplantation of neural stem cells as a potential therapy for neurodegenerative diseases and central nervous system injury. One of the multiple challenges facing this field of research is to define the conditions needed for an efficient migration of the transplanted stem cells towards the appropriate location.

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