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Astrocytes and the TGF-β1 Pathway in the Healthy and Diseased Brain: a Double-Edged Sword

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Abstract

Transforming growth factor betas (TGF-βs) are known as multifunctional growth factors that participate in the regulation of key events of development, disease, and tissue repair. In the brain, TGF-β1 has been widely recognized as an injury-related cytokine, particularly 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 might be a crucial regulator of cell survival and differentiation, brain homeostasis, angiogenesis, memory formation, and neuronal plasticity. In this review, we will discuss the emerging scenario of TGF-β1 as a key regulator of astrocyte differentiation and function and the implications of TGF-β1 as a novel mediator of cellular interactions in the central nervous system. First, we will discuss the cellular and molecular basis underlying the effect of TGF-β on astrocyte generation and its impact on angiogenesis and blood-brain barrier function. Then, we will focus on the role of astrocytes in the development and remodeling of synapses and the role of TGF-β1 as a new mediator of these events. Furthermore, we present seminal data that contributed to the emerging concept that astrocyte dysfunction might be associated with neurodegenerative diseases, with a special focus on Alzheimer's disease, and discuss the pros and cons of TGF-β signaling deficits in these processes. Finally, we argue that understanding how astrocytic signals, such as TGF-β1, regulate brain function might offer new insights into human learning, memory, and cognition, and ultimately, this understanding may provide new targets for the treatment of neurological diseases.

Keywords TGF-β1 · Astrocyte · Synapse · Radial glia · Angiogenesis · Alzheimer's disease

Abbreviations

AD	Alzheimer's disease
AβO	Aβ oligomers
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BLBP	Brain lipid binding protein
BMP	Bone morphogenetic protein
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
CNS	Central nervous system
CR3	C3 receptor
CREB	AMP responsive element binding transcription factor
ECM	Extracellular matrix
ECs	Endothelial cells
FGFb	Fibroblast growth factor beta
GDFs	Growth and differentiation factors
GFAP	Glial fibrillary acidic protein
GGT	γ-Glutamyl transferase
GLAST	Astrocyte-specific glutamate-aspartate transporter
Gpr124	G protein-coupled endothelial receptor 124
HHT2	Hereditary hemorrhagic telangiectasia type 2
i.c.v.	Intracerebroventricular injection
IL-6	Interleukin 6
JNK	c-jun-N-terminal kinase
LAP	Latency-associated peptide
LIF	Leukemia inhibitory factor
LPS	Lipopolysaccharide
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
NPCs	Neural progenitor cells
PAI-1	Plasminogen activator inhibitor-1
PAP	Perisynaptic astrocyte processes
PD	Parkinson's disease

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PDGF-b	Platelet-derived growth factor beta
PI3K	Phosphatidylinositol-3 kinase
PNVP	Perivascular neural plexus
PNS	Peripheral nervous system
RG	Radial glia cells
RGCs	Retinal ganglion cells
SASP	Senescence-associated secretory phenotype
SVZ	Subventricular zone
TGF-β1	Transforming growth factor beta one
TβR1	TGF-β type I receptor
TβR2	TGF-β type II receptor
TβR3	TGF-β type III receptor
TNF-α	Tumor necrosis factor alpha
TSP	Thrombospondin
V E G F A	-Vascular endothelial growth factor A
VZ	Ventricular zone
ZO-1	Zonula occludens-1
β–Gal	β-galactosidase

Introduction: Astrocytes, Beyond Nervenkitt

In the mid-nineteenth century, the German pathologist Rudolf Virchow announced the discovery of a connective tissue in the brain of postmortem human tissues that he called Nervenkitt (nerve glue; neuroglia) (Virchow, 1846 quoted from Somjen, 1988). Since its description more than 150 years ago, the view of glial cells as passive, neuronal support cells has been challenged. In particular, over the past two decades, a complete evaluation of this scenario has revealed that central glial cells, such as microglial cells, oligodendrocytes, and astrocytes, play key roles in several events for brain development and function leading to a paradigm shift; although glial cells do not directly communicate by chemical synapses, they modulate the transfer of neural information by changing the brain environment through the secretion of several gliotransmitters and trophic factors, by regulating neurotransmitter availability, and by the propagation of calcium waves.

Astrocytes are the second largest glial cell population in the human neocortex, comprising approximately 20–40% of the total number of glial cells [1, 2] and their number and variety accompany the phylogeny and complexity of brains [3]. In rodents, astrocytes constitute ~ 10–20% of the total cell number in most central nervous system (CNS) regions based on SOX9 immunolabeling [4]. Nevertheless, to date, the description of a universal marker for all types of astrocytes in the CNS has been a challenge due to the great heterogeneity in the expression profile of molecular markers, which also reflects their large morphological diversity.

The term astrocyte (i.e., star-like cell) has greatly evolved since its first description at the end of the nineteenth century, particularly due the advent of new staining and physiological and molecular biology techniques. Currently, the emerging concept of astrocyte heterogeneity indicates how diverse this cell type is in terms of not only morphology and function but also its gene signature in brain development, aging and pathological contexts. Recent evidence has suggested that astrocytes express distinct phenotypes with aging and disease, which might be identified by a specific gene signature [5, 6]. However, so far, there is a lack of evidence concerning the impact of these phenotypes on astrocyte function in different physiological and pathological contexts.

Two main types of astrocytes have been previously described: protoplasmic astrocytes, which are highly branched and are present in the gray matter; and fibrous astrocytes, which have fewer and longer branches than the protoplasmic astrocytes and are present in the white matter [7]. More recently, however, many other subpopulations of astrocytes have been distinguished not only based on their morphology but also due to their location in the brain. For example, surface-associated astrocytes are present at the cortical surface where they send processes to layer I and to the pial vessels [8]; velate astrocytes, located in the olfactory bulb and cerebellum, have shorter processes with a high surface-volume ratio allowing them to surround granular neurons [9]. Radial astrocytes (also known as adult radial glia), which differ from the radial glia present in the developing brain that are notable for their neurogenic functions, are present in brain regions different from the adult neurogenic niches, where they mainly have homeostatic functions and may play an important role in adult neurogenesis. For a more complete view on subpopulations of astroglial cells, we recommend other comprehensive reviews [1, 10].

Interestingly, there are at least three additional types of astrocytes specifically present in the brain of higher primates (such as monkeys and humans): interlaminar, polarized, and varicose projection astrocytes. These cells are present at distinct locations in the cerebral cortex and show a common characteristic: very long processes (up to 1 mm in length) that cross the cortical layers [11]. Although the functional impact of these astrocytes is still unknown, it is reasonable to think that their very long processes might be important for contacting distant cells and hence for the integration of cortical layers.

It is interesting to note that besides variety, human astrocytes are morphologically and functionally distinct from astrocytes in all other species [12]. They display a higher architectural complexity, represented by a larger volume and diameter of their cellular domains, as well as approximately 10 times more primary processes compared to a protoplasmic murine astrocyte. These more robust features enable human astrocytes to make contact with 270,000 to 2 million synapses, while their rodent counterparts contact 20,000 to 120,000 synapses in the cerebral cortex [11]. All these unique characteristics suggest the importance of astrocytes for neuronal

communication and circuitry, raising questions concerning the involvement of these cells on information processing and human cognition. The involvement in human cognition has been extensively investigated and examined from the perspective of not only astrocyte morphology but also the prominent functions of these cells in the CNS.

Astrocytes have always been described by their supportive functions for neurons and hence for homeostatic maintenance of the CNS. However, several lines of evidence from the past decades have shown that astrocytes have more functions than previously expected. In fact, they are coupled by gap junctions and form a syncytial structure allowing them to be highly integrated into neural networks, making contact with synapses through their perisynaptic astrocyte processes (PAP) [13] as well as with the vasculature by their vascular endfeet. This highly organized cytoarchitecture enables astrocytes to perform crucial functions in ion homeostasis, pH control and water transport. Astrocytes are also important for the reuptake of released neurotransmitters into the synaptic cleft, as well as providing neurons with precursors for neurotransmitter synthesis and energy substrates. Likewise, through their vascular endfeet, astrocytes regulate local blood flow and brain metabolism. In addition, together with microglia, astrocytes constitute the immune defense system of the CNS [14] and they also respond to several types of insults through changes in their morphology, proliferation and function, characterizing the reactive astrogliosis [15].

Several lines of evidence have shown that astrocytes are the main sources of trophic factors, cytokines and growth factors in the CNS, and the secretion of these molecules is an important mechanism for the interaction between different glial cells as well as neuro-glial communication. During the last decade, several astrocyte-derived molecules and their mechanisms of action have been identified, including growth factors, cytokines, hormones, extracellular matrix molecules, neuromodulators, lipids and adhesion molecules [16–28]. The identification of astrocytic proteome and secretome profiles has provided new insights into the mechanisms underlying neuron-astrocyte interactions for brain function [6, 29–32].

Neuron-astrocyte interactions regulate key events during brain development, including proliferation and neuronal migration, cellular differentiation, axonal growth and synapse formation and refinement [33–36] and during later stages, including adult neurogenesis, synaptic plasticity and elimination [37, 38].

Thus, it is likely that astrocyte dysfunction might be associated with brain diseases. In fact, alterations in the ability of astrocytes to secrete synaptogenic and trophic factors can lead to drastic synaptic changes and hence, cognitive impairments in different rodent models [5, 39–41]. In this review, we will focus on transforming growth factor beta 1 (TGF-β1) signaling, a pathway that mediates several astrocyte functions. We will discuss data that corroborate the idea that astrocytes are active components in the pathogenesis of Alzheimer's disease and other neurological disorders and shed light on the role of TGF-β1 as a key molecule in brain development, brain homeostasis in adulthood and neural pathology. We will also present recent studies that suggested the involvement of astrocytes and the TGF-β1 pathway in the context of brain aging, and we will argue that modulation of TGF-β1 pathway might represent an alternative pathway to enhance/restore or prevent damage to cognitive function.

TGF-B Family

The TGF-β family consists of a group of at least 30 members of structurally related polypeptide growth factors, including activins, nodals, TGF-βs, bone morphogenetic proteins (BMPs), and growth and differentiation factors (GDFs). These subgroups may even be composed of smaller groups based on their similarity in the amino acid sequence and the level of evolutionarily molecular homology among different organisms, such as *Homo sapiens*, *D. melanogaster,* and *C. elegans*. Members of the TGF-β family are synthesized and secreted in an inactive form associated with a large latent polypeptide. These factors become activated after proteolytic cleavage by different proprotein convertases, e.g., SPC1/Furin and SPC4/PACE4, a process that serves as a mechanism of local control of protein activity [42, 43]. Alternatively, some members can be secreted in the active form and are subject to local inhibition by antagonists such as noggin, chordin, cerberus, and follistatin [42, 43].

