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Regulation of polarity protein levels in the developing central nervous system

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Abstract

In the course of their development from neuroepithelial cells to mature neurons, neuronal progenitors proliferate, delaminate, differentiate, migrate, and extend processes to form a complex neuronal network. In addition to supporting the morphology of the neuroepithelium and radial glia, polarity proteins contribute to the remodeling of processes and support the architectural reorganizations that result in axon extension and dendrite formation. While a good amount of evidence highlight a rheostat-like regulation by signaling events leading to local activation and/or redistribution of polarity proteins, recent studies demonstrate a new paradigm involving a switch-like regulation directly controlling the availability of polarity protein at specific stage by transcriptional regulation and/or targeted ubiquitin proteasome degradation. During the process of differentiation most neurons will adopt a morphology with reduced polarity which suggests that polarity complex proteins are strongly repressed during key step of development. Here we review the different mechanisms that directly impact the levels of polarity complex proteins in neurons in relation to the polarization context and discuss why this transient loss of polarity is essential to understand neural development and how this knowledge could be relevant for some neuropathy.

Keywords

Polarity protein; Pard3; Neuron

Introduction

The central nervous system (CNS) has little self-renewing ability, and its intricate complexity develops through a precise sequence of events that must be tightly orchestrated. Nevertheless, most neurons originate from the neuroepithelium and follow fairly similar developmental sequences from birth to maturity (Fig.1). Even at the neural tube stage, cells are organized in a single layer and already display apico-basal polarity, with the apical side being oriented toward the lumen of the neural tube. The cells subsequently undergo symmetric divisions and transition into radial glia progenitors (RGPs), which exhibit more

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pronounced apico-basal asymmetry as they start to elongate and maintain their adhesion to the ventricular zone and the external pia. From that point, RGPs begin to divide asymmetrically to produce a neuronally committed post-mitotic cell or an intermediate progenitor cell (IPC). Each of these cell types requires a delamination process to modify its adhesion preferences and undergoes an apparent transient loss of polarity. At this stage in its development, a cell may migrate over short or long distances: for example, glutamatergic neurons from the cortex migrate only a short distance into the subventricular zone [1], whereas cerebellar granule neuron progenitors (GNPs) from the cerebellum originate from RGPs in the upper rhombic lip (not to be mistaken with RGPs from the rhombomere 1 VZ that give birth to Purkinje cells), delaminate and migrate tangentially over long distances on the surface [2]. IPCs proliferate further and eventually give rise to two post-mitotic cells. These newborn neurons must reacquire polarity and transition from a multipolar morphology to a bipolar morphology, extend an axonal process, migrate to their final position (often through radial glia-guided migration), and finally extend their dendritic tree [3] (Fig.1).

Mature neurons are polarized from their dendrites to their axon, one end receiving the other transmitting electrical current thus their morphology ensures the proper flow of information. During the development of neurons, their polarity and growth of extension from the soma must be tightly regulated and is even sometimes repressed during mitotic and early post-mitotic stage of IPCs [4]. Many neurodevelopmental disorders arise from a dysregulation of the IPC population [5], and in evolutionary terms, IPCs are also thought to be responsible for the increase in the size of the CNS [6, 7]. Thus the non-polar phase seems like a hotspot in neurodevelopment and yet very few studies have reported how the level of polarity complex are regulated during the transition from progenitor to mature neurons.

Recent studies have highlighted the similarities between the well-described epithelial-to-mesenchymal transition (EMT) of epithelial cells and the transitions observed during the asymmetric division of RGPs, which leads to the delamination of a post-mitotic neuron or IPC. Characteristics common to these transitions include the deregulation of adherens junctions through the loss of E-cadherin, the loss of cell-to-cell contact, and the expression of vimentin [4, 8]. Most important is the loss of apico-basal polarity through the deregulation of the polarity protein complex [8]. However, the process that contributes to post-mitotic neurons reacquiring their polarity is often referred to as a multipolar-to-bipolar transition [9, 10] and has been described as resembling a counterpart of the EMT termed the mesenchymal-to-epithelial transition (MET). A recent study of transitions in the cerebellum has highlighted further similarities between the MET and the transition of GNPs to post-mitotic neurons, with the expression of the main transcriptional factor directly repressing the expression of the polarity protein complex in GNPs [11]. There is also evidence that the overexpression of polarity complex proteins is sufficient to promote the differentiation of IPCs in mature polarized neurons [11, 12].

