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REVIEW

The Role of Astrocytes in the Development of the Cerebellum

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Abstract

Astrocytes, initially described as merely support cells, are now known as a heterogeneous population of cells actively involved in a variety of biological functions such as: neuronal migration and differentiation; regulation of cerebral blood flow; metabolic control of extracellular potassium concentration; and modulation of synapse formation and elimination; among others. Cerebellar glial cells have been shown to play a significant role in proliferation, differentiation, migration, and synaptogenesis. However, less evidence is available about the role of neuron-astrocyte interactions during cerebellar development and their impact on diseases of the cerebellum. In this review, we will focus on the mechanisms underlying cellular interactions, specifically neuron-astrocyte interactions, during cerebellar development, function, and disease. We will discuss how cerebellar glia, astrocytes, and Bergmann glia play a fundamental role in several steps of cerebellar development, such as granule cell migration, axonal growth, neuronal differentiation, and synapse formation, and in diseases associated with the cerebellum. We will focus on how astrocytes and thyroid hormones impact cerebellar development. Furthermore, we will provide evidence of how growth factors secreted by glial cells, such as epidermal growth factor and transforming growth factors, control cerebellar organogenesis. Finally, we will argue that glia are a key mediator of cerebellar development and that identification of molecules and pathways involved in neuron-glia interactions may contribute to a better understanding of cerebellar development and associated disorders.

Keywords Cerebellar development · Thyroid hormones · Epidermal growth factor · Transforming growth factor beta 1 · Migration · Synapse

Introduction

A relatively simple structure with well-defined anatomy and physiology, the cerebellum has long been recognized as the primary center of motor coordination in the central nervous system (CNS). Classically, the cerebellum acts as a motor coordination center, using sensory stimuli from the periphery of the body to refine movement and balance [1]. However, it is now known that the cerebellum is also related to various brain mechanisms, such as cognitive and emotional responses [2–5].

Critical biological processes such as proliferation, differentiation, migration, and synaptogenesis occur during the development of the cerebellum, and dysfunction related to these events can trigger serious neurological problems, such as ataxias, developmental disorders, autism [6, 7] attention deficits, hyperactivity, schizophrenia, as well as neuroendocrine disorders and pediatric tumors [8].

The development of the cerebellum is a rigidly regulated process giving rise to a characteristically organized laminar structure. This structure includes the formation of a cerebellar territory along the antero-posterior and dorsal-ventral axes of the neural tube, initial specification of cerebellar cell types, their subsequent proliferation, differentiation and migration, and, finally, the formation of the cerebellar circuit [9]. Cerebellar glial cells have been shown to play a significant role in controlling many of these events as neurogenesis, cellular migration, axonal growth, synapse formation and function, maintenance of the blood-brain barrier, and control of homeostasis and vascular tone [10–12]. Together with the role of glial cells in brain physiology, emerging evidence from recent decades has associated deficits in glial function with several neurological diseases that affect specific brain regions, such as cerebral cortex, midbrain, and spinal cord [13–16].

The apparent simplicity and geometric disposition of the cerebellar cortex have appealed to many scientists as an

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excellent model for the study of mechanisms involved in the development of the CNS [17]. The cerebellum is divided macroscopically into three regions, a medial portion called the vermis, lateral regions on either side of the vermis in areas called the paravermis, and lateral portions adjacent to each paravermis, known as the hemispheres [18]. The conserved foliation patterns in the mammalian adult cerebellum are anatomically divided into ten lobes [9, 19, 20], which are separated by a series of fissures that extend to a specific depth in the cerebellum, giving each lobe a unique shape [20, 21]. The lobes are divided into sublobes that vary in number according to the species [19, 22] (Fig. 1a, b).

Microscopically, the cerebellar cortex of adult mammals is composed of eight different neuronal populations: Purkinje cells (PCs), Golgi cells, granule cells, basket cells, stellate cells, Lugaro cells, unipolar brush cells, and candelabrum cells [17, 23, 24] and astroglial and oligodendroglial cells that are classified into four main distinct categories according to their morphology: fibrous astrocytes and oligodendrocytes, protoplasmic astrocytes (velate), neuroepithelial cells known as Bergmann's glia (BG), a specialized glial type, and a fourth type of cerebellar glia neglected by scientists, the cells of Fañanas [25], classified as a subtype of BG [26–28] (Fig. 1c).

Together with the various neuronal types, the astroglial and oligodendroglial cells give the cerebellum its anatomical and functional complexity. The cerebellar cortex is composed of a very basic structure formed by three distinct layers, each composed of distinct types of cells. The most superficial layer, the molecular layer (ML), is a region of low cell density but a high incidence of synapses and is formed by granule cell axons, the dendritic processes of PCs, basket cells, and stellate cells. The cell bodies of PCs are organized into a single row. These cells together with candelabrum cells and aligned with the BG create a monolayer between the ML and the granular layer (GL) known as the Purkinje cell layer (PCL). Above and below this layer is found a second type of glia, the Fañana cells [25, 29]. The GL is the deepest layer, with the highest cell density, containing millions of granule cells, Golgi cells, Lugaro cells, velate astrocytes, and a unipolar brush cell [30–33]. Below the three layers is the white matter containing a dense network of fiber tracts and cells including fibrous astrocytes and oligodendrocytes [34].

The development of the cerebellum is controlled by many signaling molecules: fibroblast growth factor (FGF) family participates in the scaffold formation of BG fibers and in the migration of granule cells, regulates the generation and correct positioning of BG among other functions [35, 36]; Wnt/β-catenin pathway is critical for cerebellar foliation and lamination [37]; Notch signaling plays a key role in the development of BG phenotype and regulation of granule cell migration [38–42]; and Sonic hedgehog (Shh) modulates the proliferation of GCPs and determines the pattern of cerebellar foliation [21, 43–46].

Here in this review, we will highlight three other molecules, essential for cerebellar morphogenesis: thyroid hormone (TH), epidermal growth factor (EGF), and astrocytic transforming growth factor beta-1 (TGF-β1).

TH deficiency during the perinatal period dramatically affects cerebellar morphogenesis [47, 48], resulting in various abnormalities, including neuronal cell loss, impaired neurite growth and myelination, delayed proliferation and migration of granule cells, reduced number of synapses between granule cells and PCs, aberrant patterns of connections, and loss of correct cerebellar structural organization patterns [48–52]. Furthermore, hypothyroidism is associated with abnormalities in the cerebellar cortex, such as persistence of the EGL and altered foliation pattern [52–57]. The majority of cell subsets in the developing cerebellum express the receptors for this hormone, thyroid receptors TRs [58]. Activation of these receptors leads to activation of different signaling pathways related to proliferation and differentiation processes [59, 60], such EGF pathway, as it will be discussed later in this review.