TGF-β1, one of the members of the TGF-β family, is a multifunctional and versatile cytokine expressed in virtually all body tissues. TGF-β1 plays an essential role in several key biological events both physiologically and in disease and during embryogenesis and in adult life, such as extracellular matrix deposition, cell cycle control, and the immune response [44–46].

TGF-β1 is a disulfide-linked homodimeric protein secreted in inactive form associated with the latency-associated peptide (LAP). After secretion, TGF-β1-LAP is proteolytically cleaved at the extracellular matrix, which leads to release of the prodomain of the active form of TGF-β1 that diffuses and acts in an autocrine or paracrine manner as a soluble factor [47, 48].

TGF-β1 exerts its actions by activating the transmembrane heteromeric serine threonine kinase type II receptor, TβRII, and the type I receptor, TβRI. Type III receptor (TβRIII) (also known as betaglycan) is composed of a large extracellular domain with a short cytoplasmic tail that binds different members of the TGF-β family. The TβRIII receptor plays an important role in recruiting and presenting the ligands to type I and II receptors. Upon ligand binding to TβRII, this receptor

promotes phosphorylation of TβRI, which in turn phosphorylates cytoplasmic protein mediators of the canonical transcription factors, Smad2 and Smad3 (receptor regulated Smads), that in turn, bind to Smad4 (co-mediator Smad), forming a protein complex that translocates to the nucleus and controls expression of TGF-β1 target genes [42, 49]. Smad6 and Smad7 (inhibitory Smads) mediate negative modulation of the TGF pathway by at least 4 mechanisms: (1) by competing with R-Smads for receptor or co-Smads interaction; (2) by targeting receptors for degradation; (3) by triggering receptors' dephosphorylation, and (4) by facilitating the endosomal localization of receptors, possibly leading to their lysosomal degradation. Smad6 preferentially inhibits Smad signaling by the BMP type I receptors, ALK-3 and ALK-6, whereas Smad7 inhibits both TGF-β- and BMP-induced Smad signaling [50, 51].

Noncanonical signaling cascades have also been described as alternative downstream pathways activated by TGF-β1. These pathways include several intracellular protein mediators such as RasGTPase, mitogen-activated protein kinase (MAPK/Erk), p38, phosphatidylinositol-3 kinase (PI3K/Akt), and c-jun-N-terminal kinase (JNK) [45, 52–54]. Although these pathways can be independently activated, canonical and noncanonical pathways can be transactivated and participate synergically in diverse events [49].

Although the activation of canonical/noncanonical signaling pathways results from TGF-β1 receptors activation, recently, the trafficking pathway modulator, Beclin 1 protein, has been proposed to also mediate Alk5/TβRI recycling within endosomal system [55]. This event positively controls TGF-β1 signaling and its availability in neuronal cells [55].

In the following sections, we will present this dual role of TGF-β1 as modulator of several steps of brain development/function and disease.

TGF-β in the Healthy Brain

TGF-β1 has been demonstrated to play essential roles in neurogenesis [56–60], neuronal migration [59, 60], synapse formation [35, 61, 62], regulation of growth and axonal targeting [63], gliogenesis [33, 52, 53, 64, 65] and angiogenesis [66–68].

TGF-β1 and its receptors were identified in progenitor zones of the developing cerebral cortex, spinal cord, and mesencephalon [59, 64, 69, 70]) and are widely distributed in different brain regions in the adult brain [71–74]. Expression of TβRI and TβRII in vitro and in vivo was demonstrated in neurons, astrocytes, oligodendrocytes, microglia and brain endothelial cells [62, 65, 68, 71, 75].

The crucial functions exerted by TGF-β1 signaling pathway were demonstrated by using several TGF-β1 knockout or mutant mice models [76]. Complete TGF-β1 knockout mice presented with severe vascular and hematopoiesis deficits, increased inflammation and autoimmunity, and die at embryonic age 9.5–11.5 [77–79], similar to ALK1 and TβRII knockouts [80, 81].

Specifically, in the CNS, E14.5 TGF-β1 mice mutants exhibited brain hemorrhage throughout the neuroepithelium with associated glomeruloid vascular malformations [82]. Moreover, TGF-β1 ablation induced widespread increased neuronal degeneration accompanied by reduced expression of synaptogenic markers and ECM proteins and microglial activation [56]. This finding is consistent with more recent data showing that TGF-β1-deficiency in the adult mouse brain resulted in reduced brain weight and neuronal loss in the CA1 hippocampal region, accompanied by a loss of astrocyte glutamate transporter (GluT) proteins GLT-1 (EAAT2) and GLAST (EAAT1) and decreased glutamate uptake in the mouse hippocampus [83].

Together, data from TGF-β1 deficiency/overexpression mutations suggest that multiple functions exerted by astrocytes might be potentially mediated by TGF-β1 signaling, raising the idea that astrocytes might act as sources or targets of this cytokine in the healthy brain and pathological states (Fig. 1).

TGF-βs in Radial Glia Differentiation and Astrocyte Formation

Astrocytes are derived from radial glia (RG) multipotent stem cells, transitory progenitors that under specific molecular signals give rise to neurons and astrocytes in most of the regions of the CNS [53, 84, 85].

In addition to their typical radialized morphology, RG cells can be identified by their specific genetic profile characterized by expression of genes associated with undifferentiated potential of neural stem cells, such as nestin/RC2 and vimentin intermediate filaments, and transcription factors *Pax6, Sox2, Dlx2, Olig2, Nkx2.1, Gsh2, Emx2, Foxg1*, expressed in specific patterns in a brain region-dependent manner [86–88]. However, mammal RG cells also express typical glial markers such as BLBP (brain lipid binding protein), GLAST (astrocyte-specific glutamate-aspartate transporter), and GFAP (glial fibrillary acidic protein), with the latter only in primates [89, 90].

Currently, RG cells are considered the main source of astrocytes in different organisms including humans, nonhuman primates, rodents and carnivores [91–95]. Recently, a transcriptome-based study revealed specific gene expression in human RG/neural progenitor cells (NPCs), suggesting that this might contribute to the huge heterogeneity within human astrocytes [96].

In the mammalian telencephalon, at early developmental stages, RG cells originate neurons, followed by a change of this neurogenic potential to the gliogenic, late in development.

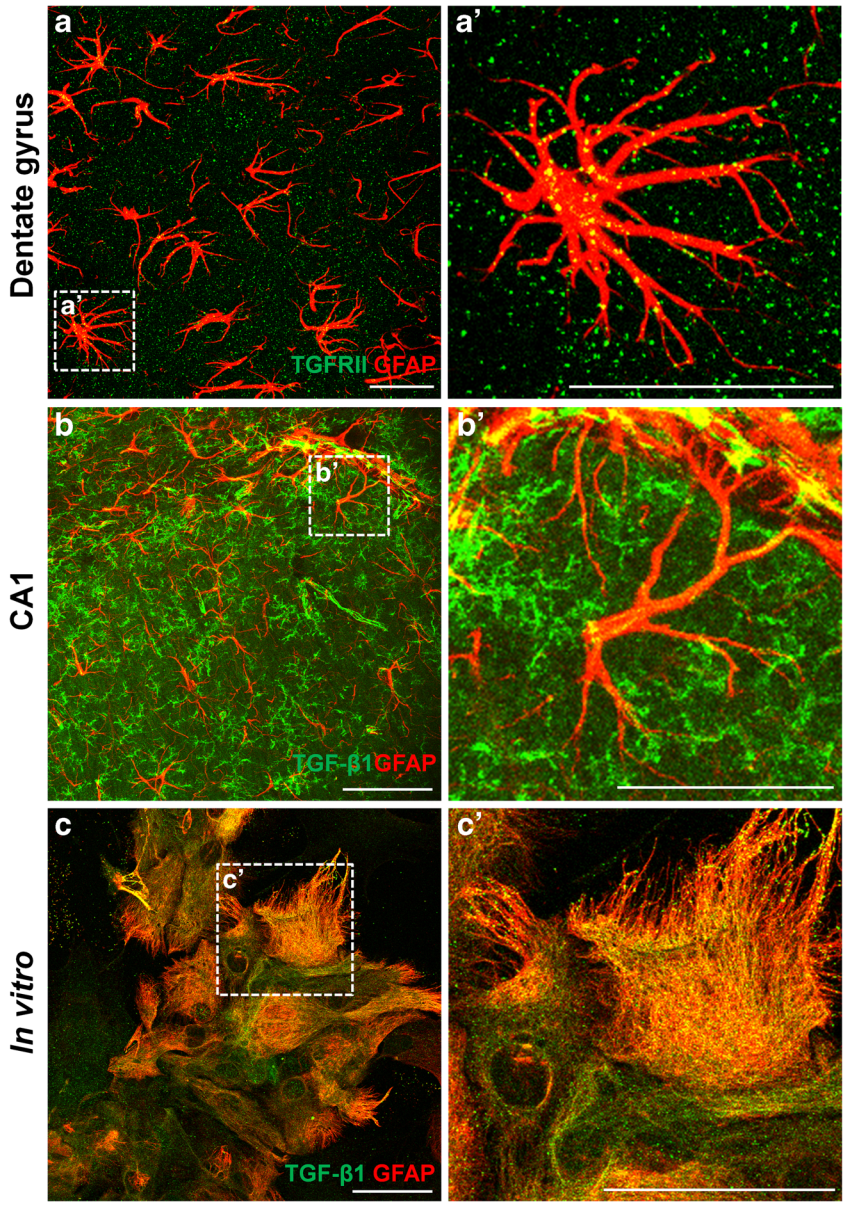

Fig. 1 Astrocytes are a source and target of TGF-β1. High-resolution images showing the expression and distribution of TβRII (**A**) and TGF-β1 (**B**) in GFAP-positive hippocampal astrocytes from the molecular layer of dentate gyrus and stratum radiatum of CA1, respectively; TGF-β1 in hippocampal astrocytes in vitro (**C**). Scale bars: 30 μm (**A**, **A'**), 50 μm (**B**, **C**, **C'**), and 25 μm (**B'**)

The main hypothesis of the "neurogenic to gliogenic" switch is that it directly depends on molecular signals derived from the migratory and immature postmitotic neurons generated at earlier stages, thus controlling over time, the potential of different populations of RG cells (Kriegstein and Alvarez-Buylla, 2009; Miller and Gauthier, 2007) (Fig. 2).

