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The molecular pathway regulating Bergmann glia and folia generation in the cerebellum

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Abstract

Evolution of complex behaviors in higher vertebrates and primates require the development of sophisticated neuronal circuitry and the expansion of brain surface area to accommodate the vast number of neuronal and glial populations. To achieve these goals, the neocortex in primates and the cerebellum in amniotes have developed specialized types of basal progenitors to aid the folding of their cortices. In the cerebellum, Bergmann glia constitute such a basal progenitor population, having a distinctive morphology and playing critical role in cerebellar corticogenesis. Here we review recent studies on the induction of Bergmann glia and their crucial role in mediating folding of the cerebellar cortex. These studies uncover a key function of FGF-ERK-ETV signaling cascade in the transformation of Bergmann glia from radial glia in the ventricular zone. Remarkably, in the neocortex, the same signaling axis operates to facilitate the transformation of ventricular radial glia into basal radial glia, a Bergmann glia-like basal progenitor population, which have been implicated in the establishment of neocortical gyri. These new findings draw a striking similarity in the function and ontogeny of the two basal progenitor populations born in distinct brain compartments.

Introduction

Bergmann glia (BG), also called Golgi epithelial cells, are specialized, unipolar glial cells featuring cell bodies situated in the Purkinje cell layer and radial fibers passing through the molecular layer [1–3]. BG precursors are derived from radial glia that reside in the cerebellar ventricular zone. During their derivation process, BG precursors maintain basal processes and retract their apical processes, then relocate their cell bodies toward the cortex [4, 5] (Fig 1A). Each BG extends two to six fibers, arranging in palisade pattern, to the subpial basement membrane [6](Fig 1B). The BG radial fibers aid the migration of neurons and the

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elongation of dendrites and axons [3, 7]. In the mature cerebellum, BG actively participate in the information processing of the cerebellum. They also maintain structural integrity and synaptic connections in the cerebellum [1, 5, 8]. After induction at E13.5 in mouse embryos [4], BG precursors continue to proliferate at least until the second postnatal weeks [9–11]. In the adult cerebellum, BG express numerous stem cell markers such as Sox1 and Sox2, and they may constitute the adult neural stem cells [12–14]. For excellent reviews of BG development and their role in the mature cerebellum, readers can refer to these references [3, 5]. Here, we focus on discussing the novel understanding of BG genesis and their function in the foliation of the cerebellar cortex. Our discussion also cast these new findings in the context of the evolution of the neocortical basal progenitors and the neocortical gyrification process.

The mammalian cerebellum

The cerebellum is well known for its sensorimotor processing function. Emerging evidence indicates that the cerebellum is also involved in higher cognition. Accordingly, cerebellar pathology and dysfunction are linked to many debilitating neurodevelopmental diseases, including autism spectrum disorder [15–19]. In this regard, there is a resurging interest in studying the development and the novel cognitive role of the cerebellum.

The adult cerebellar cortex is a trilaminar structure. Purkinje neurons and BG somata comprise the middle layer, sandwiched between an internal granule layer and an outer molecular layer. The internal granule layer consists of mature granule neurons, while the molecular layer contains interneurons, granule cell axons, Purkinje dendrites, and BG radial fibers [20, 21]. Cerebellar cell types arise from two principal germinal regions of the embryonic cerebellum. The anterior rhombic lip, located at the dorsal region of the hindbrain, gives rise to glutamatergic neurons, including cerebellar nuclear neurons and granule neurons. The ventricular zone produces GABAergic Purkinje neurons, GABAergic interneurons and various glial cell types [22]. Because of its relatively simple logic in cytogenesis, the cerebellum has been serving as an excellent experimental paradigm to study neurogenesis and gliogenesis.

