

## REVIEW

## Astrocytes – friends or foes in neurodegenerative disorders

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### Abstract

Astrocytes (AS) are the most abundant glial cells in the central nervous system (CNS). They have various morphologies and numerous (50–60) branching prolongations, with roles in the maintenance of the CNS function and homeostasis. AS in the optic nerve head (ONH) have specific distribution and function and are involved in the pathogenesis of glaucoma and other neural diseases, modify their morphologies, location, immune phenotype, and ultrastructure, thus being the key players in the active remodeling processes of the ONH.

**Keywords:** astrogliosis, glaucoma, optic nerve head.

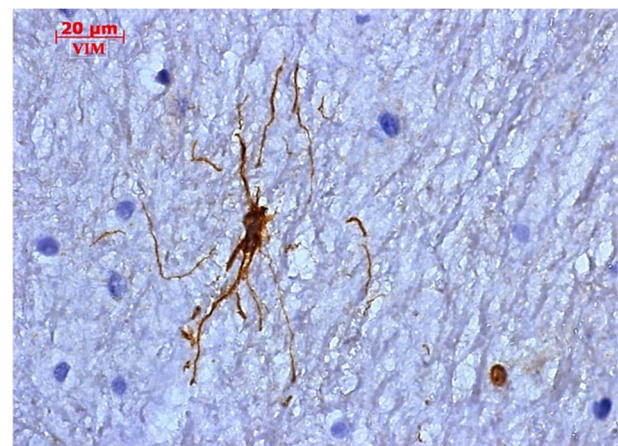
### ☞ Distribution and morphology of astrocytes

Many biologists consider astrocytes (AS) and oligodendrocytes as main glial cells of the central nervous system (CNS), while microglia, due to their erythromyeloid origin is grouped with other phagocytic cells [1].

AS play a variety of roles in the nervous system, including providing structural support, nutrients, and energy for neurons, maintaining the chemical environment of neurons, and helping to repair damage to the nervous system. AS help to maintain the chemical balance in the extracellular environment, which is crucial for normal neuronal function. Hence, AS remove excess neurotransmitters from the synaptic cleft, helping to regulate neurotransmission. They also play a role in the formation and maintenance of the blood-brain barrier (BBB), which helps to protect the brain from harmful substances in the bloodstream. AS can respond to changes in neuronal activity by contracting or expanding their processes, which can help to regulate blood flow to the neural tissue. Without AS, neurons would be unable to function properly.

AS are found in all regions of the brain, including the cerebrum, cerebellum, and brainstem. They are also found in the grey matter and white matter of the spinal cord, but are also present in retina, epiphysis, and neurohypophysis [2–4]. There are numerous subtypes of AS [2, 3, 5, 6]. AS have a distinctive shape and structure. They are typically star-shaped, with multiple processes (or branches) extending out from the cell body. These processes are often long and thin and can be highly branched. AS present a high number of intermediate filaments, which give them a characteristic “starry” appearance under the microscope. In addition, AS have a high number of mitochondria, which

provide them with the energy they need to perform their functions. The fibrous AS are distributed along white matter tracts of the CNS and have numerous intermediate filaments [7, 8]. From the stellate cellular bodies of these fibrous AS emerge long, thin, and straight processes (Figure 1) [2]. The protoplasmic AS which reside in the grey matter of the CNS have fewer glial filaments [7] and ovoid or irregular cellular bodies with numerous, short, dichotomized processes [9, 10]. Bergmann glial cells or epithelial glial cells are AS with long processes located in the granular layers of the cerebellar cortex [4]. Interlaminar AS are specific for humans and primates, the same as AS with varicose projection [8, 11–13]. Müller glial cells are radial AS uniformly distributed in the retina [14].



**Figure 1 – Vimentin-positive astrocyte within a white tract of human medulla oblongata.**

Various intermediate filaments in AS influence their morphology, thereby AS lacking glial fibrillary acidic

protein (GFAP) and vimentin have fewer long processes compared to wild-type counterparts [15].

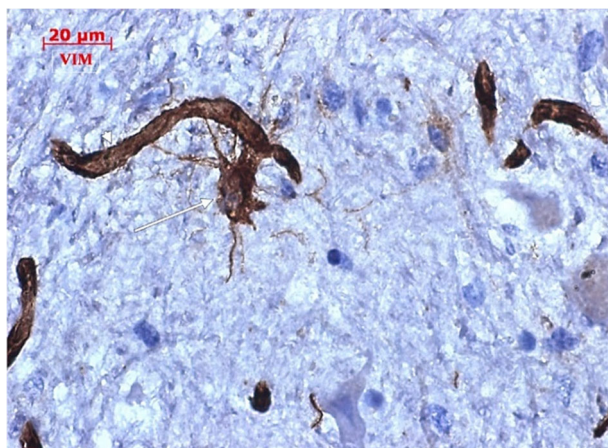
### ☞ Ultrastructure and molecular markers of AS

In transmission electron microscopy, AS are identified by the glial filaments [7]. Ultrastructural features of AS include all types of cytoplasmic organelles, glycogen granules, lipid droplets and intermediate filaments [16]. Mature AS contain scarce microtubules [16].