Many studies have shown how intrinsic and extrinsic events rearrange the asymmetric distribution of polarity proteins in a neuron and how they bring about the formation of a scaffolding structure via their interaction with the cytoskeleton to generate an axon and dendrites [10, 13]. Briefly, an extrinsic signal, such as the activation of an adhesion or

neurotrophin receptor, is translated into local lipid modifications that recruit small GTPases that can activate or repress locally proteins such as those forming the polarity protein complex. This cascade ultimately translates into the stabilization or destabilization of the cytoskeleton [10, 14]. Although this information is critical to an understanding of neuronal biology, it specifically represents the rapid and local response of a neuron at a stage in its development when it is competent to integrate such information. Early post-mitotic neurons and IPCs are often in close proximity to one another and are, therefore, exposed to similar signals. We believe that the downregulation of the polarity complex proteins that can be observed when cells adopt a multipolar or mesenchymal morphology is an underestimated feature of neurogenesis, as it could enable cells to respond differently to the extrinsic polarization signal or ignore it altogether according to their maturation status.

Little is known about the main transcriptional program or post-transcriptional events that initiate or repress polarization events in developing neurons. In this review, we focus on examples from the literature that show how the availability of polarity proteins is controlled at the transcriptional, post-transcriptional, and post-translational levels.

Polarity Proteins in Neurons

Cell polarization is a key process in development: the break in symmetry of the cells of a multicellular organism appears as early as the eight-cell stage of the embryo and enables self-organization [15]. Polarity proteins, together with cell-cell adhesion proteins, have been identified as key regulators that support the architecture of cellular asymmetry. Commonly expressed in most cell types, polarity proteins are primarily known for their role in establishing apico-basal polarity in epithelial cells. They regroup proteins of the Pard, Scribble, and Crumbs complex, which usually exhibit self-excluding localization on either the apical or basal side of the membrane [16], and this segregation can also be observed in RGP [17]. New post-mitotic cells and IPCs that exhibit low polarization also contain low levels of polarity proteins, and there is considerable evidence that the loss of Pard3 during asymmetric division from RGP correlates with the beginning of differentiation, whereas a high level of Pard protein is associated with progenitor self-renewal [8, 18, 19]. In mature neurons, however, most of the polarity proteins localize to the growing neurites, leading to their enrichment in the growth cone of the axon [10]. Polarity proteins also play a critical role in neuronal migration and in regulating cell-cell adhesion [20, 21].

Ultimately, neurons can polarize an axon in culture in the absence of a specific source of morphogens or gradient molecules [22]. Although this observation supports the view that intrinsic rather than extrinsic factors initiate the break in symmetry, its primary importance lies in the revelation of the intrinsic ability of mature neurons to polarize. Interestingly, live imaging of ex vivo slices of cortex and cerebellum has revealed that newborn neurons tend to remain at a multipolar stage for several hours, exhibiting what appears to be random migration before committing to grow an axon and finally migrate radially [23–27] (Fig.1). Because neurons tend to be born in successive waves and because the local environment is similar for multipolar neurons and for those that commit to polarization at a given time, it is reasonable to suppose that, even if extrinsic signals in vivo favor one axis of polarization over another [26], the ability to self-polarize must first be lost and then reacquired. This in

turn would be a strong argument for the existence of a transcriptional or post-transcriptional program that represses the availability of polarity complex proteins in newborn post-mitotic neurons in order to bring about their repolarization.

In utero electroporation of the cortex enables the overexpression or knockdown of genes of the polarized RGP population, whereas electroporation and growth in culture of ectopic slices of the cerebellum allows investigation on apolar IPCs like the GNPs. The possibility of affecting cells at different stages of neurogenesis allows us to draw further conclusions regarding the role of polarity proteins in the differentiation process. The overexpression of Pard3 in GNPs promotes differentiation and radial migration [12], whereas the overexpression of Pard3 or Pard6 in RGPs promotes the maintenance of progenitors [19]. Conversely, the knockdown of Pard3 in GNPs inhibits the last step in differentiation [12], whereas the knockdown of Pard3 in RGPs leads to premature cell-cycle exit [19]. Taken together, these results support the hypothesis that Pard3 is required in both RGPs and fully differentiated neurons, but they also highlight the need for polarity proteins to be repressed during the transition from progenitors to mature neurons.

In the following sections, we will review examples from the literature that show how the levels of polarity complex proteins are regulated at the different stages of neuronal development.