Members of the TGF-β family, such as BMP2/4 and TGF-β1, and those of the interleukin family such as IL-6 and cardiotrophin-1, were identified as strong inducers of astrocytic differentiation from neural progenitors. NPCs isolated from murine embryonic telencephalon, when stimulated by different combinations of BMP-2/LIF (leukemia inhibitory factor) or BMP-4/CNTF, generate cells morphologically similar to astrocytes with increased levels of GFAP gene expression, suggesting that these molecules trigger astrocytic differentiation [97, 98].

By using a transgenic mouse bearing part of the GFAP gene promoter linked to the β-galactosidase (β-Gal) reporter gene (GFAP-*lacZ* transgenic mice), we demonstrated that cortical neurons activate the GFAP gene promoter by inducing TGF-β1 secretion by astrocytes [75, 99]. We also reported that this event was regionally modulated: while cortical neurons or conditioned medium derived from them induced cortical astrocyte differentiation, they did not activate the GFAP gene promoter of transgenic astrocytes derived from midbrain and cerebellum suggesting a neuroanatomic regional specificity of this phenomenon. These data support the concept that (1) neuronal signals drive astrocyte differentiation, and (2) heterogeneous subpopulations of astrocytes distinctly respond to environmental cues.

Our group demonstrated that TGF-β1 was a potent inducer of astrocytic differentiation from RG cells. In vitro exposure

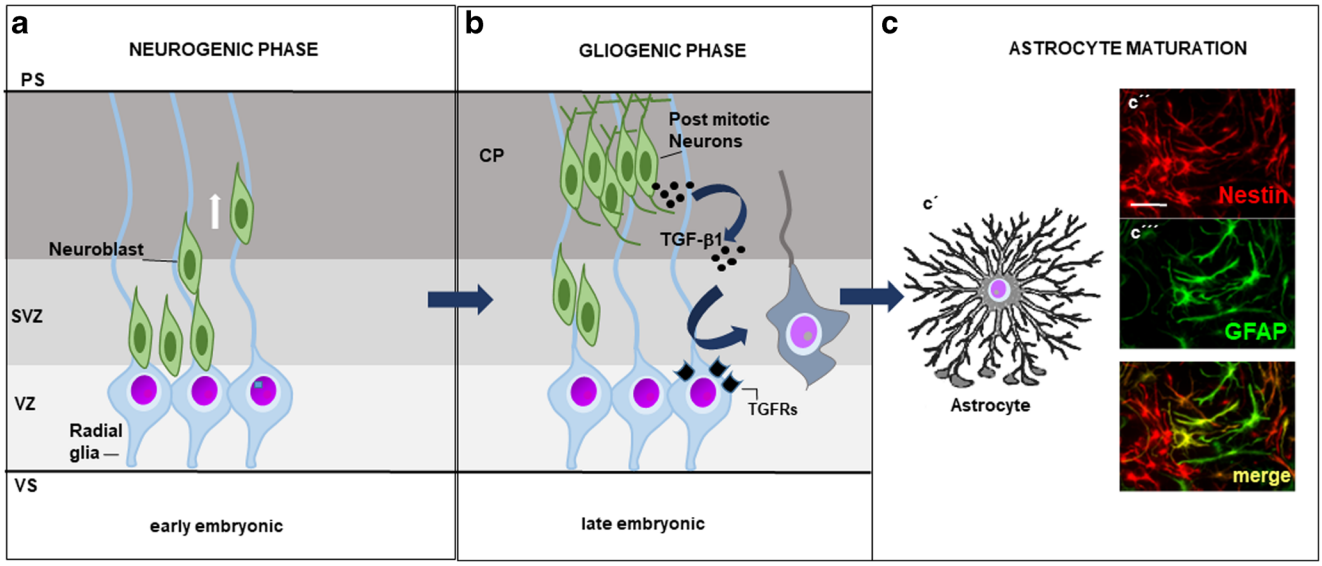

Fig. 2 TGF-β1 induces RG cells neurogenic to gliogenic switch. **A** RG cells present an elongated morphology that comprises the entire thickness of the developing cortical wall from VS up to PS, express typical markers such as nestin and BLBP, and present preponderant neurogenic potential in the early embryonic period. Newly generated neuronal progenitors accumulate in the SVZ, and neuroblasts migrate towards the PS using RG cell fibers (white arrow). **B** Upon reaching the CP, postmitotic neurons extend dendritic and axonal projections to establish connections with their cellular targets. Secretion of TGF-β1 from maturing neurons promotes the activation TGF-β receptors (TβRs) in the membrane of the RG cells promoting the switch from neurogenic to gliogenic phases by changing the differentiation potential of these cells in the late embryonic period. Astrocytic differentiation is achieved by RG fibers loss of contact with the SV and PS and gradual morphological and molecular acquisition of the astrocytic phenotype, especially observed by the expression of the GFAP marker. **C** Astrocyte maturation is evident by specific morphological specifications with the acquisition of multiple cellular processes (**c´**), gradual decreases in typical RG markers such as nestin (red, **c´´**) and increases in GFAP (green, **c´´´**) expression. PS: pial surface; SVZ: subventricular zone; VZ: ventricular zone; VS: ventricular surface; CP: cortical plate. Scale: 50 μm

of RG cultures, from embryonic cerebral cortex of mice, to TGF-β1 decreased the pool of nestin-positive RG cells [33] by activation of Smad2/3 and MAPK signaling pathways [53]. In utero intracerebroventricular (i.c.v.) injection of TGF-β1 in E14.5 mice embryos induced a robust loss of the elongated processes of nestin-positive RG cells and induced GFAP expression in vivo [64]. This event was followed by displacement of proliferative progenitor populations from the VZ to SVZ basal layers. In addition, we observed reduced neurogenesis in the VZ of TGF-β1-injected animals, suggesting that TGF-β1 signaling activation in cortical RG cells promoted astrocyte generation, thus contributing to the "neurogenic to gliogenic" switch [64].

Interestingly, gliogenic induction by TGF-β1 preferentially affected RG cells of the mid-dorsal cerebral cortex, where lateral cortical RG cells were rather responsive to TGF-β1 gliogenic induction [64]. In addition, it is important to note that, while classical evidence demonstrated that VZ/SVZ progenitor cells generate protoplasmatic or fibrous astrocytes, the astrocyte population is highly diverse across CNS regions [100–103]. These data are corroborated by our previous data that show that astrocytes from different brain regions present morphological specificities, secrete different amounts of TGF-β1 and distinctly respond to this factor [65, 104].

Altogether, these results highlight the emerging view of the regional diversity of the RG cells, which could also be implicated in the generation of the diverse heterogeneous subpopulations of astrocytes later in brain development [84, 90, 105].

TGF-βs in Blood-Brain Barrier Function and Angiogenesis

The CNS microvasculature is formed in early stages of embryonic development via angiogenesis, a highly dynamic event that involves the formation of new blood vessels from preexisting ones. As the first blood vessels are formed in neural tissue, brain endothelial cells acquire unique characteristics [106, 107] and become associated with pericytes and astrocytes, forming the structure known as blood-brain barrier (BBB) [108], which is a multicellular structure that ensures the transport of essential nutrients and oxygen to the brain and is selectively permeable to blood-derived compounds [109].

Angiogenesis is a process carefully regulated by the balance between stimulatory and inhibitory molecular signaling present in the brain microenvironment [110]. The vascular endothelial growth factor A (VEGF-A) is the most prominent angiogenic inducer described, controlling events such as vessel ingression into the neural tube, migration, proliferation and ECs survival [111–113].

In addition to the prominent role of VEGF as a master regulator of neuroangiogenesis, several studies supported the

relevance of TGF-ß1 in the regulation of endothelial differentiation, vascular network formation and maintenance of blood vessel integrity [114–116]. Deficits in components of the TGF-β signaling pathway resulted in death during the embryonic period due to severe impairment of vasculature development, characterized by the presence of leaky and hyperdilated vessels and intracerebral hemorrhages [116, 117]. The first step in neuroangiogenesis begins with the sprouting of progenitor ECs from the perivascular neural plexus (PVNP) and invasion into the neural tissue, followed by migration, proliferation of ECs and branching of the vasculature into the CNS. EC ingression into the developing neural tube depends on the expression of the G protein-coupled endothelial receptor 124 (Gpr124) in the ECs, which is positively regulated by TGF-β1 [118]. Although previous reports suggested proangiogenic actions of TGF-β1, emerging evidence supports antagonistic effects of TGF-β1 on angiogenesis, indicating that TGF-β1 might have both angiogenic and anti-angiogenic actions in a highly context-dependent manner [114, 119]. While low concentrations of TGF-β1 induced the proliferation and migration of ECs, high concentrations were inhibitory by inducing expression of angiogenesis negative regulators, such as plasminogen activator inhibitor-1 (PAI-1) [120], which is a potent inhibitor of ECs migration [121–123].

In ECs, TGF-β signals through two type I receptors, ALK5 and ALK1 [80, 124], which are believed to be responsible for the differential activation of the endothelial phenotype and therefore lead to different effects on angiogenesis. ALK1 is a receptor predominantly expressed by ECs and binds BMP9, BMP10 and TGF-β [125, 126]. Defects in ALK1 have been shown to cause hereditary hemorrhagic telangiectasia type 2 (HHT2) [127], which is characterized by the presence of hemorrhages due to vascular malformations, suggesting a critical role in the signaling of this receptor in angiogenesis. Activation of ALK1 induced phosphorylation of Smad1/5/8 and promoted proliferation and migration of ECs, whereas activation of ALK5 induced phosphorylation of Smad2/3 and led the endothelium to a quiescent state, inhibiting angiogenesis and promoting the stabilization of the vasculature [124, 128]. Despite the opposing effects produced by the activation of these receptors, it has been reported that ALK1 and ALK5 can directly interact producing complex responses. Thus, the state of endothelial activation or quiescence depends on the balance between the two different TβRI signaling, ALK1 and ALK5. Furthermore, this balance can also be modulated by endoglin [129], a transmembrane glycoprotein predominantly expressed by ECs that acts as an accessory receptor for TGF-β [130].

Although much has been learned, the mechanisms underlying the dual role of TGF-β1 signaling in controlling angiogenesis, either inducing activation or quiescence of ECs, have not been fully elucidated yet. In this context, differential activation of the two receptors, cooperation with other receptors, and the possibility of binding by different ligands of the TGF-β family provides the ECs with a repertoire of possibilities to regulate the biological responses triggered by TGF-β.