Transforming growth factor betas (TGF-βs) are multifunctional growth factors that participate in the regulation of key events related to development, disease and tissue repair. In the brain, TGF-β1 has been widely recognized as an injury-related cytokine, specifically associated with astrocyte scar formation in response to brain injury. In the last decade, however, evidence has indicated that in addition to its role in brain injury, TGF-β1 may be a crucial regulator of cell survival and differentiation, brain homeostasis, angiogenesis, memory formation, and neuronal plasticity [61]. The expression profile of the Smad family varies greatly between different CNS regions of the adult mouse. In the cerebellum, Smad2 and Smad3 are highly expressed in the ML and the PCL and less abundant in the GL, while an inverse expression pattern is observed for Smad4, whose expression is lower in the ML and the PCL and increased in the GL [62]. Additional evidence of the role of TGF-β in cerebellar development comes from genetic/molecular models. Deletion of Smad4 causes irreversible cerebellar damage, such as a decrease in the number of PCs [63], whereas disruption of Smad2 leads to aberrant development of the cerebellum and early ataxia in mice [64].

There is evidence that glial cells are the main source of growth factors/trophic factors and extracellular matrix molecules in the CNS. Through the production of active molecules, glial cells control several steps of brain development, including cellular migration [12], homeostasis [65], maintenance of the blood-brain barrier [65, 66], regulation of neurotransmission [67, 68], synapse formation [11, 69], and elimination [70], among others. However, less evidence is available about the role of neuron-astrocyte interactions during development and their impact on diseases of the cerebellum.

In this review, we will focus on the mechanisms underlying neuron-astrocyte interactions during cerebellar

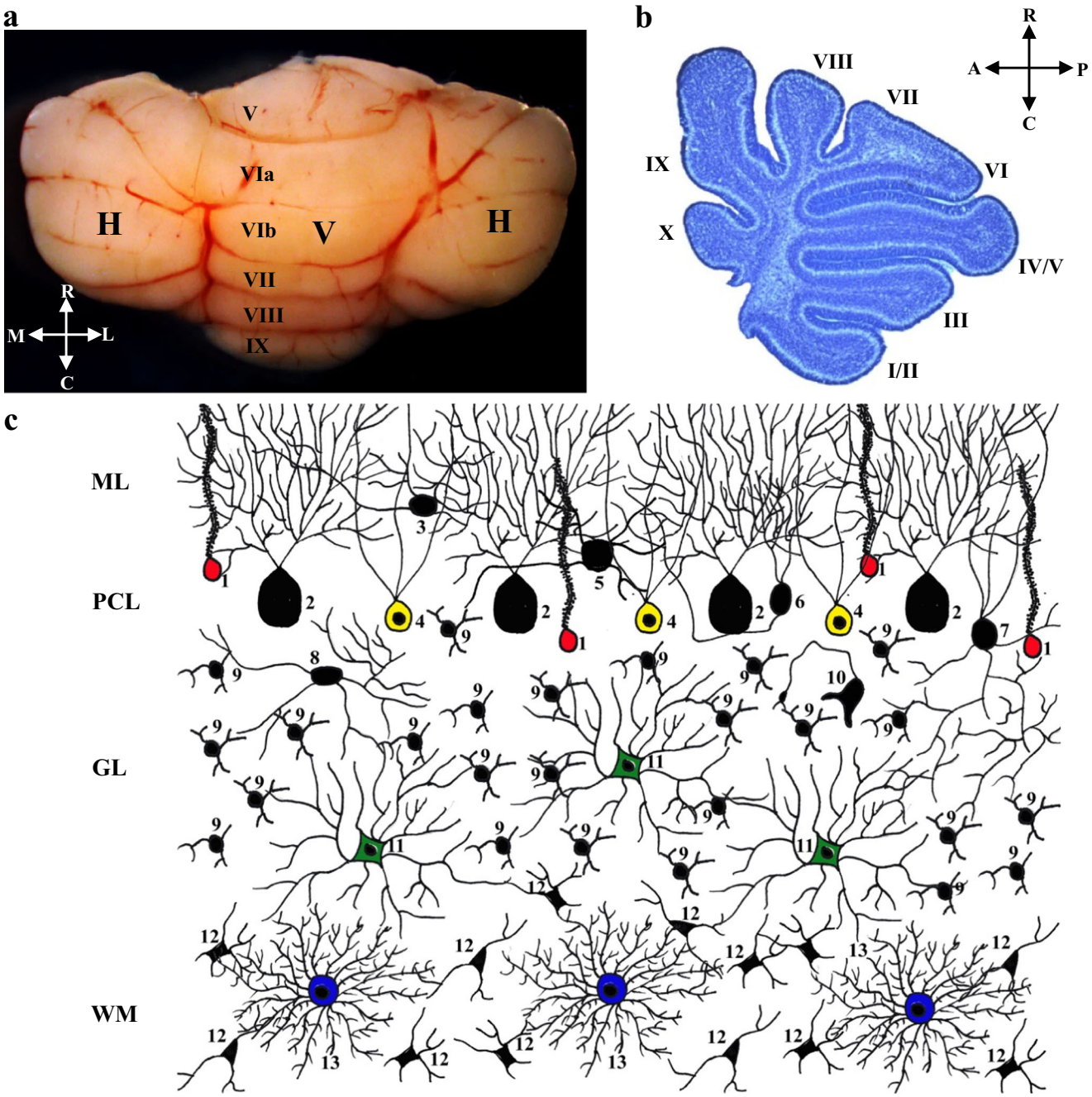

Fig. 1 Cerebellar architecture and development. **a** Dorsal view of an adult mouse cerebellum. **b** Nissl coloring of sagittal section of the P6 mouse cerebellum showing the structure of the lobules (× 4 magnification). The lobules are labeled with Roman numerals. **c** Scheme representing the structure of the cerebellar cortex with the arrangement of the cells in their layers. Abbreviations: A, antero; C, caudal; H, hemisphere; L, lateral; M, medium; P, posterior; R, rostral; V, vermis; 1, Fañana cell; 2, Purkinje cell; 3, stellate cell; 4, Bergmann glia; 5, basket cell; 6, candelabrum cell; 7, Golgi cell; 8, Lugaro cell; 9, granule cell; 10, unipolar brush cell; 11, protoplasmic astrocyte; 12, oligodendrocyte; 13, fibrous astrocyte; ML, molecular layer; PCL, Purkinje cell layer; GL, granular layer; WM, white matter

development and function. More specifically, we will provide data on how astrocytes, THs, and growth factors secreted by glial cells, such as EGF and TGF-β1, control cerebellar organogenesis. Finally, we will present and discuss evidence of how deficits in neuron-glia interactions impact cerebellar function and may contribute to cerebellar dysfunction.

Cerebellar Glia: Astrocytes and Bergmann Glia

The majority of cerebellar astrocytes are generated during embryonic development and in the late postnatal period [71, 72]. Chronologically, the astrocytes appear after the major periods of neurogenesis and neuronal migration are completed in the mammalian brain. Astrocyte differentiation and

maturation are distinct between the different regions of the brain, and these events are essential for several processes of CNS ontogenesis [73].

There is evidence that during development of the cerebellum, the progenitors in the EGL generate granule cells and glial fibrillary acidic protein (GFAP)-positive cells [74], but it is unclear whether these cells that are multipotent in vitro [75] can differentiate into mature astrocytes in vivo.