Most commonly used markers of AS are GFAP and S100 $\beta$  [17–19], although not all AS are GFAP positives [20]. Other useful markers include *N*-myc downstream-regulated gene 2 (NDRG2) [19], caveolin-3 [21], connexin 30 [22], connexin 43 [21] and aldehyde dehydrogenase 1 L1 [23]. Vimentin is an intermediate filament protein that is found in AS and other types of glial cells, but which has been proven indispensable for cell division of immature AS [24]. Aquaporin 4 (AQP4) is a water channel protein that is found in AS and other types of glial cells [25, 26]. AQP4 is often used as a marker for AS in the brain and spinal cord. Recent data suggest that AQP4, besides their feature as a water channel protein, play important neuroimmunological roles by interacting with microglial cells [27]. Nestin is often used as a marker for AS progenitor cells [28].

### ☞ Functions of astrocytes

AS function as regulators of nervous system development [29] and play an important role in synaptogenesis [30], synaptic remodeling, motility, and stability [31]. AS are responsible for glutamate, ion, and water homeostasis [32] required for proper synaptic transmission [2]. AS got endfeet processes containing glucose transporters, receptors and ion channels which are in contact with blood vessels (Figure 2) and synapses [32–34], thus adapting the blood flow upon synaptic activity and delivering the energy from glycogen storage granules for intense neuronal activity or in hypoglycemia [2, 35]. AS adjust the neuronal activity by releasing adenosine triphosphate (ATP), glutamate [8] and D-serine [36]. In *medulla oblongata*, AS act as respiratory chemoreceptors for the arterial brain blood pH [37].



**Figure 2** – A vimentin-positive astrocyte (arrow) within the white matter of medulla oblongata projects thin processes on a neighbor microvessel (arrowhead).

By participating in the formation of the BBB [38] and the glymphatic system [39], AS ensure the CNS maintenance

and prevents the invasion of pathogens [40, 41]. AS are implicated in sleep behavior and cognitive deficits after loss of sleep [42, 43], in learning and memory consolidation [44].

### ☞ Astrocytes and astrogliosis

Astrogliosis is a process in which AS become activated and proliferate in response to injury or disease. Recent research has focused on understanding the mechanisms underlying astrogliosis and its role in various neurological conditions. Studies have shown that astrogliosis can both protect and harm neurons, depending on the specific context. The dysfunction of AS determines *via* astrogliosis numerous neurodegenerative diseases, such as Alexander’s disease, hepatic encephalopathy, Alzheimer’s disease (AD), Huntington’s disease (HD), Parkinson’s disease (PD) and amyotrophic lateral sclerosis [45].

Astrogliosis refers to the large spectrum of reactive AS changes in response to various CNS injuries: cellular and nuclear hypertrophy, elongation of cellular prolongations, increase of GFAP expression, and production of extracellular matrix (ECM) proteins, proliferation, and scar formation [46, 47]. The glial scar prevents the lesions expansion [48]. Reactive AS changes are found in human and animal models of glaucoma and/or traumatic injuries of the optic nerve head (ONH) [49]. In contrast to other CNS regions, in the ONH, inflammatory cells do not participate, and a glial scar does not appear [48].

Although AS activation [50] and consequent astrogliosis [51] have been demonstrated in coronavirus disease 2019 (COVID-19) infection, the pathogenesis, and mechanisms of neuropsychiatric COVID-19 sequela and AS involvement are not yet very clear [41, 52, 53].

Gliosis has been studied using various approaches, including fractal analysis [54] and different animal models, documented in a recent review [55].

### ☞ Astrocytes in the optic nerve head

Glaucoma is an optic neuropathy causing an irreversible and progressive loss of retinal ganglion cells (RGCs) and blinding [56]. Glaucoma is associated with histopathological changes in the *lamina cribrosa* of the ONH, an AS-rich region where the axons of the RGCs are incorporated in the optic nerve (ON) exiting the eye [57].