Recently, interactions between ECs and NPCs have emerged as new mechanisms that contribute to brain angiogenesis. Vascular sprouting during development is regulated by interactions between neuroepithelial cells and ECs through complexes between the αvβ8 integrins, expressed by the neuroepithelium, and the endothelial transmembrane protein, Nrp1, which led to the modulation of extracellular matrix (ECM)-bound latent TGF-β activation [67]. Selective genetic deletion of αv or β8 integrin in the neuroepithelium resulted in vascular hypersprouting and cerebral hemorrhage [67, 131] [82, 132]. Furthermore, deletion of TβRII in ECs resulted in vascular malformations and intracerebral hemorrhages [67, 116]. In addition, deletion of Nrp1 in ECs induced increased phosphorylation of Smad3 in blood vessels, disturbed the activation of the canonical pathway of TGF-β1 and resulted in altered vascular sprouting [67]. These data together demonstrate that deficits in the neuroepithelial-ECs interaction by dysregulation of the αvβ8-TGFβ-Nrp1 signaling axis during development result in defects in vascular network formation.

TGF-β signaling can modulate the secretion profile of angiogenesis-related molecules by neural stem cells [66, 68] that resulted in impaired EC migration and abnormal angiogenesis [66, 68]. We previously demonstrated that RG controlled ECs migration, promoted endothelial tube-like formation in vitro and induced blood vessel branching in the developing cerebral cortex in vivo though TGF-β1 signaling [68].

In addition to acting in the regulation of the angiogenic sprouting phase [67], TGF-β1 has been described as a strong inducer of vascular ECs specialization and stabilization of the BBB (reviewed by [133]). TGF-β1 contributes to the maintenance of BBB functions as it modulates TJ zonula occludens-1 (ZO-1) protein expression [134], induces the reduction of endothelial permeability, and increases activity of the P-glycoprotein (P-gp) efflux pump in ECs [135], which are functional hallmarks of brain ECs.

The proper establishment of the BBB involves the association between blood vessels, pericytes and astrocytes. After ensheathing capillaries, pericytes induce maturation and stabilization of the vasculature during development and subsequently regulate other functional aspects of BBB, such as vessel contraction and blood flow control in response to neural activity [136–139]. The coupling between ECs and pericytes occurs early in the development of the cerebral blood vessels and is mediated by various soluble factors, including platelet-derived growth factor (PDGF-b) and TGF-β [108, 140].

During early development of the brain vasculature, TGF-β induced upregulation of the ECs adhesion protein, N-cadherin, and led to increased attachment between the pericytes and the ECs [141]. Further, activation of the ALK5/Smad2/3 pathway in the pericytes stimulated the

production of ECM components [142], which may contribute to maturation of the developing blood vessels. Deletion of Smad4 in ECs resulted in detachment of vessel pericytes and increases in BBB leakage and intracerebral hemorrhages [141].

In addition to the pericytes, perivascular astrocytes are also responsible for inducing the BBB phenotype in ECs, including increasing TJ expression, and inducing polarized expression and localization of specific endothelial proteins, such as PgP and the glucose transporter GLUT-1 (reviewed by [109]). It has been shown that astrocytes increased γ-glutamyl transferase (GGT) activity in the ECs by direct contact or through the secretion of soluble factors in a TGF-β1-dependent manner [143]. Furthermore, astrocytes inhibited endothelial migration through activation of the TGF-β-avb8 pathway in ECs and increased vascular stabilization by enhancing expression of PAI-1 and thrombospondin-1 (TSP-1) genes [144] (Fig. 3).

Thus, astrocytes modulated endothelial functions by activating the TGF-β pathway, which contributed to vascular integrity and establishment of the BBB.

The bifunctional effects of TGF-β on endothelial activation or quiescence for years raised the question about its role in the regulation of CNS angiogenesis. The anti-angiogenic action of TGF-β signaling described in some contexts, however, might be associated with its potential in promoting blood vessel maturation and stabilization. It is now widely accepted that this multifactorial cytokine is involved in different stages of vascular development, which comprises initial angiogenic sprouting and culminates in the establishment of BBB functions.

Astrocyte and TGF-βs in Synapse Formation, Pruning and Function

Over the past decades, there has been an increasing interest in studying the involvement of astrocytes in synaptic control under physiological and pathological contexts. This increased interest is due to evidence from the early 1990s showing that astrocytes exhibit a form of excitability and cell communication involving variations in the levels of intracellular calcium, which could be propagated through calcium waves [145, 146]. This work, together with the description of bidirectional communication between astrocytes and neurons, shed light on the concept of the "tripartite synapse" [147–149]. From this perspective, it is well known that synapses are formed by the pre- and postsynaptic terminals and the astrocytic perisynaptic processes. Important studies have demonstrated that neurons cultured in the presence of astrocytes have an approximate sevenfold increase in synapse number and a greater synaptic efficacy than when cultured in the absence of these cells [150, 151].

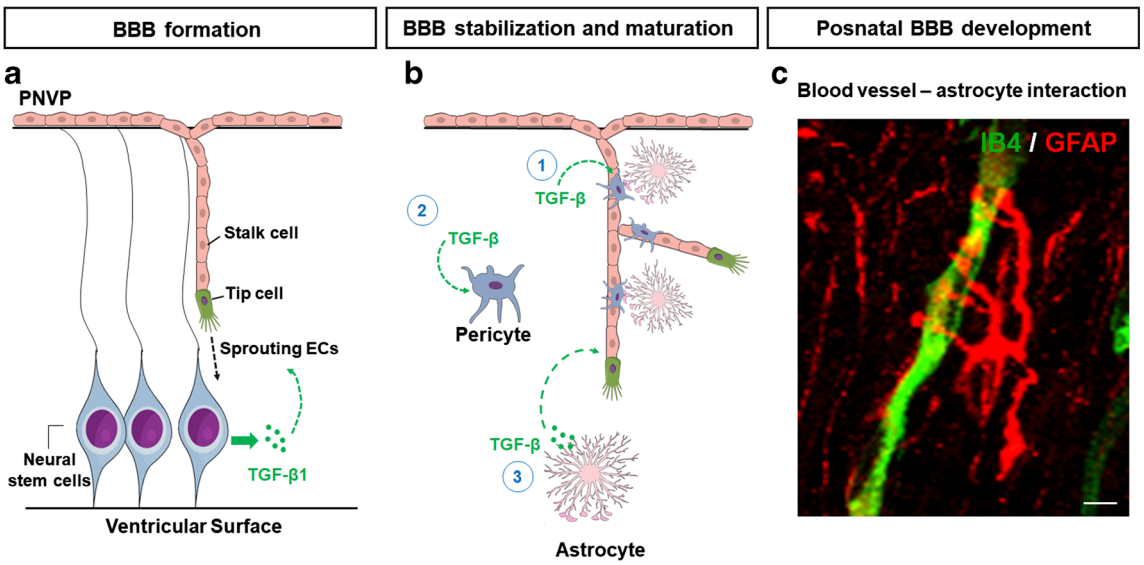

Fig. 3 Cerebral-vascular interactions mediated by TGF-β signaling. **a** During embryonic development, precursor ECs from the PNVP invade the neural parenchyma guided by factors produced by NPCs. ECs activation by these factors leads to the specification of two distinct cellular phenotypes: tip and stalk cells. Tip cells, characterized by dynamic filopodia, migrate to guide the vascular sprout, while stalk cells are highly proliferative and contribute to elongation and vascular lumen formation. ECs migrate towards the ventricular surface using the RG fibers as support. RG cells can induce the migration of ECs and blood vessel branching through TGF-β1 signaling. Additionally, TGF-β1 modulates the release of RG-derived angiogenic factors. **b** TGF-β signaling contributes to the interaction between ECs and pericytes during BBB establishment. TGF-β activation on ECs promotes upregulation of N-cadherin, leading to pericyte adhesion to nascent blood vessels (1). In pericytes, TGF-β signaling leads to the production of extracellular matrix (ECM) molecules, contributing to blood vessel stabilization (2). The establishment and maturation of BBB also depends of EC-astrocyte interactions mediated by the TGF-β pathway. Through activation of TGF-β, astrocytes promote EC barrier properties and increase vessel stabilization (3). **c** Confocal image showing GFAP-labeled astrocytes ensheathing blood vessels stained with isolectin-B4 (IB4) in the cerebral cortex of neonatal mice. Scale bar: 10 μm

The first direct evidence that glia enhanced synapse formation was obtained in the late 1990s with studies from cultured retinal ganglion cells (RGCs) [150]. Since then, the idea of glial cells as modulators of synapse formation, stabilization, elimination and efficacy has been validated with different cell lines and models in both the peripheral nervous system (PNS) and CNS as discussed below.

Currently, we know that astrocytes control synapse formation and plasticity through two distinct mechanisms: secretion of soluble factors and expression of contact molecules [152]. Cholesterol and the extracellular matrix protein, TSP, were the first described synaptogenic soluble factors secreted by astrocytes [18, 21]. Since then, many others were identified, such as TNF-α [20], estrogen [19], BDNF [153], D-serine [27], glypicans 4 and 6 [154], hevin [155] and TGF-β1 [62]. The control of synapse formation by astrocytes seems to be a conserved property across different species, including humans, as well as from different population of astrocytes in the CNS [104]. Data from our group showed that both murine and human astrocytes were able to induce the formation of excitatory and inhibitory synapses through the secretion of TGF-β1 [61, 62, 156].

Evidence has accumulated over the last decade suggesting a role of TGF-β family members in CNS synaptic plasticity and memory in different animal models and regions of the CNS and PNS.

The first evidence of TGF-β1 regulating synaptic events was reported in relation to plasticity of synaptic function and was evaluated in invertebrate models. In the *Aplysia*, TGF-β1 induced long-term changes in neuronal excitability, and this event was dependent on the activation of the MAPK pathway and the cyclic AMP responsive element binding transcription factor (CREB) [157, 158]. Several studies in *Drosophila* confirmed the involvement of members of the TGF-β family and their pathways in plasticity and synapse formation [159–163].

The role of TGF-β1 in regulating plasticity in vertebrates has been described more recently. Blockade of the endogenous TGF-β1 signaling pathway has been shown to impair long-term potentiation (LTP) formation and object recognition memory. In contrast, administration of exogenous TGF-β1 rescued these effects in a mechanism dependent on CREB activation [164]. Corroborating this data, the group of Fernando Pitossi verified that the overexpression of TGF-β1 in the hippocampal dentate gyrus during postnatal development led to a long-term decrease in social interaction and a long-term increase in self-grooming and depression-related behaviors. In contrast, chronic expression of TGF-β1 during adulthood resulted in transient and opposite effects on these behaviors. These results suggested the role of TGF-β1 in the generation of behavior changes during development [165]. In agreement with the idea of the involvement of TGF-β1 in plasticity, a study from Fernando Pitossi's group demonstrated that TGF-β1 enhanced neurogenesis in adult rats [166]. In addition, the group found that exposure to prenatal inflammatory insults impaired adult neurogenesis as well as object recognition memory due to a reduction in TGF-β1 levels. Chronic overexpression of TGF-β1 rescued these effects [167], confirming the role of this cytokine in these developmental events and neural plasticity.