Altman and Bayer identified two main sites of cellular proliferation in the embryonic ventricular neuroepithelium: a posterior, located anterior to the rhombic lip, and an anterior one, near the isthmus and the superior cerebellar peduncle. They also observed that the cells continue dividing into the overlying tissue and therefore have suggested that cerebellar glia can be generated by progenitors that proliferate in the cerebellar parenchyma [76].

Studies of Notch activity in the cerebellar primordium indicated that both cerebellar neurons and glia can originate from common ancestors [77]. Notch is expressed from E10.5 in mouse ventricular neuroepithelium, but not in the rhombic lip. The lack of Notch results in early neuronal differentiation [77, 78], leading to a rapid decrease of progenitor cells and a hypomorphic cerebellum [78]. In E9.5, the constitutive activation of Notch in the cerebellar progenitors favors the generation of astrocytes at the expense of the neurons [77].

Classical works propose that BG, a specialized type of astrocyte, derive directly from the radial glia through the retraction of ependymal processes, the progressive displacement of the cellular body toward the cortex and the maintenance of basal processes adjacent to the pial surface [79–81]. The ontogenesis of the cerebellum depends greatly on the interactions between neurons and glial cells, as we shall see below.

Glial cells were previously regarded as merely supportive and passive elements of the CNS. The past decade, however, has been marked by a thorough revisitation of the role of these cells, not only in healthy brains but also in brain disease. Astroglial cells have emerged as key mediators of brain development, function, and plasticity, highlighting the critical need to better characterize the mechanisms underlying their development and interaction with neurons. While there is compelling evidence regarding the impact of astroglia function in the cerebral cortex and hippocampus [11, 12, 65, 66], there is still a lack of data on the role of astroglial cells in the cerebellum and cerebellar dysfunction.

In cerebellar development, glial cells are of the utmost importance, as evidenced by conditional ablation of GFAP expressing cells in the cerebellum [82]. The ablation of 50% of GFAP-positive cells shortly after birth leads to a hypoplastic cerebellum without well-defined histological layers, with decreased granule cell numbers and ectopy of PCs. This is supported by several additional studies that show that abnormal glial development leads to defective cerebellar formation [82, 83]. Furthermore, it has been demonstrated that astrocytes give rise to GCPs in the EGL [74], providing further evidence that astroglial cells are pivotal to the generation of neurons, as has been observed in other structures of the CNS. In this section, we will review several studies that support the hypothesis that astroglial cells are major regulators of cerebellar development.

As mention earlier, the cerebellar cortex has two main astroglial types: BG, a specialized type of astrocyte located at the PCL, and velate astrocyte, a protoplasmic astrocyte present at GL [84, 85] typical of areas of high neuronal density such as the cerebellar cortex. In contrast with fibrous astrocytes that are found in white matter and are much less elaborate than protoplasmic astrocytes, processes from velate astrocytes are longer, are of higher caliber and establish contacts with the nodes of Ranvier of neuronal axons. Velate astrocytes have large cell bodies, and their many thick extensions create a shrub-like structure [84, 86]. The large membrane extensions wrap granule cells synapses with mossy fibers, separating the glomeruli into distinct entities [87]. The astrocytes enclose the glomeruli and control the infiltration of dendrites and axons in this structure [88] and also limit the diffusion of neurotransmitters away from the synaptic location, isolating synaptic complexes that convey different information [89, 90]. Velate astrocytes also assemble around blood vessels, forming flattened sheet-like board around the basal lamina [90, 91] making part of the blood-brain barrier. Recently, it was observed that each velate astrocyte forms a syncytial network through gap junctions with nine neighbors, resulting in a highly coordinated structure in the cerebellum [92]. In fact, this astrocyte syncytial organization may be responsible for controlling the diffusion of small molecules throughout neighbor cells, such as a calcium waves in the cerebellum [93], which may be associated with diverse cerebellar astrocytic functions, as blood flow and synaptic modulation. Additionally, as will be described later in this review, our group has shown that cerebellar astrocytes are associated with neuronal proliferation [94], differentiation [95, 96], GCP migration, BG development [97], and cerebellar synaptogenesis [98]. However, more information about cerebellar astrocytes is scarce, and there are still more questions than answers about their role in cerebellar physiology.

BG are a unique glial subtype of the cerebellar cortex that are generated from the radial glia (RG) of the ventricular zone of the medial portion of the fourth ventricle [99] This cell type presents its cell body in the PCL and emits its processes to the pia matter surface,

passing through the ML, constituting the glial limiting membrane [100]. The BG role is similar to RG support in cortical development. Both types of glial cells have radial morphology and act as a framework for neuronal migration, guiding neurons in their arrival at their correct locations. However, BG and RG have a fundamental difference; after the migratory period, RG in the cerebral cortex disappear by differentiating into astrocytes [101–103]. Unlike RG, BG do not disappear in the adult and play a key role in cerebellar function in adulthood [79]. Interestingly, BG continue to display a guiding capacity for neurons as showed by Sotelo and coworks, that demonstrated that grafted PC in the adult cerebellum uses BG for their migration and integration in the cerebellar cortical circuitry [104, 105].

BG play an important role in almost all phases of cerebellar corticogenesis, including foliation, orientation, stratification of granule cells, neuronal migration, neurite outgrowth, and synaptogenesis [106]. BG are also important in adult cerebellar function, including extracellular ion homeostasis [107], synaptic stability [108, 109], plasticity [110, 111], metabolic function, and neuroprotection [112, 113].

During cerebellar development GCPs are found in close contact with glial cells [106, 114], and BG play a major role by providing a scaffold for GCPs migration from the EGL to the IGL, which is essential for GCPs survival [115, 116] . In 2014, Li and coworkers demonstrated that mice lacking Shp2 protein present a smaller cerebellum without visible foliation. These animals have impaired BG formation, and as a result, although GCPs proliferate at the EGL, they do not migrate to the IGL, leading to failure in folia formation [117]. Similarly, another group has shown that when BG cells have disrupted fibers, which fail to reach the surface of posterior lobes, ectopic granule cells are detected, and PCs are irregularly aligned [118]. Additionally, our group and others have shown that THs strongly influence BG formation and, in turn, cerebellar morphogenesis. The expression of a non-binding TRβ receptor, which impairs 3,5,30-triiodothyronine (T3) activity, leads to BG defects and, consequently, malformations in cerebellar laminar organization [119]. Moreover, the expression of a truncated thyroid receptor α1 (TRα1) isoform in BG results in BG mislocalization, and the appearance of twisted fibers that do not reach the pial surface impairs GCP migration from the EGL to the IGL and thus the maturation of granule cells in the IGL [120]. BG also participate in cell proliferation and differentiation in the cerebellum. Cheng and coworkers have recently demonstrated that Shh signaling in BG controls GCP proliferation. Inhibition of Shh signaling by ablation of Shh activator, Smoothenerd (Smo) in BG leads to a reduction in GCP proliferation and an increase in GPC differentiation status, resulting in decreased EGL thickness. This demonstrates that BG cell signaling maintains CGP proliferative capacity [16].