Similar to the gyri in the neocortex, the amniote cerebella undergo stereotypic folding of their cortex resulting in the establishment of an elaborate set of folia. The formation of these extensive folds in the cerebellar cortex correlates with the evolution of increasingly complex behaviors in animals [23–25]. From sharks to primates, the cerebellum and neocortex grow regularly and disproportionately to the rest of the brain, with the extent of gyrification reflecting the size of these structures [26]. These observations suggest that convolution of the cerebral and cerebellar cortices represent an evolutionary adaptation to accommodate more complex functions and behaviors.

Ptpn11 is essential for Bergmann glia induction

Perturbations of signaling pathways, including Notch [27–31], Erbb [32–34], thyroid hormone [35], integrin [36–38], Pten [39], sonic hedgehog [40, 41], Wnt/β-catenin [42, 43], and FGF [44–46], result in abnormal number and/or morphology of BG. The mechanism

that control the induction of BG precursors, or the transformation process from radial glia to BG precursors, was still unclear until more recent studies revealing an essential function of *Ptpn11*.

Ptpn11 (protein tyrosine phosphatase non-receptor type 11, also known as Shp2) belongs to a family of protein tyrosine phosphatases that modulate diverse signaling. Mutations in the human *PTPN11* gene result in various developmental syndromes and cancers [47, 48]. In the neocortex, *Ptpn11* deletion altered the extracellular signal-regulated protein kinase (ERK) and Stat3 signaling pathways, leading to an imbalanced genesis of neurons and glia [49, 50]. Deletion of *Ptpn11* at embryonic stage (E)10.5 using a *Nestin-Cre* (*Nestin;Ptpn11*^{CKO}) resulted in a disorganization of BG fibers and an abnormal lamination of the cerebellar cortex [51]. Based on *in vitro* data, the authors concluded that the cerebellar phenotype was attributed to a cell-autonomous requirement of Ptpn11 in granule cell precursors (GCP). However, a subsequent study showed that specific removal of *Ptpn11* from GCP does not alter layering of the cerebellar cortex [52]. By contrast, deletion of *Ptpn11* from the cerebellar progenitors using *En1-Cre* (*En1;Ptpn11*^{CKO}) from an earlier embryonic stage (E8.5) resulted in similar, but more severe, defects in the cerebellar cortex than those found in *Nestin*^{cre}*;Ptpn11*^{CKO} mice [51, 52]. Cell labeling, marker gene analysis, and genome-wide transcriptome profiling demonstrated that *Ptpn11* deletion blocked the induction of BG precursors, whereas the generation of Purkinje neurons, interneurons, and granule neurons were less affected [52, 53]. Interestingly, the astrocytes in the granular layer, but not those in the white matter, were missing in *En1;Ptpn11*^{CKO} cerebella [52]. This suggests that the granule layer astrocytes and BG may be derived from a different lineage from the white matter astrocytes. The *En1;Ptpn11*^{CKO} mice represent the first characterized mouse mutation that completely blocks the induction of BG precursors.

The Ptpn11-controlled FGF-ERK-ETV axis is important for BG formation

It was found that *Ptpn11* deletion affected ERK, but not AKT, signaling pathway [52]. The authors showed that robust phosphorylated ERK immunoreactivity was detected in the ventricular zone as well as the radial fibers of BG precursors in the wildtype mouse cerebellum [52]. Expression of a constitutively active MEK1 (MEK1^{DD}), which phosphorylates ERK independently of extracellular signals, rescued BG formation in the *En1;Ptpn11*^{CKO} mice [52, 53]. These observations demonstrate the importance of Ptpn11 in the induction of BG precursors through ERK signaling.

During cerebellar development, multiple FGF ligands are expressed at defined developmental stages and in distinct cerebellar regions [54]. Transcripts of *Fgfr1* and *Fgfr2,* which code for FGF receptors, are first present in the ventricular zone, and later in the Purkinje cell layer where the cell bodies of BG reside [45, 54]. Single, double, and triple deletions of *Fgfr1*, *Fgfr2,* and *Fgfr3* resulted in progressively more severe defect in the generation of BG precursors [44–46]. In fact, deletion of *Fgfr1*, *Fgfr2*, and *Fgfr3* from the cerebellum results in a nearly complete loss of BG similar to *En1;Ptpn11*^{CKO} [44, 53]. These findings suggest that Ptpn11 mediates the FGF-ERK signaling in the induction of BG precursors.