Transcriptional Regulation of the Polarity Complex

Negative regulation

As mentioned above and as their name suggests polarity complex proteins are commonly expressed in every cell type that exhibit an asymmetric distribution of protein at their membrane as it is the case with RGPs and mature neurons. Nevertheless the transition from one to the other, from cell cycle exit to differentiation, require a reboot of polarity associated with an apparent change of morphology and an active loss of polarity. Although some transcription factors have been associated with the maintenance of the neuroepithelial stage and/or the process of differentiation to become a mature neuron, only a few of those factors have been identified as direct regulator of the transcription of polarity complex proteins.

In the mouse cerebellar granule neuron (CGN) system, the Zinc-finger and homeobox transcription factor Zeb1 controls neuronal differentiation by binding to and directly repressing the mRNA expression polarity proteins at the Pard3 and Pard6 gene loci, along with some other adhesion proteins [11]. Zeb1 is highly expressed in GNPs but diminishes in CGNs that have become postmitotic, illustrating that polarity is actively repressed in GNPs and CGN competency to polarize is due to relief of an inhibitory pathway. Consistent with a Zeb1-Pard complex antagonistic relationship, Zeb1 overexpression was found to maintain GNPs in the germinal zone while inhibiting their migration. This phenotype could be rescued by restoring the expression of Pard3 or Pard6, showing that polarity proteins are sufficient to promote differentiation in GNPs [11]. Zeb1 and Zeb2 have been studied in epithelial cells and are key regulators of EMT and have been shown to repress E-cadherin, Crumb3, Hugel2, and Patj and inhibit the formation of adherens junctions [28]. Studies in carcinomas have revealed a negative-feedback loop between the Zeb proteins and the

miR-200 microRNA family (miR-429, miR-200a, miR-200b, miR-200c, and miR-141). These miR-200s directly repress Zeb mRNA and promote MET [29]. In neurons, miR-200s are induced by nerve growth factor in culture and promote neuronal differentiation [30, 31]. Although it remains to be determined whether miR-200s also act in this context by repressing Zeb transcription factors, these findings reinforce the apparent similarity between EMT and MET-like transitions during the successive stages of neurogenesis.

In *Drosophila*, the knockdown of the retinoblastoma tumor suppressor Rb homologue Rbf1 affects the polarity of retinal and wing development. The knockdown of Rbf1 upregulates the apico-basal polarity genes *aPKC* and *par6*, as well as the planar cell-polarity genes *vang*, *pk*, and *fmi* [32]. Rb is a conserved cell-cycle regulator that acts as a co-repressor of the E2F family of transcription factors and prevents the entry of the cell into S-phase. In the mouse CNS, although there is no direct evidence that Rb directly represses the expression of polarity proteins, several studies have shown it to be involved in regulating neurogenesis and the migration of neuronal progenitors [33–36]. Furthermore, during development, a high level of phosphorylated Rb has been observed in the subventricular zone of the cortex, where the multipolar neurons reside [37], raising the possibility that Rb contributes to regulating the loss of polarity observed during multipolar transition. Further experiments are needed to confirm whether Rb or E2Fs directly affect polarity protein levels in CNS development.

In epithelial cell culture, the transcriptional repressor Snail antagonizes the expression of Crumbs polarity proteins [38]. Nevertheless, although Snail has been shown to be involved in regulating aspects of the survival, proliferation, and differentiation of neuronal precursors in the cortex, no link has been established between Snail and the regulation of polarity complex proteins in neurons [39].

Positive regulation

The transcription factor AP-2 γ , a member of the AP-2 family of transcription activator proteins, regulates tight-junction formation in blastocyst development. Its knockdown represses the expression of Pard6b, ZO-2, and Claudins, but not Pard3, suggesting that it positively transcriptionally regulates these genes [40]. It should be noted that this is one of the few examples in which there is a positive effect on the transcription level of a subset of polarity proteins. The bone morphogenic protein Bmp4 directly upregulates AP-2 γ through Smad1 [41]. As Bmp4 signaling is involved in the differentiation of CGNs in the cerebellum [42, 43], we can speculate that it contributes to the repolarization of progenitors by upregulating Pard6 through AP-2 γ activation.