In the PCL, BG provide structural support for PC dendritic extension [103] and act as the third element of the PC synapses, supporting synapses made between PC and their patterns [80] and wrapping Purkinje dendrites and synapses from the early postnatal period onward [121]. These processes are responsible for maintaining the rapid clearance of synaptic glutamate. If any alteration occurs in this structure, BG glutamate uptake capacity is reduced, leading to the formation of aberrant synapses between PCs and climbing fibers [108, 121, 122] which can be associated to comportamental alterations. Accordingly, it has recently been shown that a mouse model for leukoencephalopathy exhibited abnormal development of BG, which led to ectopic localization of BG cell bodies and deficits in synaptic wiring. In these mice, PC dendrites are not completely wrapped by BG cell processes and atypical synaptic formation is observed, most likely due to the inability to eliminate unwanted synapses [123]. Besides glutamatergic connections, BG also participates in GABAergic innervation formation between PC and stellate cells. Ango and coworkers have shown that BG processes serve as a scaffold for stellate axons to reach PC dendrites and properly form GABAergic connections, leading to a precise pattern of circuit organization [124].

Moreover, it was suggested that BG had a role in generating other cell types in the mature cerebellum. In the mature structure, BG express molecules such as Sox1 and Sox2, which are involved in cell self-renewal and maintenance of undifferentiated neural progenitors [125, 126]. Another finding that corroborates the hypothesis of BG as cerebellar progenitor was that the cerebellum of adult rabbits is apparently able to give rise to synantocytes [127] which are newly described NG2-positive glial cells that have the ability to proliferate. In vitro, they differentiate into astrocytes and oligodendrocytes, but in vivo, they only express markers of cells involved in the oligodendrocytic lineage, such as O4 and Gal-C [128, 129] and the their capacity to proliferate is not clear. Grimaldi and Rossi have shown that infusion of growth factors in physiological context or PC depletion did not induce a significant proliferation even though there are mitotic cells in the cerebellum, such as NG2-positive cells [130]. Nevertheless, other groups have shown that, instead of BG cells, there are progenitor cells in the cerebellum that give rise to astroglial cells of the adult. Parmigiani and collaborators have shown that the postnatal cerebellum presents two pools of astroglial-like progenitors cells. One gives rise to GABAergic interneurons and astrocytes at the prospective white matter, while the other astroglial-like progenitors generate astrocytes and BG in the PCL [131, 132]. Also, after

depletion of granule cells in the EGL of neonate mice, immature astrocytes suffer an adaptive reprogramming and change their progenitor cell markers. This change leads to expression of GCP genes by these newly differentiated cells and repopulation of the EGL [133]. Furthermore, Ahlfeld and colleagues demonstrated that there are Sox2-positive cells intermingled with BG, which are responsible for neurogenesis induced by exercise in the adult cerebellum [134]. In that way, it seems that the cells that are responsible for the generation of newly cells in the adult would be the progenitors cells present in the adult cerebellum.

In the cerebellum, beyond the astrocytes and the BG, there is another type of radial astrocytic cell, the "feathered cell" of Fañanas [25–27, 135], a subtype of short BG cells [28] often overlooked by scientists. These cells are very similar, but not identical to BG cells, which makes their identification difficult by simple morphology. A recent work reveals two potassium channel-related polypeptides, Kv2.2 and calsenilin (KChIP3) as potential marker proteins for these cells. Through immunocytochemistry assays, it was established three morphological criteria that may differentiate the BG from the cells of Fañanas. They differ in size and shape from cell bodies: BG exhibit an epithelioid appearance whereas Fañanas cells are smaller and resemble fibrocytes. Fañanas cells are located in a much wider range above and below PC's and do not form a single row as the BG; further, BG send unbranched processes to the pial surface while the Fañanas cells do not [29].

Signaling Pathways Involved in the Development of the Cerebellum: Role of Astrocytes

Although the cerebellum is one of the first structures of the CNS to differentiate itself, it reaches its mature configuration only a few months after birth in humans and 15 days after birth (P15) in mice [136]. This period of postnatal development has advantages and disadvantages since the cerebellum is an easily accessible structure, it is widely used in experimental studies, but its developmental profile leaves the cerebellum vulnerable to irregularities throughout development.

The beginning of rodent cerebellar development occurs around the eighth embryonic day (E8) and ends at P15 when the cerebellum exhibits an organization with all its cell types distributed in three layers (ML, PCL, GL) and a morphology that correlates with the location of specific cerebellar circuits.

The massive postnatal proliferation of GCPs in the EGL and their subsequent migration lead to extensive growth of the cerebellum after birth [137], and the disappearance of the EGL at the end of the third postnatal week and the formation of internal granular layer (IGL) [138] gives rise to the stereotyped three-layer structure of the adult cerebellum. After its formation, the initial structure of the cerebellum is replaced by a foliated pattern that is conserved through evolution [139] (Fig. 2).

Thyroid Hormones and Epidermal Growth Factor

In rodents, after birth, GCPs extensively proliferate in the EGL during the first postnatal week [43, 140–142]. During the second postnatal week, GCPs reach peak proliferation, differentiating during migration through the ML and PCL to reach their mature state in the IGL by the end of the third postnatal week [9]. This period coincides with the accumulation and differentiation of precursors, radial neuronal migration, cerebellar foliation, and the maturation of PCs [143–145]. These steps are tightly regulated by a balance between intrinsic and extrinsic molecules, growth factors and hormones that trigger multiple signaling pathways [21, 43, 46, 48, 95, 97, 146–150]. In the cerebellum, glial cells are reported to produce several molecules that are associated with these developmental events, such as components of the extracellular matrix: laminin, fibronectin, and proteoglycans [95, 151–155]; growth factors: EGF [95, 97], FGF [154], TGF-β1 [98], and Shh [119]. In this section, we review how cerebellar glia control GPCs proliferation, differentiation, and migration through the activation of two of these molecular signaling pathways: THs and EGF.

THs, thyroxine (T4) and T3, are key modulators of cellular metabolism and are essential for embryonic development. T4 is able to cross the blood-brain barrier [156] and then is taken up by astrocytes. Once inside astrocytes that express type 2 iodothyronine deiodinase, T4 is deiodinated to produce T3 [157] which is considered a biologically active hormone. THs exert their functions through the nuclear TH receptor (TR: TRα1, TRβ1, and TRβ2), a ligand-dependent transcription factor [158]. THs control several steps of cerebellar development and function [119, 159, 160], including glial cell differentiation and function; neuronal migration, axonal arborization, and growth; and synapse formation [95, 97, 98, 160]. A lack of TH signaling during fetal and early postnatal periods results in severe mental retardation, such as cretinism in humans [47, 159, 161, 162].