In hippocampal neuronal cultures, it has been observed that synaptic activity regulated the expression and release of TGF-β2 and TGF-β3. The K^+-induced depolarization caused Smad2 translocation to the nucleus and regulated target genes of TGF-β [168]. One of the members of the TGF-β family that was reported to regulate plasticity and synapse formation was TGF-β2. The genetic deletion of TGF-β2 in mice generated synaptic dysfunction and cognitive and functional changes in the respiratory center, which caused perinatal death [169]. Furthermore, it was shown that TGF-β2 regulated synaptic plasticity through CREB activation [170]. In addition, TGF-β2 agonists have been shown to increase the postsynaptic response to spontaneous and evoked release of acetylcholine, whereas TGF-β2 antagonists have the opposite effect [171].

The regulation of synaptogenesis by TGF-β1 has been demonstrated in the vertebrate PNS, where Schwann cells, the myelinating glia of the PNS, regulate synapse formation through the secretion of this cytokine [172]. Subsequently, our group demonstrated that mouse and human astrocytes increased the density of structural and functional glutamatergic synapses through the release of TGF-β1 in the cerebral cortex [62]. In addition, we found that this effect was mediated by the regulation of the levels of the amino acid, D-serine, described as the main NMDA receptor coagonist in the cerebral cortex [173]. We demonstrated that TGF-β1 induced the synthesis and secretion of D-serine; deletion of the serine racemase gene in astrocytes inhibited the synaptogenic effect of these cells, indicating a mechanism by which astrocytes induced the formation of excitatory synapses in the cerebral cortex [62]. Confirming our findings, it was demonstrated that in an experimental animal model of epilepsy, albumin, which is released by BBB disruption, induced the formation of excitatory synapses in vitro and in vivo and this effect was dependent on astrocytes and TGF-β/ALK5. Treatment with a specific ALK5/TGF-β inhibitor prevented the synaptogenic effect of TGF-β1 and the epileptic seizures in animals [174]. Similar to this study, the addition of exogenous TGF-β1 has been shown to increase neuritic growth and the distribution of presynaptic puncta through a Smad-3-dependent mechanism. In contrast, the conditioned medium of astrocytes stimulated with TGF-β1 had an opposite effect, reducing the neuritic growth and the distribution of synapsin puncta. One of the mechanisms proposed in the study was that the activation of Smad3 resulted in increased release of proteoglycans that had blocking effects on synapse formation [175]. Thus, this study suggested that the signaling pathway of TGF-β1/Smad3 has a dual role in astrocytes and neurons, and could be involved in diseases with synaptic dysfunctions.

Supporting our data, TGF-β1 overexpression in astrocytic cells in vivo led to intense hippocampal gliosis and increased levels of the subunits of the ionotropic receptors, NMDA and AMPA. Treatment of hippocampal neuronal cultures with TGF-β1 increased dendritic growth and glutamate-evoked currents, suggesting a role for this molecule in synaptic regulation [176]. In contrast, the conditional deletion of TGF-β1 in astrocytes induced intense astrogliosis, loss of dendritic spine density, dysfunctions in LTP and LTD, and deficiency of glutamate transport by the astrocyte cell [83]. A possible explanation for this duality of results is: (1) It has already been described that TGF-β1 activates the GFAP gene promoter and increases astrocyte maturation [52, 65]; within this context, it is likely that overexpression of astrocytic TGF-β1 would be able to increase GFAP levels and induce astrogliosis; (2) TGF-β1 is an endogenous anti-inflammatory cytokine [177, 178]; within this perspective, the conditional deletion of TGF-β1 would contribute to induction of neuroinflammation and astrogliosis.

More recently, our group demonstrated that the synaptogenic capacity of TGF-β1 was also observed in the cerebellum [156] indicating a conservation of the synaptogenic mechanism of this cytokine in different structures of the CNS and the heterogeneity of neuronal responses for this molecule.

Excitatory synaptic transmission is regulated primarily by glutamatergic synapses, while synaptic inhibitory transmission involves GABAergic and glycinergic signaling that is established during development and maintained throughout life. In homeostatic conditions, there is a functional balance between the formation and function of excitatory and inhibitory synapses [179]. Together, these systems provided the spatial and temporal structure for the transfer of physiological information in the brain. Our group showed that, in addition to TGF-β1 regulating excitatory synapse formation, TGF-β1 from murine and human astrocytes increased the formation of inhibitory synapses through a mechanism dependent on both glutamatergic synaptic activity and activation of the signaling pathway of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). Activation of this pathway induced translocation and cluster formation of the synaptic adhesion protein, neuroligin 2, in inhibitory postsynaptic terminals. Our results identified the TGF-β1/CaMKII pathway as a new mechanism by which astrocytes regulated inhibitory synapses formation in the cerebral cortex [61]. Together with our previous data [62], these results contributed to the concept that the balance between excitatory and inhibitory inputs is controlled by astrocyte signals via the TGF-β1 pathway. Our data corroborated the findings that Smad4 deletion in mice caused changes in cerebellar inhibitory neurons [180] and in the hippocampal GABAergic synapses [181]. These data are corroborated by recent information that the loss of TGF-β signaling caused a lack of control in the ratio of excitatory/inhibitory inputs in dopaminergic neurons [182]. Reinforcing this proposed role for TGF-β in the formation of inhibitory synapses was the evidence of the association between dysfunction in levels or signaling of TGF-β1 in neurological disorders with inhibitory synapse dysfunction, such as autism [183], epilepsy [184] and depression [185, 186].

One of the likely mechanisms by which TGF-β1 can regulate synapse formation is through the regulation of axonal and neuritic growth. TGF-β1 treatment enhanced neurite growth and dendritic synapse density in dopaminergic neurons [187] and hippocampal neurons [176]. Subsequently, it was shown that one of the possible mechanisms of regulation of axonal growth was Smad3 activation and translocation mediated by TGF-β1 [175]. In addition, TGF-β appeared to have an essential effect on axonal formation, since the deletion of TβRII in neocortical neurons prevented the formation of axons during development. In contrast, the exogenous addition of the factor rescued growth and axonal targeting [63]. Contrary to these findings, recent work has shown that the activation of Smad-dependent canonical signaling by TGF-β negatively regulated neuronal morphogenesis during neuronal development. Hippocampal neurons treated with TGF-β1, BMP2 or BMP4 inhibited morphogenesis of neurites. The same effect was observed with overexpression of Smad1, Smad2 and Smad4 [188]. One of the possible mechanisms for these discrepancies is the variety of neuronal type, the microenvironment and the physiological and developmental stage evaluated. In addition, it has been shown that the downstream signaling pathway and molecules activated by TGF-β1 are crucial to determine the specific effect. Activation of different class of Smads, protein interactions and posttranslational modifications of the Smads may explain the distinct effects in signaling pathway [189, 190].

During development, the formation of mature neural circuits requires selective elimination of inappropriate synaptic connections, an event classically known as synaptic pruning or elimination. In 2007, Beth Stevens demonstrated that microglia identified the inappropriate synaptic connections with the presence of members of the complement family (C1q and C3) and performed the synaptic pruning through microglial phagocytic activity [191, 192].

In 2013, the same group demonstrated that through the secretion of TGF-β, astrocytes regulated the expression of neuronal C1q protein and this process directed the neurons to the process of synaptic refinement [36]. Neurons in TβRII-deficient mice (TβRII-KO) had a reduction in C1q levels in retinal ganglion cells and a reduction in complement localization in the dorsal geniculata lateral nucleus. Taken together, these findings demonstrated a new role for the TGF-β cytokine signaling pathway in the regulation of C1q expression in neurons, and the initiation of complement-dependent synaptic refinement in the developing CNS.

Several studies have correlated alterations in cytokine levels and signaling in several pathological models with synaptic changes and astrocytic function as epilepsy [174, 193], depression [194], Alzheimer's disease (AD) [195] and Parkinson's disease (PD) [196]. We describe below the main findings of the involvement of TGF-β levels and signaling in healthy aging processes, as well as the involvement of this cytokine in AD, the most prevalent neurodegenerative disease in the world.

TGF-β1 in Aging and Neurodegenerative Diseases

Astrocytes, TGF-β1 and Aging

The aging in mammals is accompanied by a decline in cognitive function. Although the cellular and molecular mechanisms responsible for the age-related cognitive decline are not completely understood, evidence suggests that these alterations are mainly due to synaptic deficits, especially in the hippocampal formation and prefrontal cortex [197, 198]. Although age-related neuronal death has also been described in human, nonhuman primates and rodents [199–201], several studies suggest that the synaptic dysfunction and/or reduction in spine density and stability precede this event in different brain regions of rodents [202–205] and monkeys [206].

Moreover, another important characteristic of aging is a chronic, low-grade, and systemic inflammation referred as "inflamm-aging," a notable risk factor for morbidity and mortality in elderly people [207]. Inflamm-aging may be a result of different mechanisms, such as: (1) the aging immune system (immunosenescence), which is the age-related dysregulation of the innate immune system; (2) the endogenous host-derived cell debris that accumulate over the course of aging, inducing a persist inflammation; (3) an increased activity of the coagulation system and fibrinolysis, leading to a higher risk of thrombosis in elderly people; (4) cellular senescence, which results in cell dysfunction and secretion of several pro-inflammatory cytokines, namely senescence-associated secretory phenotype (SASP) [208]. Despite these facts, a possible interplay between inflamm-aging and synaptic deficits during aging has not been investigated.

Within this context, glial cells emerge as key targets for understanding the underlying mechanisms of age-related synaptic dysfunction/loss and neuroinflammation, since they play a preponderant role in synapse formation, maintenance and pruning, as well as being notable components of the inflammatory environment, characteristic of aging.

Astrocytes and microglia acquire a reactive phenotype during aging. Astrocytes show upregulation of the GFAP content and become hypertrophic, with enlargement of cell body, surface and volume upon aging [209–212]. Moreover, evidence has shown that aging astrocytes exhibit a more inflammatory phenotype, with increased expression and secretion of pro-inflammatory molecules, and downregulation of genes related to antioxidant defense compared to young astrocytes [6, 213, 214]. Likewise, microglial cells undergo notable morphological and metabolic alterations with aging, characterized by reduced arborization [215], the presence of lipofuscin granules and a dual inflammatory profile represented by increased expression levels of both pro-inflammatory, such as TNF-α, IL-1β and IL-6, and anti-inflammatory, such as IL-10 and TGF-β1, cytokines [216].