Another example of positive regulation has been observed in the cerebellum, where the knockdown of the transcription factor family Foxo down-regulates not only Pard6 but also other proteins that are critical to the establishment of polarity, such as pak1, R-Ras, APC, and CRMP2 [44]. Foxo activity itself has been shown to be controlled by the levels of the antagonistic SnoN isoforms SnoN1 and SnoN2 [9, 45]. Interestingly, in *Caenorhabditis elegans*, Foxo is induced by insulin signaling [46]. This is noteworthy because IGF-1, an insulin receptor, was recently shown to be crucial for the transition from multipolar to bipolar morphology in the cortex [47]. The knockdown of IGF-1 arrested the cells at a multipolar stage and, lacking polarity, they were unable to form axons [47]. However, the

link between Foxo or SnoN isoforms and insulin signaling has yet to be confirmed in a vertebrate model.

Other transcription factors that influence neuronal polarity are involved in maintaining progenitors or promoting differentiation, and they often regulate the levels of proteins that interact with polarity proteins, adhesion proteins, or cytoskeletal components. However, because they have not been linked to the direct transcriptional regulation of polarity proteins in neurons, they will not be discussed here.

Newly born neurons and IPCs appear to require a transient loss of polarity and despite the predominant function of polarity complex proteins in neurogenesis few studies have reported evidence of direct transcriptional regulation. It seems necessary for a better understanding of neuronal development to push forward and investigate further. For example, pathways that are known to maintain IPCs in a proliferative state like hypoxia [48] should be studied in regard to their ability to repress directly or indirectly polarity complex proteins.

Post-Transcriptional Regulation of the Polarity Complex

Keeping polarity complex proteins at the appropriate level cannot solely rely on genetic regulation, post-transcriptional regulations allow the cell to control locally the presence of a protein, either by controlling its mRNAs level, localization and translation initiation, or by controlling protein level itself by targeting it for degradation by the proteasome or segregating it in asymmetric division. These mechanisms are often triggered by extrinsic signaling event and act on a faster time scale than transcription.

mRNAs Level Regulations

MicroRNAs are small non-coding RNAs involve in post-transcriptional regulation of gene expression by silencing specific mRNAs or targeting them for cleavage, therefore limiting protein translation. In zebrafish, one example describes the role of microRNA miR-219 in directly reducing the levels of Pard3 and aPKC in the neuroepithelium of the neural tube, thus promoting delamination and cell-cycle exit [49]. Furthermore, there is a negative-feedback loop with the mitogen Sonic hedgehog (Shh) signaling, as inhibition of Shh signaling rescued the phenotype of miR-219 depletion, whereas elevated Shh phenocopied miR-219 deficiency [50].

Local translation is another means by which protein expression can be spatially and temporally restricted in some subcellular compartments. In neurons, the axons contain ribosomes and the translational machinery necessary for local translation of a specific subset of mRNAs [51]. While mRNA transport to specific localization of subcellular domains ultimately rely on a pre-existing cell polarity, on-site translation is efficient to generate and stabilize protein asymmetry [52]. With regard to polarity proteins, local translation of Pard3 in the growth cone has been observed in response to NGF and Netrin-1 signaling and to promote axonal elongation in neurons in culture [53]. A recent study has shown that synthesis and degradation are linked events in the growth cone and are triggered by local signaling [54]. This example with NGF promoting local Pard3 translation, as well as BDNF preventing Pard6 degradation by Smurf1, demonstrate that extrinsic cues that are known to

promote differentiation also have a positive impact on the amount of polarity protein available in subcellular compartment of the maturing neurons.

Ubiquitin Ligases and Proteasome Degradation

The Pard family protein, the hallmark of polarity complex protein discovered in the embryo of *c. elegans* using genetic screens, originally contain among them PAR-2 a RING finger protein with single-subunit E3 ubiquitin ligase capable of auto-ubiquitination [55], suggesting that proteasome activity could be a core component of polarization. Surprisingly PAR-2 is the only protein that has no known homolog in *Drosophila* and vertebrates [56]. Nevertheless few examples of targeted degradation of polarity complex proteins by E3 ubiquitin ligase proteins have been described in the vertebrate nervous system.