Several evidences from transgenic animals studies, knockout or knockin for TRs, strongly support a role of TH in the development and function of the cerebellum [119, 120, 163, 164]. For example, mutation of TRα1 in PCs leads to severe deficits in PC morphogenesis [120] and expression of mutant TRβ1 as early as P2 results in decreased PC dendritic arborization and reduced granule cell migration [164] leading to cerebellar ataxia. We also reported that target inactivation of TRβ-TH binding leads to a smaller cerebellum area characterized by impaired lamination and foliation. Furthermore, TRβ mutant mice presented severe deficits in proliferation of GCPS, arborization of PCs, and organization of BG fibers [119].

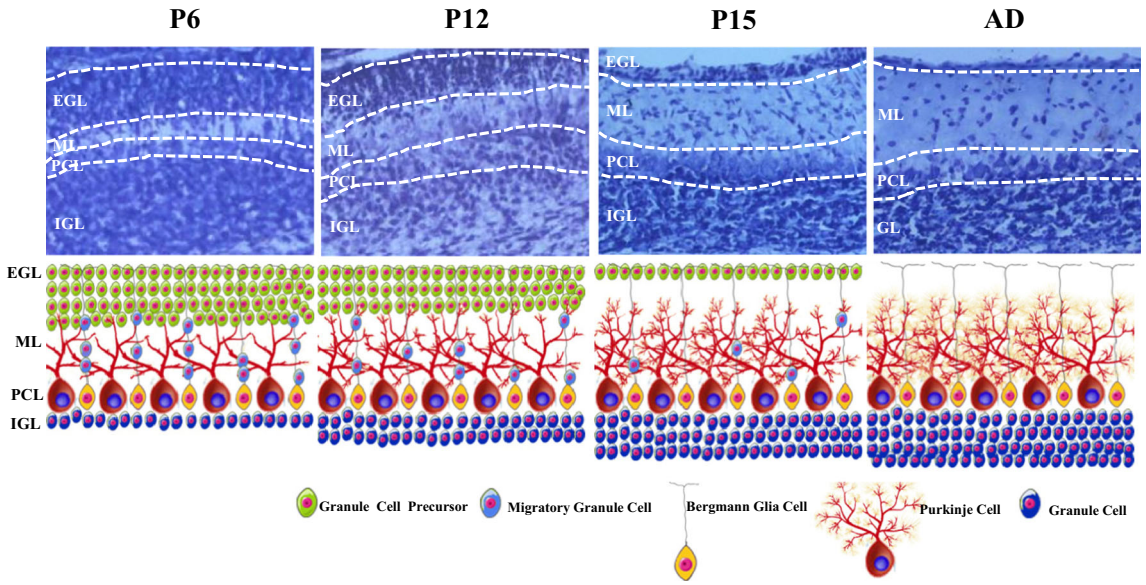

Fig. 2 Sagittal section of the mouse cerebellum and scheme representing the sections (× 20 magnification). The granule cells proliferate in the EGL and migrate through the Purkinje cells layer to form the IGL, by using the Bergmann cells as support. Abbreviations: AD, adult; EGL, external granular layer; GL, granular layer; IGL, internal granular layer; ML, molecular layer; P, postnatal day; PCL, Purkinje cell layer

Most of the effects of THs on cerebellar development and function have been attributed to their direct actions on neurons [47, 164–166]. Alternatively, we and other authors have shown that TH actions on cerebellar development can be mediated by growth factors and extracellular matrix molecules produced by astrocytes. For example, T3 induces EGF, tumor necrosis factor beta (TNF-β), and FGF release from astrocytes [94, 96, 154, 167]. Additionally, this hormone has been demonstrated to regulate the cerebellar expression of extracellular matrix and adhesion molecules that are important for neuronal migration and development, such as tenascin-C [156], reelin [168], laminin, and fibronectin [95, 154, 169, 170]. Our lab demonstrated that conditioned medium derived from T3-treated (T3CM) cerebellar astrocytes induced cerebellar precursor proliferation and morphological differentiation in vitro [94]. Our work was of the first to demonstrate an indirect effect of T3 mediated by cerebellar astrocytes instead of an exclusive and direct role for the hormone in neuronal function. This indirect effect was mainly mediated by enhanced production of EGF by astrocytes in response to T3 [94–96].

EGF is a growth factor that was initially noted for its ability to stimulate ectodermal and mesodermal cell proliferation [80, 171–173] by stimulating EGF receptors (EGFR). Once activated, these receptors stimulate a series of signaling pathways, such as ERK MAPK, AKT-PI3K, and PLC-1-PKC [174], that can lead to global phosphorylation of approximately 2000 proteins within the cell [175]. Currently, EGF has mainly been observed to be related to a series of human cancers, and the development of cancer therapies based on inhibition of these receptors has inspired extensive research [176, 177]. In the CNS, EGF induces neuronal differentiation in the neural tube [178], proliferation in the hippocampus [179, 180], neurite outgrowth of forebrain neurons [181], migration and proliferation of stem cells in adults [182–184], and long-term potentiation in the hippocampus [185]. Furthermore, EGF also plays a key role in cerebellar and hippocampal astrocyte proliferation [186, 187] and differentiation in the telencephalon and hippocampus [187, 188]. Further support for the action of EGF in CNS comes from EGFR deletion which leads to embryonic defective cortical neuronal migration [189], early postnatal neurodegeneration and impaired astrocyte proliferation [190].

Our group has provided growing evidence over the last decades strongly indicating a role for EGF produced by glial cells in cerebellar development. By using different methodological approaches, we have found that astrocytes stimulated with T3 release EGF and increase GCP proliferation through PKA pathway activation. Additionally, EGF is also able to increase extracellular levels of laminin and fibronectin in the cerebellum, two extracellular matrix molecules that provide directional cues for neurite development [169, 170], leading to GCP neurite outgrowth by stimulation of MAPK and PI3K signaling [95, 96]. In agreement with these data, Mendes-de-Aguiar and coworkers observed that astrocytes from hypothyroid rats present reduced fibronectin and laminin distributions, leading to impaired neuritogenesis of cerebellar neurons [191]. Although it is well known that hypothyroidism results in abnormal PC dendritic arborization [47, 164, 166, 192], our data shed light on astrocytes as important targets of this phenomenon. Furthermore, astrocytic EGF is also a key molecule in BG differentiation and neuronal migration. Incubation of cerebellar explants from P7 rats with conditioned medium derived from T3-treated astrocytes induced elongation of

BG processes and increased neuronal migration by activation of MAPK in an EGF-dependent manner [97]. This is supported by the location of EGFR mRNA within the EGL at the inner premigratory area. Interestingly, EGFR mRNA levels decrease when migratory cells arrive in the IGL as a result of granule cells migration [193, 194]. Furthermore, EGFR activation is related to neural progenitors and astrocytes migration in the telencephalon [195] and cortex [196, 197]. Moreover, EGFR KO mice have ectopic neurons in the white matter of the hippocampus, suggesting that EGF plays a role in cellular migration [190].