The interaction between astrocytes and microglia plays a fundamental role in brain homeostasis. It has been shown that under an inflammatory stimulus, microglia cells secrete IL-10, which induces astrocytes to produce TGF-β, that, in turn, acts on microglia controlling its pro-inflammatory response [217]. However, with aging, astrocyte-microglia communication seems to be disrupted and fail in controlling neuroinflammation. One of the mechanisms behind this event may be the impaired induction of TGF-β by astrocytes, leading to an uncontrolled activation of microglial cells in aged animals. In fact, it was reported that following an in vivo lipopolysaccharide (LPS) immune challenge, aged astrocytes presented a differential molecular signature associated with a reduced responsiveness to microglial IL-10, which in turn reduces TGF-β secretion by astrocytes [218].

It is interesting to note that astrocyte-microglia interactions in aging may affect not only microglial activation, but also the astrocytic activation itself. It has been reported that pro-inflammatory microglia secrete IL-1α, TNF and C1q, and these molecules in turn induce astrocyte activation, converting them to a neurotoxic reactive phenotype (called A1 astrocytes) [40]. In fact, it was observed an enrichment of A1 reactive astrocytes in the hippocampus and striatum of aged mice. As it will be discussed later, in this review, this phenotype was also upregulated after an LPS immune challenge in experimental models and in AD human brains [40]. In contrast, aged mice that lacked the microglial-secreted cytokines IL-1α, TNF and C1q had a reduced number of A1 astrocytes, suggesting that microglia induce astrocyte activation in aging through secretion of cytokines and complement cascade molecules [6].

Within this context, astrocyte and microglia activation during aging may be a strong contributor for the sustained neuroinflammation characteristic of this process. It is interesting to note that although increased levels of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α are biomarkers of aging [207], several evidences have pointed that increased levels of anti-inflammatory cytokines, particularly TGF-β, are also present over the course of aging, including in animal models and human tissue [219–221].

TGF-β signaling is higher in the brains of aged animals and upregulated after stroke in both young and aged mice [219]. Likewise, increased hippocampal levels of TGF-β1 have been

reported in adult mice compared to young ones [220]. In agreement, elevated levels of TGF-β1 were present in the hippocampus from postmortem human brain tissue with aging [221]. On the other hand, there was no change in the expression of TGF-β1–3 in aging astrocytes isolated from the cerebral cortex [213], visual cortex, motor cortex and hypothalamus [32]. It is noteworthy that the differences in the expression of TGF-β observed across studies might be related to the brain region and cell type analyzed. Moreover, the expression profile may not directly reflect the level and secretion of TGF-β. Interestingly, an in vitro study showed that cultured hippocampal astrocytes from adult rats presented higher pro-inflammatory response, decreased secretion of growth factors, such as GDNF and BDNF, but increased secretion of TGF-β1, compared to cultured astrocytes from young rats [222]. Despite these data, it is still unclear what is the role of increased levels of TGF-β1 during brain aging.

As mentioned before, another feature of aging is the synaptic dysfunction and loss. Recent data suggested that the involvement of astrocytes in age-related synaptic deficits may be related to an upregulation of inflammatory mediators and synapse elimination. It was demonstrated that astrocytes isolated from the hippocampus and striatum of aged mice showed an upregulation of phagocytic genes involved in synapse elimination, such as Megf10, as well as the complement cascade genes C4b and C3 [6]. These two genes have also been shown to be upregulated in aged astrocytes from the cerebral cortex, hypothalamus and cerebellum [32].

On the other hand, conflicting results are related to the genes involved in synapse formation and function. While the expression of some of these genes was increased in aged astrocytes from the hippocampus and striatum, such as Sparc and Sparcl1, most of the genes did not change upon aging within these regions [6]. Similarly, there was no change in the expression of TGF-β1-3 in aging astrocytes isolated from the cerebral cortex [213], visual cortex, motor cortex and hypothalamus, except for TGF-β2 in the aged cerebellum [32]. However, it is noteworthy that most of these known synaptogenic factors are secreted molecules, and therefore, their expression profile may not directly reflect their status of secretion by astrocytes. Moreover, it is relevant to point that astrocytes can also control synapses through the expression of adhesion molecules, such as γ-protocadherins [223, 224] and, therefore, a more complete view on astrocyte capacity in regulating synapse formation and function in the context of aging should also include an investigation of these molecules.

Altogether, these data raise many intriguing questions: (1) Is the increased level of TGF-β1 a compensatory mechanism in response to the pro-inflammatory environment and synaptic deficits/loss present in the aged brain?; (2) What is the role of TGF-β1 within this context?; and (3) Which cell type is the main source of TGF-β1 under the aging process? Answering these questions will not only provide new insights into the cellular and molecular mechanisms involved in aged-related cognitive decline and the pathogenesis of age-related diseases, but it might also shed light for the development of TGF-β based new therapeutic strategies to prevent and/or treat the harmful side of the brain aging process.

Astrocytes and TGF-β1 in Alzheimer's Disease

Alzheimer's disease (AD) is the principal cause of dementia in the aging population and one of the most costly health conditions worldwide. The clinical condition is characterized by a subtle decline in episodic memory, followed by a more general decline in cognitive abilities, such as the inability to remember the recent past, followed by a loss of long-term memory, a change in personality, and a loss of other cognitive functions, including language and attention [225].

Histopathologically, the disease is characterized by the presence of aggregates of β-amyloid peptide (Aβ) extracellular deposits (plaques) in the patients' brains, as well as by the presence of the phosphorylated cytoskeletal protein tau, which results in the formation of intracellular neuronal tangles. Although the Aβ peptide was suggested to be the initiating factor in AD, which led to the "amyloid cascade hypothesis" [226], subsequent work described the soluble oligomers of Aβ (AβO) as the toxic species responsible for initial anomalies associated with AD. These cellular and molecular deficits include abnormal dendritic spine morphology, altered composition of synaptic receptors, synaptic loss [227], reactive oxygen species formation [228], tau protein hyperphosphorylation [229], prolonged LTD [230], inhibited LTP and cell death [231].

Interestingly, it has been shown that glial changes may precede the characteristic histopathological alterations of AD. In particular, astrocyte morphological and functional changes seemed to be directly related to the synaptic deficits and loss that accompanied the early stages of AD [232]. In two transgenic mouse models of AD (3xTg-AD and PDAPP-J20), an astrocyte atrophy characterized by a reduction in the number of cellular processes and a shrinkage of astroglial domain in different brain regions has been observed [233–236]. These alterations persist into the later stages of the disease, and the astrocyte atrophy seemed to be exclusive to those cells localized distant from the neuritic plaques, whereas astrocytes surrounding the plaques were highly hypertrophic [233, 234]. In agreement with these findings, our group has shown that an astrocytic atrophy, comprising reduced number of processes, decreased cell area and lower GFAP content, also occurred in another AD mouse model induced by the i.c.v. injection of AβO [39].

Astrocyte changes also undermine the neurovascular coupling in the early stages of AD [237]. In arctic β-amyloid (arcAβ) mice, an AD mouse model characterized by extensive vascular lesions, there was a retraction of astrocyte endfeet as

well as reduced levels of GLUT1 and lactate transporters in the early stages of pathology [238]. Moreover, alterations in the distribution and levels of aquaporin 4 (AQP4), which is the main astrocytic transporter in a neurovascular unit, in perivascular astrocytes have also been observed in arcAβ and 5XFAD mouse models [239, 240].

It is noteworthy that the loss of astrocyte morphological complexity might impair the synaptic coverage by these cells, thus affecting synaptic function and plasticity in the early stages of AD. However, the mechanisms underlying glial and synaptic dysfunction remain unclear. On the other hand, several lines of research have characterized the cellular and molecular mechanisms that occur in the later stages of AD when Aβ plaques begin to form.

Transcriptome analysis of astrocytes isolated from APPswePS1dE9 double-transgenic AD mouse model aged 15–18 months revealed that these cells were more reactive than those isolated from wild-type mice and expressed higher levels of GFAP and pro-inflammatory cytokines. In addition, they displayed reduced levels of important genes involved in neuronal support and communication, suggesting that the astrocyte dysfunction and inflammation strongly contributes to AD [241].

In fact, inflammation plays a critical role in the pathogenesis of degenerative diseases such as AD. AD is characterized by reactivity of glial cells, microglia and astrocytes that surround β-amyloid plaques, which showed an increase in the expression and secretion of pro-inflammatory modulators, such as IL-1β, IL-6, TNF-α and nitric oxide, and a reduction in the production of the anti-inflammatory cytokines TGF-β and IL-10 [242].

Glial activation has been considered an endogenous defense mechanism against plaque deposition, while on the other hand, persistent activation and associated inflammation may also contribute to AD progression [243]. Thus, the contribution of astrocytes in AD, i.e., whether it is beneficial or harmful, is still a controversial issue. Several lines of evidence suggest that cytokines produced during the inflammatory process, such TGF-β1, may contribute to the development of AD, either initiating or exacerbating the Aβ deposit [244].

The involvement of TGF-β1 in AD has been subject of controversy. Here, we will discuss the main findings that suggest the association of this molecule with early or late events in the progression of the pathogenesis of this disease, as well as its beneficial or detrimental role in the progression (Table 1).

One of the first reports in the literature that associated alterations in TGF-β levels with AD in humans was described more than 20 years ago by Chao et al. [245]. This group reported elevated TGF-β1 levels in both cerebrospinal fluid and serum samples from patients with AD, shortly after death. In addition, serum TGF-β1 levels were also markedly elevated prior to patient death. In this study, the authors suggested that elevated levels of TGF-β1 in AD might have represented a protective response against neuronal death observed in the later stages of the disease. This increase in the levels of TGF-β in the cerebrospinal fluid of AD patients was later confirmed [246]. In another study, however, Mocali et al. found a reduction in the levels of total and cleaved (active) forms of TGF-β1 in the plasma of patients with AD [247]. This discrepancy might be due to the evaluation of the levels of this cytokine in distinct stages of AD, which sometimes it is difficult to determine due to the lack of the patients' clinical histories.