Transcription factors *Etv4* and *Etv5*, which are known targets and mediators of FGF [55, 56], are highly expressed from early embryonic stages through perinatal stages in the cerebellum [52, 54]. Initially, *Etv5* is expressed in the whole cerebellar anlage and later gradually restricted to BG precursors; presenting strong evidence of a key functional role of FGF signaling during the induction phase and the subsequent development of BG precursors. Deletion of *Ptpn11* resulted in the loss of *Etv4* and *Etv5* expression, whereas ectopic expression of $Mek1^{DD}$ restored their transcription [53]. Finally, forced expression of *Etv4* or *Etv5* rescued the formation of BG in the $En1;Ptpn11^{CKO}$ cerebella [53]. Altogether, these observations demonstrate that the FGF-ERK-ETV axis is important for the induction of BG precursors.

Bergmann glia are essential for the folding of the cerebellar surfaces

An elegant study described the formation of the so-called anchoring centers in the cerebellar cortex that will become the base of each fissure [57]. Although the authors determined that granule cell precursors were the primary drivers of the location and timing of fissure formation, coordinated changes in the Purkinje cell layer and BG fibers were observed at the onset of the forming anchoring centers [57]. Numerous studies suggest that the interaction between BG and the basement membrane is important for cerebellar foliation [31, 36, 38, 39, 58–63]. Examining postnatal $En1^{cre};Ptpn11^{CKO}$ mice uncovers that their cerebella failed to form any visible folia and displayed a smooth surface morphology [52]. Interestingly, the inward converging movement of granule cell precursors persists in the absence of BG in the $En1;Ptpn11^{CKO}$ cerebellum, leading to the accumulation of granule cell precursors immediately beneath the external granular layer [52]. This demonstrates that granule cell precursors invagination alone is insufficient to cause folding of the Purkinje cell layer and the pial basement membrane. Importantly, rescuing BG formation by reactivating the MEK/ERK pathway restores both the formation and organization of cerebellar folia [52]. These findings demonstrate that BG are essential for cerebellar foliation, likely by coordinating the invagination of granule cell precursors with that of Purkinje cell layer and the pial membrane (Fig 2).

Neocortical basal radial glia and cerebellar Bergmann glial precursors bear similar gene signatures

In the neocortex, radial glia can generate neurons either directly by asymmetric divisions or via an intermediate progenitor cell lineage normally occupying the subventricular zone [64]. More recent studies have discovered additional basal progenitors residing in the subventricular zone aside from the already known intermediate progenitor cells [65–67]. Bearing similarities to the genesis of BG precursors, this novel basal progenitor population, called basal radial glia (bRG) or outer radial glia, selectively loses their apical processes and move their soma to the outer subventricular zone at mid-neurogenesis [65–68]. Remarkably, bRG are abundantly present in the gyrencephalic cortices [65–67], but are relatively rare in lissencephalic cortices, such as the mouse [43, 69]. It has thus been speculated that bRG expansion is responsible for the emergence of convolutions in the neocortex [67, 70–77].

Given their high similarity in cytogenesis and their potential roles in cortical folding, the transcriptomic profiles of human bRG and mouse BG precursors were studied [53]. By exploring the published single-cell RNA-sequencing datasets [78, 79], Heng et al. found that over 50% of the bRG markers were coexpressed in BG precursors. The authors also identified a panel of BG candidate genes by extensive RNA-sequencing analysis and gene co-expression network analysis [53]. Multiple statistical model analyses demonstrated that this BG candidate gene list bore significant similarity with that compiled from the bRG [53]. These data further demonstrate that BG and bRG not only share functional similarity in cortical folding and stem cell property, but also a highly similar transcriptomic signature.