Together, our data propose a mechanism by which THs influence cerebellar development: first, astrocytes uptake T4 hormone and metabolize it to T3, which is released and acts in a paracrine way on astrocytes and on neurons. By activating different downstream pathways, EGF influences neuronal proliferation and differentiation (PKA pathway), neurite growth (through modulation of extracellular matrix molecules via MAPK and PI3K pathways), granule cell migration, and BG process elongation (Fig. 3). However, the mechanisms by which these signaling pathways modulate these processes are still an open question, and a demonstration of this proposed model in in vivo models are yet to come.

Astrocytic Transforming Growth Factor Beta-1

The correct development of the CNS depends on the requisite number and function of synapses that are critical for the formation of neural circuits. However, due to the large number of synapses and circuitry types in the mammalian brain, much remains to be discovered about the mechanisms that control the development of these events.

Synaptic connections are formed, maintained or eliminated by molecules called synaptic organizers that collectively define the function of neuronal circuits. In the cerebellum, these organizers include several secreted factors and adhesion molecules such as neurexins and neuroligins that determine the properties of specific synapses [198, 199]. Such organizers include brain-derived neurotrophic factor (BDNF) that is secreted by PCs and promotes the elimination of climbing fiber synapse [149] glutamatergic receptors of the NMDA type that are essential for cerebellar synaptic elimination [200] and functional inhibition of GABAergic synapses [201], and cerebellin 1, which is specifically required for the formation and maintenance of parallel fibers synapses, together with the δ2 glutamate receptor (GluD2) [202, 203], among others.

Astrocytes regulate the maintenance and elimination of synapses by regulating the overall architecture and activity of neural circuits through direct contact [204–207]. Thus far, there is a lack of information about astrocytic-derived factors that control cerebellar synaptogenesis, although we recently identified TGF-β1 as an astrocyte-secreted protein that induces synapse formation in the cerebral cortex and hippocampus [11, 69, 208].

We previously demonstrated the involvement of TGF-β1 pathways in several events of brain development and disease, including gliogenesis and RG differentiation [94, 160, 209, 210]; astrocyte differentiation [211, 212]; angiogenesis [213]; synapse formation [11, 69, 98, 208, 214]; and in Alzheimer's disease (AD) [13], and septic encephalopathy [215].

Recently, our group identified TGF-β1 as a new molecule involved in the regulation of excitatory and inhibitory synapse formation in the cerebral cortex and hippocampus. We have shown that TGF-β1 induces the formation of excitatory functional synapses in mice through induction of the secretion of the NMDA receptor co-agonist, D-serine [69]. In contrast, induction of inhibitory synapse formation by TGF-β1 is dependent on glutamatergic activity and activation of CaM kinase II, which leads to the localization and cluster formation of the synaptic adhesion protein, Neuroligin 2, in inhibitory postsynaptic terminals [69].

More recently, we have shown that TGF-β1 secreted by astrocytes plays a key role in cognitive processes under physiological and pathological conditions. We have demonstrated that TGF-β1 secreted by astrocytes improves the memory of healthy adult mice [208] and protects against memory loss in AD animal model [13].

TGF-β1 and Smads are expressed in different regions of the CNS during development and in adulthood [216–218]. In the adult rat cerebellum, the mRNA for TGF-β1 is found in the molecular layer, in the PCL, and in the GL [218]. We have shown that TGF-β1 is expressed during the development of the cerebellum by granule cells and astrocytes [98, 214]. Granule cells and PCs express the TGF-β1 receptor (TβRII) in vivo, suggesting that these cell types are targets of this factor [98] (Fig. 4).

The TGF-β1 pathway is triggered by its binding to TβRII, which recruits TβRI, leading to its self-phosphorylation and the initiation of a phosphorylation cascade that involves downstream effector proteins from the Smad family. After Smad2/3 recruitment and phosphorylation, these proteins form a complex with Smad4 that translocates to the nucleus and binds to TGF-β1-activated genes [61, 219].

These studies reinforce the importance of the role of TGF-β1 in cerebellar development; however, less is known about its role in astrocyte involvement in cerebellar synapse formation.

Genomic studies from our group and others has revealed that astrocytes from the cerebral cortex, hippocampus, midbrain, and cerebellum vary considerably in their gene expression profile for some synaptogenic factors, including TGF-β1, SPARC, Hevin, glypicans 4 and 6, and TSP. These data suggest that astrocytes from these regions have different synaptogenic potentials [214, 220, 221]. Interestingly, we have observed that cerebellar astrocytes are the most efficient