Flenders and coworkers observed an increase in the levels of TGF-β2 in autosomal dominantly inherited AD with linkage to 14q24.3 patients (FAD-14). In contrast, levels of TGF-β1 and TGF-β3 were not altered in the brain of these patients, suggesting a heterogeneity of response of these cytokines in genetic cases of AD as well as in the later stages of AD [248]. Corroborating this study, TGF-β2 levels were significantly increased in the temporal cortex of patients with AD or dementia with Lewy bodies, but not in PD. TGF-β2 also correlated with neurofibrillary tangles formation, Lewy bodies, severity of dementia and soluble Aβ42 concentration, but not with scores on neuritic plaques or total Aβ42 [249]. These results corroborate the findings that suggest the involvement of the increase in TGF-β2 levels with Aβ peptide uptake and toxicity [250, 251]. In addition to this finding, a recent in vitro study identified that hippocampal astrocyte cultures from AD transgenic animals (3xTg-AD) showed an increase in TGF-β2 and TGF-β3 levels, with no change in levels of TGF-β1. Treatment of astrocyte cultures with AβO resulted in a downregulation of TGF-β1 and an upregulation of TGF-β2 and TGF-β3 that led to a decreased synaptogenic potential of these astrocytes [252]. These results suggest that members of the TGF-β family might play distinct roles in the synaptic dysfunction observed in AD.

It is noteworthy that TGF-β3 has been described as a soluble astrocytic factor that regulated the complement-dependent synaptic refinement process mediated by microglia in the developing CNS [36]. Recently, the same group demonstrated that the complement molecule, C1q, and microglia were associated with early synapse loss and LTP impairment in the hippocampus induced by AβO [253]. It remains to be investigated, however, if astrocytic TGF-β3 is associated with regulation of neuronal C1q and synaptic deficits mediated by the activation of the complement pathway in early stage models of AD. Interestingly, increases in TGF-β3 and neuronal C1q levels in AD have been reported [254]. Furthermore, inhibition of C1q, C3, or the complement receptor of microglia (CR3) reduced the number of phagocytic microglia as well as the extent of early synapse loss in this pathology [253]. Supporting this hypothesis, it was observed that activated microglial cells secrete TNF-α, IL-1-β and C1q, which induced the transformation of healthy astrocytes into A1-type

Table 1 Summary of the controversial effects of TGF-β1 and its signaling in different animal models of Alzheimer's disease

Modulation of TGF-β1 signaling	Animal models	Mechanism of action	Type of AD phenotype	Reference
Overexpression of TGF-β1	hAPP/TGF-β1 mice line T64	Astrocyte overexpression of TGF-β1 accelerated the Aβ deposition	2–3 months	Wyss-Coray et al., 1997
Increased TGF-β1 levels	hAPP T64	No effect in Aβ deposition	2–3 months	
Overexpression of TGF-β1	GFAP-TGF-β1 line T65	Astrocyte overexpression of TGF-β1 potentiates a Aβ production and may enhance the formation of plaques burden in the brain	6 months	Lesne et al., 2003
Overexpression of TGF-β1	TGF-b1 line T64 heterozygous mice (T64−/+)	Overexpression of TGF-β1 induced perivascular astrocytosis and accumulation of vascular basement membrane proteins	3–4 months	Wyss-Coray et al., 2000
		Increase the amyloid deposition	6–9 months	
		Abnormalities in brain capillaries area	9 months	
Overexpression of TGF-β1	APP/GFAP-apoEKO 12 + TGF-β13 OP-AAV mice	Overexpression of TGF-β1 induce Aβ accumulation, amyloidogenesis of APP and astrogliosis	12 months	Zheng et al., 2017
Overexpression of TGF-β1	hAPP and hAPP/TGF-$\beta1^{Low}$ TGF-$\beta1^{Low}$	Astrocyte overexpression of TGF-β1 reduces amyloid plaque burden and inhibits Aβ accumulation in brain parenchyma due to increased microglial phagocytic activity	12–15 months	Wyss-Coray et al., 2001
Signaling blocking	Tg2576	Inhibition of TGF- β signaling in peripheral macrophages significantly reduced the presence of amyloid plaque, as well as the cognitive performance	17–18 months	Town et al., 2008
Signaling blocking	TβRIIΔk/Pmp-tTA/hAPP	Reducing neuronal TGF-β signaling in mice resulted in age-dependent neurodegeneration and promoted Aβaccumulation and dendritic spine loss in mouse model of AD	20 months	Tesseur et al., 2006
Signaling blocking	Aβ injection in rat	Pharmacological blockade of TGF-β1 signaling amplifies Aβ toxicity in the rat dorsal hippocampus	10 days after injection	Caraci et al., 2008
Increased the TGF-β1 levels	Aβ injection in rat	TGF-β1 administration after the Aβ injection ameliorated cognitive deficit and neuronal loss and apoptosis, reduced APP expression and neuroinflammation	10 days after injection	Shen et al., 2014
Increased the TGF-β1 levels	Aβ injection in rat	TGF-β1 administration before and after Aβ injection prevented neurodegeneration, proinflamatorion mediators and loss of neurotrophic factors	7 or 10 days after injection	Chen et al., 2015
Increased the TGF-β1 levels	Aβ injection in mice	Pre-administration of TGF-β1 prevents synapse loss, memory and astrocyte atrophy	24 or 48 hours after injection	Diniz et al., 2017

astrocytes, i.e., a neurotoxic phenotype, which were enhanced in the brains of AD patients [5, 40].

Thus, the characterization of the levels and the signaling pathways of the TGF-β family members during healthy aging as well as the in different stages of AD is critical and might have a great impact on the development of new biomarkers and the identification of new pharmacological targets. Furthermore, since the TGF-β pathway plays an important role in microglia-synapse-astrocyte interactions in the healthy and injured brain, this would contribute to elucidating the role of these cells in synapse loss and cognitive impairment in AD.

Although the involvement of the members of the TGF-β family has been a matter of controversy, the discussion around TGF-β1, specifically, is even more difficult.

Since inflammation is a common mechanism underlying neurodegenerative diseases, it seemed likely that an increase in TGF-β1 levels would be a common mechanism between them. However, this seems not to be the case, since increases in TGF-β1 levels were not found in the CSF of patients with amyotrophic lateral sclerosis, spinocerebellar degeneration or multiple system atrophy [255], thus suggesting that the increase of TGF-β1 in CSF is a biomarker of the later stages of AD.

Since 1997, a series of studies from Wyss-Coray has suggested that the increase in TGF-β1 levels in AD directly contributes to the onset and progression of the disease. Overexpression of astrocytic TGF-β1 along with amyloid precursor protein (APP) has been shown to result in mice with an Alzheimer-like phenotype due to accelerated β-amyloid peptide deposition [256]. One of the mechanisms by which TGF-β1 exerted this toxic effect, i.e., enhanced amyloid deposition, would be through the regulation of APP specifically in astrocytes and by the subsequent increase of Aβ peptide formation [257]. Cerebrovascular amyloid deposition and microvascular degeneration are frequently associated with AD, but the etiology and pathogenic role of these abnormalities were unknown. Mice that overexpress TGF-β1 in astrocytes had cerebrovascular anomalies and degeneration, as well as an accumulation of vascular basement membrane proteins, which was a phenomenon also observed in transgenic animals models for AD [258]. Microvessels from patients with AD showed increased levels of TGF-β1, and in addition, treatment of ECs with exogenous TGF-β1 induced an inflammatory response that suggested a contribution of TGF-β1 to the neuroinflammatory scenario of AD [259].

The current idea is that healthy aging depends on successful interactions between neural cells that ultimately maintain functional synapses. It is therefore conceivable that impairments in these interactions are associated with the cognitive decline observed in AD. Interestingly, several genetic factors that increase the risk for the development of AD have been described and include APP, presenilin 1, presenilin 2, and ApoE. Those factors are not exclusively expressed by neurons but also, if not predominantly, expressed by astrocytes [241] supporting the idea that astrocytes are important agents in the pathogenesis of AD.

Astrocytes are the main source of apoE in the nervous system, and apoE is involved in the clearance and accumulation of Aβ, which leads to amyloid plaque formation and onset of AD [260, 261]. It has recently been shown that the deletion of apoE specifically in astrocytes (APP/GFAP-apoEKO) significantly improved spatial learning and memory deficits, reduced β-amyloid protein production, and ameliorated astrogliosis in animal models for AD by inhibiting TGF-β/Smad2/STAT3 signaling. In contrast, TGF-β re-expression in these mice (APP/GFAP-apoEKO) abrogated the beneficial effects of the conditional deletion of apoE, suggesting crosstalk between the TGF-β signaling and the toxicity promoted by apoE [262].

A series of controversial data on the role of TGF-β1 in AD has been reported, and the discrepancies may be due to the different animal models used as well as the stage of pathology evaluated. Aged mice expressing human β-amyloid precursor protein (hAPP) had increased levels of astrocytic TGF-β1 that led to a reduction in the number of parenchymal amyloid plaques and dystrophic neurites. These increased levels were mostly due to increased microglial phagocytic activity that promoted the clearance of β-amyloid plaques [263]. Unlike these results, genetic inhibition of the canonical signaling of TGF-β and Smad2/3 in peripheral macrophages significantly reduced the presence of amyloid plaque, as well as enhanced cognitive performance in a mouse model of AD [264].

Additional research supported the concept that early dysfunction of TGF-β1 signaling may be a trigger for aggregation and toxicity of Aβ in neurons, as well as loss of the physiological function of this cytokine, which regulated survival, maturation, and synaptogenesis [35, 61, 62, 265, 266]. Tesseur et al. reported that decreased TGF-β1 signaling was associated with increased Aβ peptide deposition and enhanced neuronal degeneration in AD transgenic mice [267]. This study was pioneering in the establishment of a correlation between TGF-β1 signaling dysfunction and increased age-dependent neurodegeneration and progression of AD, and it suggested that the rescue of neuronal TGF-β signaling might be an alternative therapy to constrain the neurodegeneration in AD.

Knockout mice for TGF-β1 have defects in angiogenesis and vasculogenesis, in addition to the reduction of synaptic density, number of neurons and a generalized microgliosis. Heterozygous mice ($Tgfb1^{-/+}$) that had normal life expectancy had increased susceptibility to excitotoxic injury and neurodegeneration, whereas transgenic overproduction of TGF-β1 prevents degeneration after excitotoxic injury. This work was pioneering in demonstrating that the alteration of TGF-β1 levels has important implications for susceptibility to neurodegeneration [56].

Within this line of evidence, it has been reported that there was a reduction in TβRII expression [267] and deficits in the Smad downstream pathway in the brains of AD patients [268, 269]. Hippocampal neurons of AD patients had increased levels of activated Smad2 [270], along with an accumulation of phosphorylated Smad2/3 [268] in the neuronal cytoplasm instead of being translocated to the nucleus where they can regulate gene expression [270, 271]. It is believed that tau hyperphosphorylation was involved in the inadequate cytoplasmic localization that impaired Smad-TGF-β signaling [272].