In the cerebellum, GNP express a high level of the Seven in absentia homologue (Siah) E3 ubiquitin ligase that interacts with both Pard6 and Pard3 but only targets the Pard3 protein for proteasomal degradation [12]. In those experiments the knockdown of Siah2 or the overexpression of Pard3 was sufficient to promote germinal zone exit and initiate the radial migration of granule neurons, whereas the overexpression of Siah2 maintained the GNPs in the germinal zone and make them adopt a multipolar morphology in a manner that did not involve a direct inhibition of neuronal differentiation [12]. The same study also revealed that Pard3 promotes the recruitment of the adhesion proteins necessary for interactions with radial glial cells by controlling the localization of JamC, a cell-cell adhesion protein to the cell surface, thus the antagonistic relationship between Siah2 and Pard3 impacts the developmental switch of GNPs adhesive affinity for substrates that are permissive for their subsequent migration to a final laminar position [12]. While it is not yet known what controls the expression or activity of Siah2 in that context, together with the repression by Zeb1 mentioned in the previous section, it emphasizes the strong repression on polarity proteins, especially Pard3, in the GNP population (Fig.2).

Another example of targeted degradation involves the E3 ubiquitin ligase Smad ubiquitin regulatory factor 1 (Smurf1). Cheng et al. (2011) have demonstrated that in response to brain-derived neurotrophic factor (BDNF) signaling, the protein kinase A (PKA) can phosphorylate Smurf1 and modify its affinity for specific ligands. Unphosphorylated Smurf1 is promoting Pard6 ubiquitination, while phosphorylation of Smurf1 decreases its affinity for Pard6 and it is RhoA that is predominantly degraded. Whereas Pard6 tends to stabilize axonal growth, RhoA has the opposite effect. Here we have an example where the local activation by BDNF is thus able to tune the local degradation from Pard6 to RhoA via Smurf1 substrate selectivity thus promoting axon stability [57].

This section has highlighted different mechanisms that act at a post-transcriptional level allowing a more precise control of polarity protein level and distribution at a subcellular level. While some of them has been shown to be triggered by extrinsic signaling event like BDNF, others like regulation of Siah2 activity or expression of specific miRNAs still need to be fully investigated. Overall these mechanisms add another layer of regulation of polarity complex proteins in addition to transcriptional program and it might be interesting to understand how control of these ubiquitin ligase proteins and miRNAs expression are themselves activated on a developmental timeline in respect to polarity protein transcription.

Other Regulation of Polarity Protein Distribution

In addition to the canonical post-transcriptional regulation methods reviewed above, several other mechanisms have been reported to influence the asymmetric distribution of polarity proteins. These mechanisms rely on the physical sorting of polarity proteins by asymmetric division or abscission of the apical domain.

In several model systems, of which *C. elegans* is the most studied, asymmetric division has been seen to segregate polarity proteins into two groups, designated anterior PARs (aPARs) and posterior PARs (pPARs), which results in the formation of two daughter cells carrying different sets of polarity proteins [58]. This specific sorting of the membrane domains is supported by the exclusion properties of the polarity proteins, but it is initially achieved by the local activation of the centrosome after sperm entry, initiating the break in symmetry and orienting the mitotic spindle to separate the aPARs from the pPARs during division. During cortical development, asymmetric division has also been reported to segregate polarity proteins away from the post-mitotic neurons [59]. RGP can undergo either a proliferative symmetrical division with a plan of division perpendicular to the ventricular zone, in which the apical domain and the proteins associated with it are shared by the daughter cells, or a neurogenic asymmetric division in which the plan of division is slightly tilted, keeping the Pard3 domain out of the daughter cell that is fated to become a neuron [59]. However, this is a controversial issue, as some groups have reported finding no specific correlation between the fate of the daughter cells and the fraction of apical membrane that they inherit [1, 60–62].

In the neural tubes of chickens and mice, the situation is slightly different: asymmetric division produces an apical cell that is fated to become a neuron, whereas the basal cell quickly regrows an apical domain and remains proliferative [63]. The basal cell has also been reported to exhibit a higher level of Notch signaling [63]. Interestingly, despite retaining the apical domain after the division, the apical cell can undergo a specific form of subdivision in which the apical domain anchored to the VZ is abscised out of the post-mitotic neuron, resulting in the loss of apical polarity proteins such as Pard3 and aPKC [63, 64]. Recently apical end-feet abscission has been shown to be involving a precise coordination of the actin and microtubule cytoskeleton [65] and while keeping the centrosome, this event also dismantles the primary cilium that plays a key role in transducing Shh signaling and maintaining cells in a proliferative state [64].