The FGF-ERK-ETV signaling axis is involved in basal radial glia formation

From the consensus gene list compiled for bRG and ventricular zone radial glia in the human cortex, a number of early response genes for ERK signaling are identified [53]. A systematic comparison of multiple available datasets of human and mouse neocortices reveals that classical FGF targets (*Spry* and *Etv* genes) as well as ERK response genes are expressed at significantly higher levels in the human than the mouse neocortex, especially in cortical radial glia [53, 80]. Immunostaining confirmed that pERK signaling was low in the ventricular zone of the mouse cortex but readily detectable in the human embryonic neocortical tissue sections [53]. Ectopic expression of $FgfR1^{K656E}$ (a constitutively active FGFR1), $MEK1^{DD}$, or Etv4 induce bRG-like cells in the mouse cortex expressing markers such as Hopx, Sox2, Pax6, Tnc, Slc1a3 and Ptprz1 [53, 79, 80]. The induced cells are capable of self-renewal and neuronal differentiation under both *in vivo* and *in vitro* conditions [53]. These data support a model that posits a common mechanism regulating the formation of BG precursors and bRG. Such a mechanism could have co-evolved under common selection forces in different brain compartments during the speciation of amniote and primate species.

Perspective

The above findings have demonstrated that BG play an important role in cerebellar corticogenesis. Several questions, however, remain to be addressed.

First, how does the FGF-ERK-ETV signaling axis control the transformation process from radial glia into BG and bRG? It has been shown that the ERK pathway determines the mitotic spindle orientation of epithelial cells [81]. A number of studies show that increasing the proportion of horizontal divisions, in which the cleavage furrow is parallel to the ventricular surface, contributes to the generation of bRG in both the human and the mouse cortices [68, 69, 82]. Our preliminary data suggested that the loss of *Ptpn11* altered mitotic spinal orientation in the cerebellar radial glia at E14.5 (unpublished data by Leung and Li). Further studies are warranted to determine if ERK signaling controls the generation of BG precursors and bRG by regulating the spindle orientation.

Secondly, how do BG orchestrate the folding of the cerebellar cortex? Heng et al. shows that the expression of $Mek1^{DD}$ specifically expands bRG but fails to induce folding of the mouse neocortex [53]. This finding is in agreement with the notion that an abundance of bRG is

insufficient for gyrencephaly [83, 84]. Therefore, expansion of other basal progenitors, together with that for bRG, may be necessary for the successful folding of the neocortex. A notable parallel can be found in the cerebellum where both the granule cell precursors and BG play critical roles in cerebellar foliation. Understanding how BG orchestrate cerebellar corticogenesis will provide new insight into the evolution of a convoluted neocortex.

Finally, how is BG proliferation regulated? Like bRG in the human cortex, BG precursors express genes related to extracellular matrix production and receptors for growth factor signaling that are important for stem cell maintenance [53]. It is important to determine if and how BG create a self-sustaining niche that supports their proliferation, particularly in coordination with the enlargement of the granule cell pool during cerebellar foliation. This research will help us determine how BG and bRG drive brain fold formation and how brain fold formation relates to the development of complex sensorimotor and cognitive function found in mammalian species. Future research is warranted towards determining whether the appearance of BG is associated with the folding of the cerebellum in other mammalian species, and whether the abnormal formation of bRG due to malfunctions of the FGF-ERK-ETV genetic cascade contributes to human congenital conditions that affect the folding and the function of the neocortex.