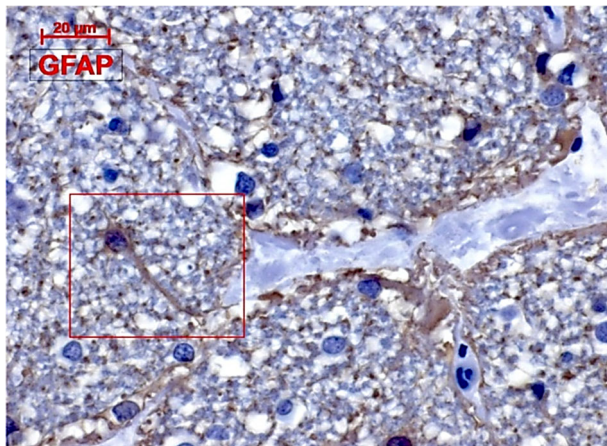
In its intraocular portion, the ON is the narrowest, being nonmyelinated [58]. The ONH comprises four parts: the nerve fiber layer (the most anterior), the prelaminar, laminar, and postlaminar regions (the most posterior). The laminar region indicates the location of *lamina cribrosa* [59]. *Lamina cribrosa*, made from AS and connective tissue, is the protective scaffold for ON in the intraocular portion. AS cover the adventitia of the central retinal vessel inside the ONH and composes a marginal layer, the border tissue of Jacoby. The astroglial layer coating the central retinal vessels intermingles with the inner limiting membrane of Elschnig, a glial layer covering the optic disc [58]. In the prelaminar region, the AS with round cell bodies compose channels traversed by nerve fiber bundles. Collagen and elastin fibers are arranged between the channels formed by AS [59]. AS ensheath axon bundles are scarcely distributed into the nerve bundles and make contact with capillaries [60]. In the *lamina cribrosa*, AS which are also distributed in a columnar manner project thick processes transversely



to the nerve bundles [48, 59]. In the ONH postlaminal region, AS with stellate morphology are located inside the nerve bundles. The AS processes cover the nerve bundles [59].

In contrast with the CNS AS, which have a very pale cytoplasm, the ONH AS cytoplasm is highly electron dense [61]. AS from the ONH are GFAP, neural cell adhesion molecule (NCAM) and vimentin positive [48], although AS from different regions of the CNS express vimentin only in immature or reactive stages [62, 63]. Reactive ONH AS overexpress GFAP due to cellular hypertrophy [48], accompanied by important morphological changes in the *lamina cribrosa* and prelaminar region of ONH: loss of AS cellular processes in the *lamina cribrosa* and elongation and thickening of the processes in the prelaminar portion [64]. In ONH, reactive AS show increased expressions of NCAM, the NCAM-180 isoform being associated with reactive AS from glaucomatous samples [65].

AS of the ONH (Figure 3) are the most important sources for the synthesis of *lamina cribrosa* ECM components [66]. Reactive AS are key players in the ECM remodeling process, for isolating the damaged axons [48]. In glaucoma, AS overexpress ECM proteins: laminin, fibulin, and collagen [67, 68]. In humans and rodents, reactive ONH AS release nitric oxide synthase (NOS) that produces high levels of nitric oxide (NO) [69]. NO mediates glutamate neurotoxicity [70]. Glutamate toxicity triggers mitochondrial alterations and cell death [71]. Recent studies involved the mitochondrial fission in the pathogenesis of glaucoma and other neurodegenerative diseases [72, 73]. Increased intraocular pressure in glaucoma alters axon–ONH AS interactions [74], resulting in axonal dysfunction and retrograde damage of retinal ganglion neurons [2, 75].



**Figure 3** – Human optic nerve. A GFAP-positive astrocyte is presented (inset).

### ☞ Astrocytes involvement in neurodegenerative disorders

AS are thought to play a role in the development and progression of neurodegenerative disorders, such as AD, PD, and HD.

In AD, AS have been shown to contribute to the formation of amyloid plaques and *tau* tangles, which are characteristic features of the disease. AS also have been found to have abnormal levels of certain proteins, including GFAP, which is thought to contribute to the progression of the disease.

In PD, AS have been found to have abnormal levels of certain neurotransmitters and to be involved in the formation of Lewy bodies, which are characteristic of the disease. AS also have been found to contribute to the degeneration of dopamine-producing neurons, which is a key feature of PD.

In HD, AS have been found to contribute to the degeneration of neurons by releasing toxic substances, such as glutamate and reactive oxygen species. AS also have been found to have abnormal levels of certain proteins, including huntingtin, which is thought to contribute to the progression of the disease.

Overall, AS play a critical role in maintaining the health of the brain, and their dysfunction or abnormal activity can contribute to the development and progression of neurodegenerative disorders.

### ☞ Conclusions

As AS appear to play a key role in the etiology of neurodegenerative disorders, a growing interest has arisen for AS-mediated pathways as targets for drugs that aim at treating the root causes of the pathology. Additionally, new findings have suggested that targeting astrogliosis may be a promising strategy for treating neurological conditions, such as AD, traumatic brain injury, and stroke. However, more research is needed to fully understand the complex mechanisms of astrogliosis and to develop effective therapies.

### Conflict of interests

The authors declare that they have no conflict of interests.

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