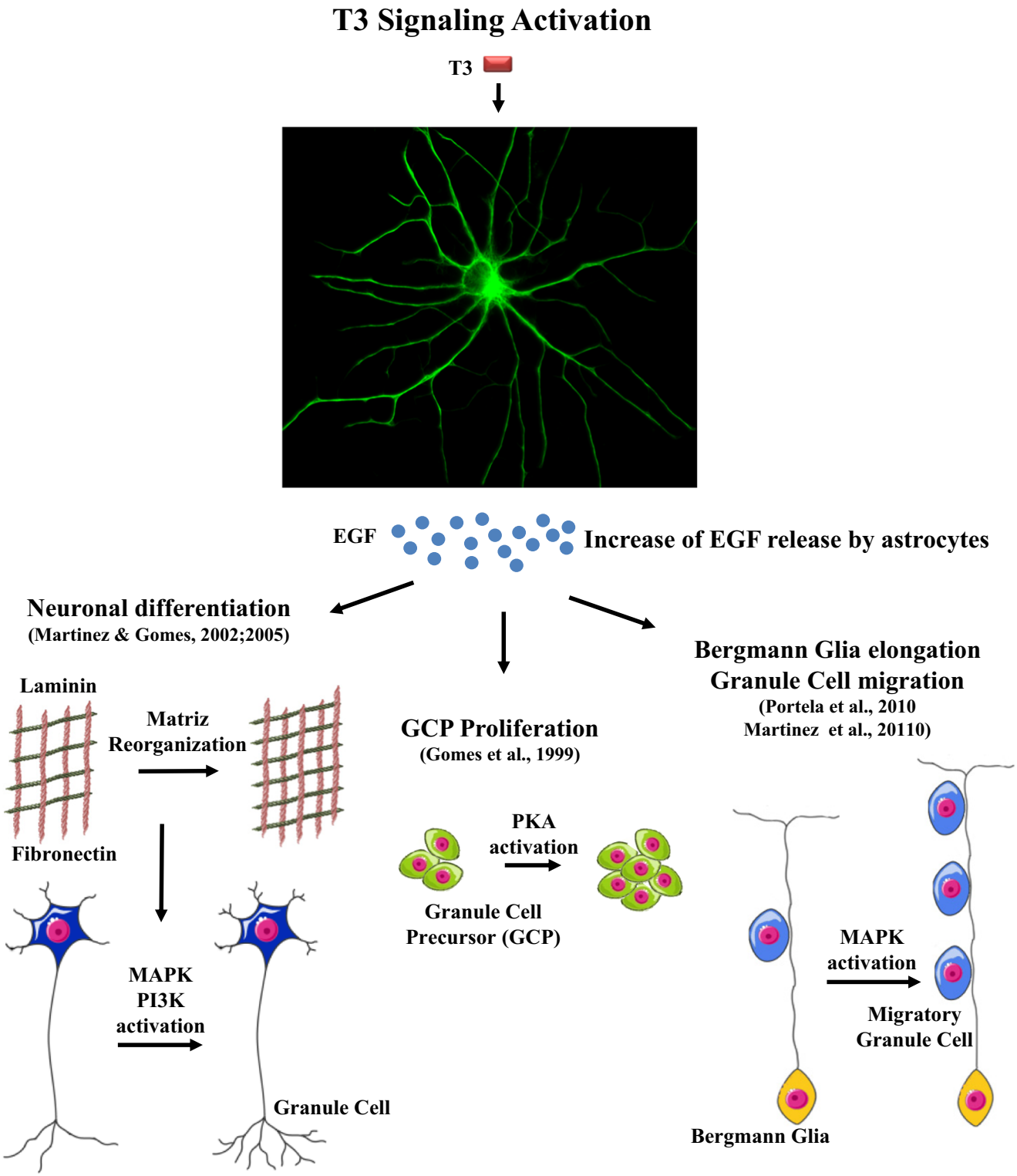

Fig. 3 Thyroid hormone actions in astrocyte functions. T3 hormone acts in a paracrine signaling resulting in increase of EGF secretion from cerebellar astrocytes. Once released, EGF induces cellular proliferation through PKA activation and extracellular matrix reorganization which results in cellular differentiation by MAPK and PI3K signaling. Through activation of EGF signaling, astrocytes also induce cellular migration and elongation of BG processes in a MAPK-dependent manner. Images from https://smart.servier.com/. Abbreviation: EGF, Epidermal Growth Factor; GCP, granule cell precursor; T3, Thyroid hormone

at inducing excitatory synapse formation when compared with astrocytes from other regions [214].

The effect of TGF-β1 on synapse formation is context and cell dependent. TGF-β1 is unable to induce the formation of

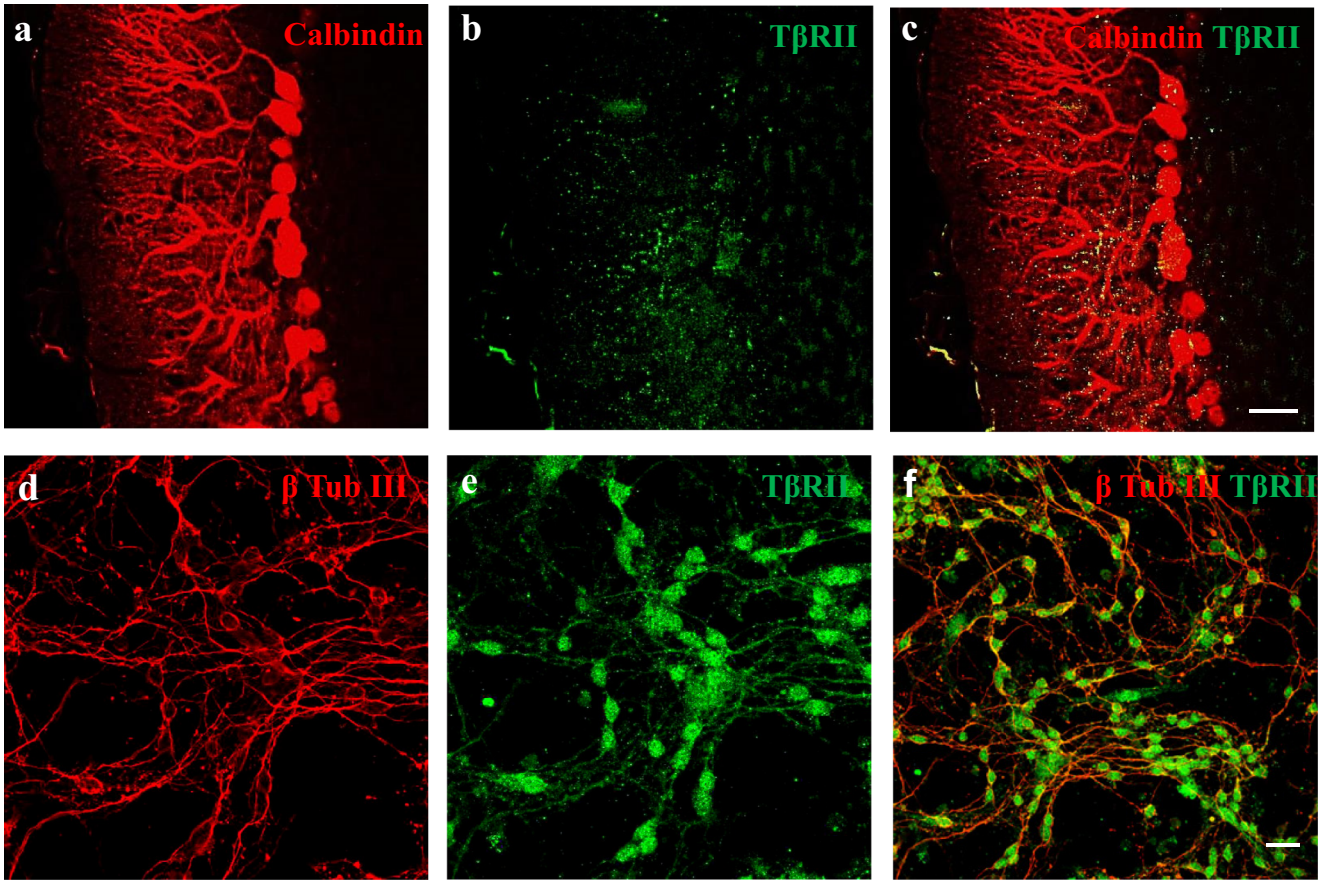

Fig. 4 TGF-β receptor's distribution in the cerebellum, in vivo and in vitro. **a** Sagittal sections of the adult mouse cerebellum stained with anti-calbindin and **b** anti-TβRII. **c** TβRII colocalizes with calbindin in the PCL. Cultured granule cells obtained from P6 mice present TβRII distribution throughout the neuronal membrane. The images show confocal microscopy analysis (**a**–**c**)

excitatory synapses between neurons of the retinal ganglion [222]; however, it induces synapses between neurons from the hippocampus [223], cerebral cortex [11, 69], and the neuromuscular junction [224]. However, the mechanisms underlying these events may vary between regions. We have also shown that TGF-β1 promotes the formation of excitatory synapses between GCPs [98]. GCPs express the TβRII, and exposure of GCP cultures to TGF-β1 increases the level of *p*-SMAD, suggesting that these cells are responsive to TGF-β1. Loss of endogenous TGF-β function in culture (by pharmacological blockade) decreases the number of synapses, while treatment of neuronal cultures with TGF-β1 increases pre- and postsynaptic protein levels, suggesting that the TGF-β pathway is important to maintain cerebellar synapses.