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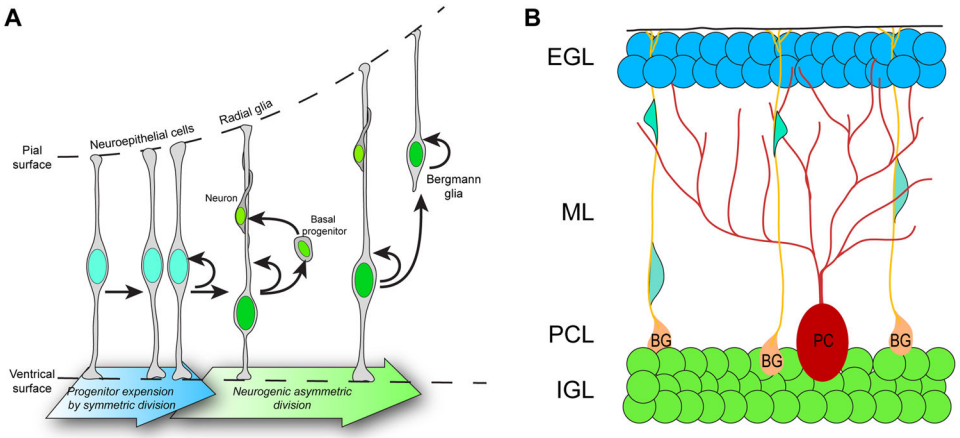

Figure 1.

(A) Progression of neurogenesis and the birth of BG precursors in the cerebellum during embryonic development. The arrows represent, either, a transformation, differentiation or cell division event. Neurogenesis in the cerebellum is a multi-step process. Neuroepithelial progenitors have direct contacts with the ventricular and pial surfaces and undergo symmetric cell division to expand the number of progenitors. As development progresses, neuroepithelial progenitors transform into radial glia cells, which still retain their pial and ventricular contacts and starts to generate basal progenitors that will directly give rise to neurons. Some of the radial glia also start to lose its ventricular processes and give rive to another type of basal progenitor, BG precursors, which retain their apical processes and serve specialized functions in the cerebellum. (B) Configuration of different neuronal and glial populations in the perinatal cerebellum. Granule neuron progenitors from the external granular layer (EGL, in grey shades) migrate along BG basal fibers towards the internal granular layer (IGL), their mature location in the cerebellum. BG – Bergmann glia; ML-molecular layer; PC – Purkinje cells; PCL – Purkinje cell layer.

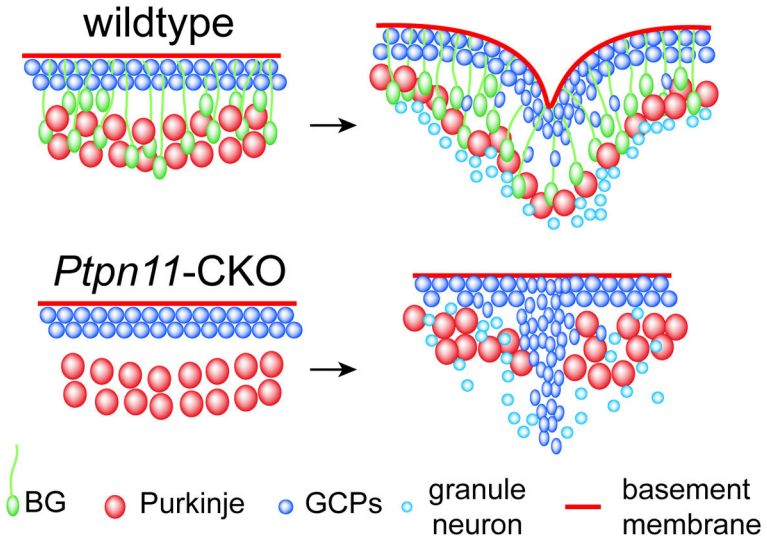

Figure 2.

Arrangement of Purkinje neurons and granule neurons before and during fissure formation in wildtype and *En1;Ptpn11*^{CKO} mouse cerebella. In wildtype, the presence of BG anchors on the basement membrane helps pull in the EGL and couple the inward movement of granule neurons with a corresponding rearrangement of the soma of Purkinje neurons. In *En1;Ptpn11*^{CKO}, failed induction of BG precursors and hence lack of BG anchors lead to uncoupling of the invasion of granule neurons with the inward displacement of the basement membrane and Purkinje neurons.