This mechanism involving asymmetric distribution of an existing pool of polarity proteins in RGP allows neuronal progenitor to produce one daughter cell with limited polarity complex proteins fated to become a post-mitotic neuron while the other daughter cell remain polarized and proliferative. This partition leads to an instant loss and allow to act ahead of any subsequent transcriptional repression programs on polarity complex proteins in the neurogenic daughter cell. Yet this raises further question onto what factors control the decision between asymmetric or symmetric division, and whether the loss of polarity protein by abscission or asymmetric distribution would itself trigger the following repression of polarity complex protein expression.

Possible integrative mechanisms of global polarity regulation.

Thus far we have provided single examples of global switch-like mechanisms controlling neuronal polarity. However, the CGN lineage illustrates that polarity inhibitory pathways co-exist in a cell type. Surprisingly, GNPs express high levels of both Zeb1, the transcriptional inhibitor of Pard complex, and Siah2, the E3 Ligase inhibits Pard complex function via Pard3 degradation (Figure 2). While Zeb1 and Siah2 co-expression in GNPs strongly emphasize the concept that neuronal polarization is actively suppressed in transiently amplifying progenitor populations, it does bring up the question: why do these cells require more than one neuronal polarity inhibitor? To answer this question one must consider the similarities and differences of Zeb1 and Siah2 function. Systematic gain- or loss-of-function studies in CGNs show that while both Zeb1 and Siah2 are necessary and sufficient for maintaining GNP GZ occupancy and controlling the timing of CGN radial migration, only Zeb1 arrests GNPs in the undifferentiated, proliferating state. The fact that Siah2 can delay polarization in cells that have become postmitotic suggests that there are multiple global polarity check points that maturing neurons must cross as they proceed to their final state of differentiation. Indeed, studies in the cerebral cortex support this notion as cortical pyramidal neurons can be arrested in a multipolar state at discrete stages of the migration to their final lamina, including in the intermediate zone, subplate and cortical plate [5]. Interestingly, a recent report documented that Siah2 can degrade Zeb1 during some forms of EMTs in epithelial-like cells [66]. This suggests a hypothesis that Zeb1 and Siah2 activity may be stratified in a cell type like the CGN lineage where Zeb1 could provide a form of polarity inhibition that is also linked to maintenance of progenitor status. Siah2 degradation of Zeb1 and Pard3 could then be permissive to a transition to a postmitotic state while still holding polarity in check. While our laboratory has used time lapse imaging to document that postmitotic CGNs transition through an unpolarized state prior to neurite extension (Laumonnerie and Solecki, unpublished results) as one would expect from a Zeb1-Siah2 stratification, epistasis analysis between Zeb1 and Siah2 will be required to order their activities and fully define neuronal polarity staging during the transition from GNP to CGN.

Concluding Perspectives

The break in symmetry supported by an asymmetric distribution of the polarity proteins arises early in the development of an organism. Proteins of the Pard complex are expressed by most cell types from these early stages onward and could be considered ubiquitous [67]. In this review, we have shown that in most cases there is direct regulation of the polarity protein complex, and specifically of the Pard family, leading to a loss of polarity proteins through different non-overlapping processes. This suggests a model involving passive activation and active repression and is consistent with the transient loss of polarity observed during neurogenesis. Of course, further evidence is needed to fully validate this model.

Polarity protein regulation is at the core of EMT and MET in epithelial and mesenchymal cells. EMT is associated with a loss of apico-basal polarity and is crucial to tumor progression, as it gives cells the ability to leave the primary tumor [68]. Further investigation of the parallels between neuronal development and the deregulation observed in cancers could be beneficial to progress in both fields. The Zeb transcription factors that we have

described as negative regulators of *Pard3* and *Pard6* are also often involved in cancer progression [28, 68]. Singh et al. have shown that *Shh* medulloblastomas in the cerebellum express high levels of *Zeb1* and that the re-expression of polarity proteins in a mouse model of medulloblastoma could promote differentiation and rescue the germinal zone–exit phenotype. These findings provide insights that could aid the development of new therapies for brain cancers [11].

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Abbreviations used

BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
EMT	Epithelial-to-mesenchymal transition
GNP	Granule neuron progenitors
IPC	Intermediate progenitor cell
MET	Mesenchymal-to-epithelial transition
RGC	Radial glial cell
RGP	Radial glial progenitor
Shh	Sonic hedgehog

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Fig. 1.
Schematic depicting the overall level of polarity complex protein associated with each main developmental stages from progenitor to mature neurons.

Fig. 2.

Representation of the control of polarity complex protein level in the developing cerebellum.