In favor of a beneficial role for TGF-β1 against Aβ peptide toxicity, several in vitro and in vivo studies reported a neuroprotective function of this cytokine in AD models. Exogenous application of purified TGF-β1 protected hippocampal neurons against toxicity induced by the Aβ peptide [273, 274]. Treatment of glial cultures with estrogen or the antidepressant fluoxetine, which induced an increase of astrocytic TGF-β1 secretion, prevented Aβ-induced neurodegeneration in glial-neuron coculture models [275, 276].

Confirming these in vitro data, Caraci et al. demonstrated that PI3K activation by TGF-β1 prevented degradation of β-catenin and hyperphosphorylation of tau, resulting in greater neuroprotection. In addition, this study demonstrated that pharmacological blockade of TGF-β1 signaling amplified Aβ toxicity in the dorsal rat hippocampus [277]. Subsequent to this work, two in vivo studies from the same group demonstrated that i.c.v. injection of TGF-β1 protected mice from several deficits (e.g., cognitive impairment, neuronal death, and glial activation) induced by Aβ1–42 [278, 279].

TSP, one of the first described astrocyte-derived synaptogenic molecule, is an important physiological activator of the latent form of TGF-β [280, 281]. Deficiency in the production of TGF-β1 and TSP is reported in experimental models for AD. Although these molecules are mostly secreted by astrocytes and regulate synapses formation throughout development, studies are needed to identify a crosstalk of the mechanism of action of these molecules as well as their neuroprotective potential. In 2013, Rao et al. demonstrated that Aβ reduces the secretion of TSP suggesting that astrocytic synaptogenic loss is directly related to Aβ-induced synaptic loss in cultured hippocampal neurons [282]. Corroborating this finding, recently, Song and colleagues have elegantly demonstrated that TPS is reduced in the brains of AD patients [283]. In addition, they demonstrated that transgenic animals for AD present reduced levels of TSP and other important synaptic proteins. Further, they found that astrocytes had impaired secretion of TSP, thus leading to reduced ability to regulate the formation of new synapses, which could explain the synaptic deficits observed in transgenic animals [283].

Our group showed that i.c.v. injections of TGF-β1 prevented the deleterious effects of β-amyloid oligomers (AβO) on synapses and memory in mice [39]. Although it is well known that astrocytes participate in the clearance of Aβ plaques, the interactions between AβO and astrocytes and their binding sites and receptors are still unknown. We found that AβO interacted with and were internalized by astrocytes, which triggered a cascade of toxicity that resulted in increased levels of reactive oxygen species and nitric oxide. In addition, AβO caused astrocytic atrophy, characterized by a loss of cell area and processes. Finally, we found that although astrocytes exhibited neuro- and synaptic-protective properties, exposure of astrocytes to AβO reduced their synaptogenic and neuroprotective capacity. This event was associated with decreased production of TGF-β1 by astrocytes, in vivo and in vitro, in response to AβO. In addition, we have shown that the exogenous addition of TGF-β1 prevented Aβ-induced synaptic damage in vivo, suggesting that increased astroglial production of TGF-β1 may provide a useful strategy for the treatment of the early stages of AD (Fig. 4) [39].

Outcomes: Implications for Novel Therapeutic Targets

The understanding about glial cell function in brain development and disease has been extensively challenged in the last decade. This research area has clearly benefited from the emergence of novel technological tools to study glial cells, including proteome/transcriptome analysis, generation of iPS-derived glial cells from patients with neurological disorders, identification of new molecular markers and the production of antibodies against them and ultimately, the development of new techniques to efficiently isolate glial cells from animal and human tissues. This work resulted in the characterization of many new functions of glial cells and the identification of the mechanisms and molecules underlying these events. Here, we have summarized many studies that contributed to change the old concept of the passive glia described by Virchow nearly a century ago to the current understanding of astrocytes' functions. We argued that understanding how astrocytic signals, such as TGF-β1, regulate brain function might offer new insights into human learning, memory, and cognition, and ultimately, these insights may provide new targets for the treatment of neurological diseases.

The fact that human astrocytes are morphologically and functionally distinct from those of other mammals [11, 284, 285] suggests the question of whether the increase in the complexity of human astrocytes is associated with prominent roles in the modulation of neural circuits. On the other side, one might argue that dysfunctions or phenotypic alterations in astrocytes would greatly impact human brain development. This idea is strengthened by several observations that astrocyte dysfunctions are associated with several pathologies [5, 39, 286–288]. Whether glial dysfunction is the primary deficit or a consequence of neuronal damage remains to be investigated for each pathology.

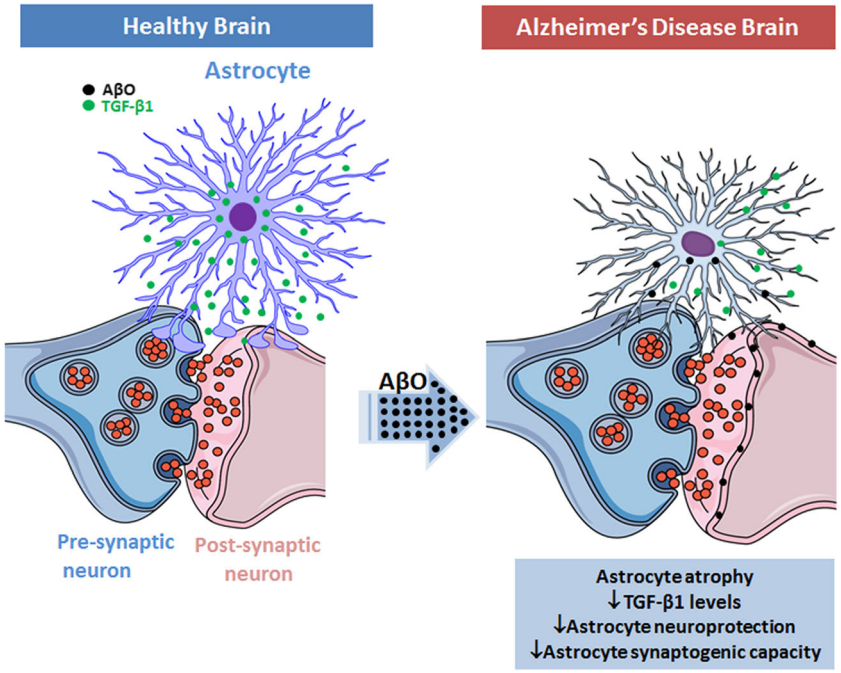

Fig. 4 AβO decreases levels of astrocytic TGF-β1 and its neuroprotective and synaptogenic effect. In a physiological situation, astrocytes contact neurons and secrete several molecules, such as TGF-β1, that promote synaptogenesis and protect neurons from the binding of AβO. In the presence of AβO, there is cellular atrophy, reduced levels of TGF-β1 and decreased synaptogenic astrocyte capacity. This fact affects the ability of astrocytes to protect neurons against the binding and deleterious actions of AβO in the synapses

An elegant study from the group of Maiken Nedergaard and Steven Goldman provided the first in vivo evidence of the involvement of human glia in synaptic plasticity, learning and memory. They demonstrated that chimeric mice that received human glia progenitor cells transplanted into their forebrains displayed improved LTP and learning compared to control mice that received murine astrocytes [289]. Furthermore, it was suggested that these effects were associated with increased secretion of TNF-α by human astrocytes [289].

Although a link between glial cells and cognitive dysfunction might support the relevance of human astrocytes in the unique cognitive abilities of humans, our understanding of the role of human glia in synapse formation and function is relatively new and incomplete. Furthermore, considering the enormous genetic variability in humans, whether the mechanisms underlying these features are consistent or variable within the human species remains to be investigated. Future studies are needed to better address these questions and to elucidate the contribution of astrocytes to the function of the human nervous system and to the susceptibility to neurological disorders.

Recently, the concept that the glial expression profile is strongly associated with brain function has been reinforced by the demonstration that glial-specific genes predict age with greater precision than neuron-specific genes [201]. Soreq et al. had undertaken an elegant and extensive characterization of aging-altered gene expression changes across ten brain regions from 480 individuals ranging in age from 16 to 106 years. They showed that astrocyte- and oligodendrocyte-specific genes, but not neuron-specific genes, shifted their regional expression patterns with aging, particularly in the hippocampus and substantia nigra, which are two main regions involved in neurodegenerative diseases. Thus, the data suggested that astrocyte phenotype/differentiation is strongly associated with neuron-glia interactions in aging and late-life diseases.

Despite the great advance the glial field has undergone in the past decades, there are still many unanswered questions about glial biology: (1) *Is astrocyte functional diversity maintained under pathological conditions?* (2) *Does astrocytes' communication impact synaptogenesis?* (3) *How regionally-specific are astrocyte responses to physiological and pathological events throughout the brain?* (4) *Does signaling diversity exist in different subpopulations of astrocytes regarding their interactions with other units, such as neurons, synapses and the vasculature?* Answers to these questions would certainly provide a better understanding of glial biology and of neuron-glia interactions during brain development and aging. Given the implications for astrocyte/TGF-β signaling dysfunction in human brain disorders, as discussed in this review, answering these questions will be of fundamental importance for our understanding of the mechanisms underlying astrocyte interactions, and ultimately, for developing astrocyte-based therapeutic strategies for the treatment of neurological diseases.

As discussed in this review, several synaptogenic molecules have been shown to be secreted by human astrocytes that control synapse formation and neural circuit function including TSP-1 [290], TNF-α [289], and TGF-β1 [62, 291]. The fact that some of these molecules, e.g., TGF-β1 as described here, or their downstream pathways are decreased in

neurological diseases might open a new venue to explore new targets for brain disease in humans. Recently, our group has demonstrated that the flavonoid hesperidin enhances the synthesis and signaling of TGF-β1, leading to increase in hippocampal glutamatergic synapses density and memory in mice [292]. In addition to these data, Caraci's group has investigated drugs/molecules that increase the expression or release of astrocytic TGF-β1: agonists of group II metabotropic glutamate receptor (mGlu), antipsychotic drugs (such as lithium), antidepressant drugs (such as specific inhibitors of serotonin reuptake) and TGF-β1 itself [278, 293, 294] (for more details see Caraci review [295]). Although depression is considered a high risk factor for the development of AD and those results might be promising, they have been shown to be contradictory [296]. Mainly to the lack of a deep understanding of the mechanism underlying the action of these drugs in early disease, which precedes the formation of β-amyloid plaques and neuronal death.

Since impaired levels of TGF-β1 and its signaling are important features in neuronal deficits, the use of drugs that rescue these conditions arises as an important pharmacological strategy to halt the onset and progress of AD. Identification of such molecules/drugs and their mechanisms of action could help to elucidate the synaptogenic properties of human astrocytes and to design potential therapeutic screens for identifying target glial molecules.

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