Additional evidence regarding the role of TGF-β1 in cerebellar synapse formation and function has come from the demonstration that TGF-β1 acts on the electrophysiological properties and maturation of GCPs from rats by increasing the expression of the GABA receptor α-6 subunit and reducing the influx of extracellular calcium [146]. Furthermore, TGF-β1 decreases the gene and protein expression of the major intracellular calcium transporters in rat cerebellar granule cells, thus affecting membrane excitability, mitochondrial fusion, and intracellular homeostasis [225].

These findings, together with the fact that TGF-β1 and its receptors are expressed during the synaptogenic period of cerebellar development in vivo and that granular neurons are responsive to TGF-β1 signaling, support the concept of TGF-β1 as a key molecule in the formation/function of synapses in the cerebellum.

Glia and Diseases: Impact on Cerebellar Dysfunction

Accumulating evidence has shown that astrocytes are important components of numerous pathologies of the CNS [226, 227], such as Down's syndrome [228, 229], Parkinson's disease [230], epilepsy [231, 232], Huntington's disease [233, 234], and AD [13, 235]. Because glial cells play several major roles in cerebellar development and function, we hypothesize that astrocytic dysfunctions may play a key role in the development of cerebellar diseases. Although this issue has been explored in relation to several CNS regions, glial alterations in cerebellar pathologies have not received sufficient attention. Nevertheless,

some groups have implicated glial cells in diseases of the cerebellum, such as ataxia, leukoencephalopathy, autism, and attention-deficit/hyperactivity disorder (ADHD) [236–239]. In agreement with our hypothesis, it was recently shown that cerebellar astrocytes from GIT1 KO mice, an animal model for ADHD, have decreased intracellular GABA content and impaired tonic inhibition capacity. Consequently, granule cells have a higher excitation/inhibition ratio, which could be associated with the hyperactivity observed in ADHD [239]. Regarding autism, Wegiel and coworkers have reported that autistic patients exhibit several alterations in BG morphology, such as loss of their vertical processes and impaired cell body arrangement in the ML. These subjects also show profound disorganization of granule cells, mainly due to BG alterations, since BG are essential for granule cell migration [240]. Likewise, two different groups have identified that autistic patients exhibit higher levels of GFAP mRNA in the cerebellum [241, 242], which may indicate glial activation in this disease.

Another disease linked to cerebellar alterations and severely affected by glial dysfunction is hypothyroidism. As discussed in the previous sections, this disease leads to several deficits in cerebellar development and is associated with ataxia and cretinism [47, 48, 243]. Our group investigated cerebellar glial cells in transgenic mice that express a natural human mutation (Δ337 T) in the TRβ locus, resulting in the expression of a non-binding receptor and thereby impaired T3 action. These mice present dramatic alterations in cerebellar glia development and morphology, such as poor radialization of BG cells in vivo, a reduction in the number of BG fibers that reach the pial surface and a decreased number of BG-derived astrocytes in vitro. These glial alterations led to severe abnormalities in cerebellar foliation, such as fusion of lobules VI and VII at P21 and impaired laminar organization [119].

Deficits in glial function are also associated with ataxia. Cvetanovic reported that GLAST protein levels are reduced in the BG of animal models for spinocerebellar ataxia type 1 [236], which can be associated with the loss of PCs in this model [236, 244], probably due to impaired glutamate uptake from BG, which may lead to glutamate excitotoxicity. Furthermore, astrocytes from A-T mice (a model for ataxia–telangiectasia studies) present reduced antioxidant capacity due to decreased glutathione levels, which leads to impaired neuronal support [245]. Moreover, ablation of frataxin, a protein linked to Friedreich's ataxia, in GFAP-positive cells results in impaired cerebellar development, as shown by the absence of GL, disorganized PCL and increased astrocyte reactivity. Interestingly, glial cells from the forebrain do not exhibit the same sensitivity as cerebellar astrocytes, which show higher oxidative stress levels when compared with forebrain astrocytes [238]. These data suggest that cerebellar astrocytes might be more susceptible to frataxin impairment than cortical astrocytes, and this could be a key factor in Friedreich's ataxia.

Astrocytes from different brain regions present distinguishable features with respect to metabolism, developmental origin, neurogenic and proliferative potential, protein expression profile, physiological properties and synaptogenic potential [198, 246–251]. They also present different responses to pathological insults and aging. Boisvert and collaborators have recently shown that gene expression during aging is differentially regulated in astrocytes from the cortex, hypothalamus, and cerebellum. Moreover, the transcriptome status of astrocytes from different areas of the brain (cerebellum, cerebral cortex, hippocampus and spinal cord) also exhibited a distinct pattern of expression in a model of multiple sclerosis [248].

The heterogeneity of astrocytes in response to pathological insults and aging leads to a question of whether astrocyte diversity might contribute to different vulnerabilities of brain areas to specific diseases. For example, AD does not affect the brain uniformly. During its development, the appearance of Aβ plaques follows a specific timeline; in initial stages, Aβ plaques are detected in the neocortex and hippocampus, while only in later periods are these plaques observed in the cerebellum of AD patients [252]. In APP/PS1 mice, an animal model for AD, the onset of deposition of Aβ plaques in the cortex and hippocampus occurs within 2 months postnatally, and at 8 months, these regions are replete with deposits of Aβ plaques [253]. However, in the cerebellum, Aβ deposits are detected only after 12 months, when these animals begin developing motor deficits. An increase in astrocytic glial reactivity is observed in the cerebellum after 18 months [254], whereas in the hippocampus of these animals, glial reactivity occurs after 6 months [255]. It is already accepted that astrocytes play an important role in AD, such as in Aβ production and metabolization and the production of inflammatory mediators and reactive oxygen species [256–258]. Recently, we have shown that Aβ oligomers (AβO), the main toxin associated with neuronal deficits in AD [259, 260], impair the synaptogenic and neuronal protector potentials of hippocampal astrocytes. Our group has also demonstrated that cerebellar astrocytes have a higher synaptogenic potential when compared with astrocytes from the hippocampus [214].

Taken together, the evidence presented here leads to some unanswered questions that need to be addressed in the upcoming years: are cerebellar astrocytes less sensible to AβO insult than astrocytes from other brain areas? If so, does this make the cerebellum more resistant to AD impairments when compared with other parts of the brain? We suggest that the answers to these questions will lead to a better understanding of the development of AD.

Concluding Remarks

The cerebellum presents a diversity of functions, from motor behaviors involving coordination, learning and balance [261–264] to non-motor behaviors such as cognition,

emotion, language, and spatial navigation [4, 265–267]. This diversity implies that cerebellar dysfunction is associated with several diseases, ranging from neurological conditions such as ataxia, dystonia, and tremor [268] to neuropsychiatric disorders such as dyslexia, schizophrenia [269], mood disorder and anxiety [270], attention deficit hyperactivity disorder [271], and autism spectrum disorder [272, 273]. As discussed in this review, glial cells participate in numerous events of cerebellar development and physiology; however, studies regarding glial alterations in pathologies related to cerebellar function are still scarce. We argue that a better understanding of glial cell physiology and how these cells are affected in the cerebellum during disease development may provide new insights for improved treatment of cerebellar illnesses.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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