REVIEW

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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].

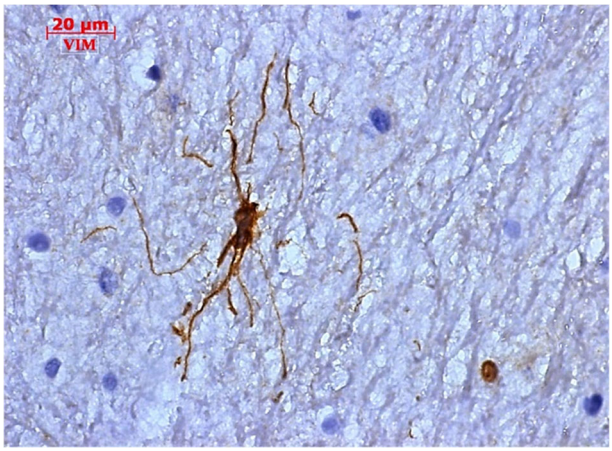

Figure 1 – ***Vimentin-positive astrocyte within a white tract of human medulla oblongata.***

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

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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*β* [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].

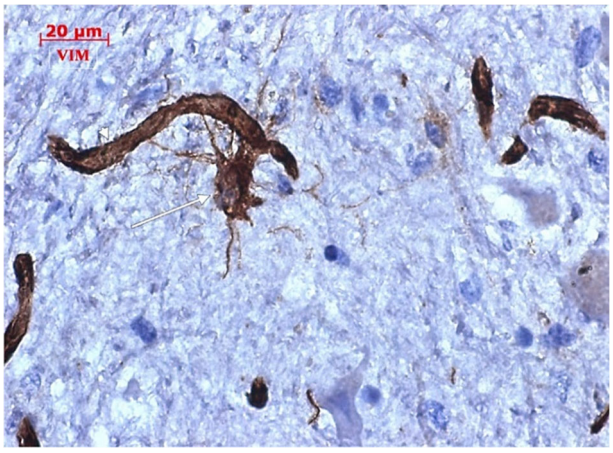

Figure 2 – ***A vimentin-positive astrocyte (arrow) within the white matter of medulla oblongata projects thin processes on a neighbor microvessel (arrowhead).***

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 postlaminar 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].

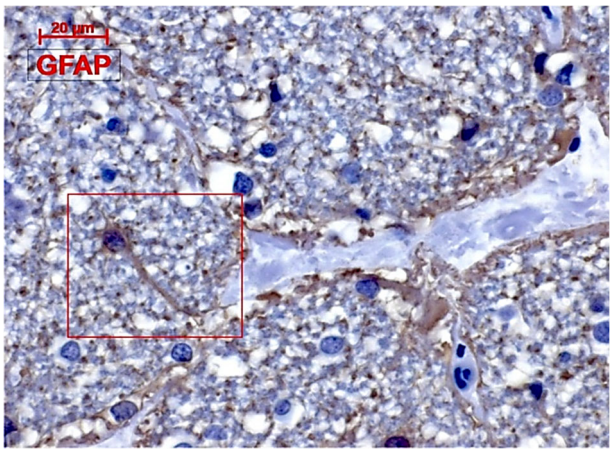

Figure 3 – ***Human optic nerve. A GFAP-positive astrocyte is presented (inset).***

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.

References

[1] Kierszenbaum AL, Tres L. Histology and cell biology: an introduction to pathology. 4th edition, Elsevier Health Sciences–Saunders, Philadelphia, PA, USA, 2015. https://www.worldcat.org/title/926999135

[2] Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol, 2010, 119(1):7–35. https://doi.org/10.1007/s00401-009-0619-8 PMID: 20012068 PMCID: PMC2799634

[3] Kettenmann H, Verkhratsky A. Neuroglia: the 150 years after. Trends Neurosci, 2008, 31(12):653–659. https://doi.org/10.1016/j.tins.2008.09.003 PMID: 18945498

[4] Şovrea AS, Boşca AB. Astrocytes reassessment – an evolving concept part one: embryology, biology, morphology and reactivity. J Mol Psychiatry, 2013, 1(1):18. https://doi.org/10.1186/2049-9256-1-18 PMID: 26019866 PMCID: PMC4445578

[5] Andriezen WL. The neuroglia elements in the human brain. Br Med J, 1893, 2(1700):227–230. https://doi.org/10.1136/bmj.2.1700.227 PMID: 20754383 PMCID: PMC2422013

[6] Emsley JG, Macklis JD. Astroglial heterogeneity closely reflects the neuronal-defined anatomy of the adult murine CNS. Neuron Glia Biol, 2006, 2(3):175–186. https://doi.org/10.1017/S1740925X06000202 PMID: 17356684 PMCID: PMC1820889

[7] Miller RH, Raff MC. Fibrous and protoplasmic astrocytes are biochemically and developmentally distinct. J Neurosci, 1984, 4(2):585–592. https://doi.org/10.1523/JNEUROSCI.04-02-00585.1984 PMID: 6366155 PMCID: PMC6564905

[8] Oberheim NA, Goldman SA, Nedergaard M. Heterogeneity of astrocytic form and function. Methods Mol Biol, 2012, 814:23–45. https://doi.org/10.1007/978-1-61779-452-0_3 PMID: 22144298 PMCID: PMC3506190

[9] Oberheim NA, Wang X, Goldman S, Nedergaard M. Astrocytic complexity distinguishes the human brain. Trends Neurosci, 2006, 29(10):547–553. https://doi.org/10.1016/j.tins.2006.08.004 PMID: 16938356

[10] Volterra A, Meldolesi J. Astrocytes, from brain glue to communication elements: the revolution continues. Nat Rev Neurosci, 2005, 6(8):626–640. https://doi.org/10.1038/nrn1722 PMID: 16025096

[11] Oberheim NA, Takano T, Han X, He W, Lin JHC, Wang F, Xu Q, Wyatt JD, Pilcher W, Ojemann JG, Ransom BR, Goldman SA,

Nedergaard M. Uniquely hominid features of adult human astrocytes. J Neurosci, 2009, 29(10):3276–3287. https://doi.org/10.1523/JNEUROSCI.4707-08.2009 PMID: 19279265 PMCID: PMC2819812

[12] Colombo JA, Reisin HD. Interlaminar astroglia of the cerebral cortex: a marker of the primate brain. Brain Res, 2004, 1006(1): 126–131. https://doi.org/10.1016/j.brainres.2004.02.003 PMID: 15047031

[13] Colombo JA, Yáñez A, Puissant V, Lipina S. Long, interlaminar astroglial cell processes in the cortex of adult monkeys. J Neurosci Res, 1995, 40(4):551–556. https://doi.org/10.1002/jnr.490400414 PMID: 7616615

[14] Reichenbach A, Bringmann A. New functions of Müller cells. Glia, 2013, 61(5):651–678. https://doi.org/10.1002/glia.22477 PMID: 23440929

[15] Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. Glia, 2005, 50(4):427–434. https://doi.org/10.1002/glia.20207 PMID: 15846805

[16] Nag S. Morphology and properties of astrocytes. The blood-brain and other neural barriers: reviews and protocols. Methods Mol Biol, 2011, 686:69–100. https://doi.org/10.1007/978-1-60761-938-3_3 PMID: 21082367

[17] Bignami A, Eng LF, Dahl D, Uyeda CT. Localization of the glial fibrillary acidic protein in astrocytes by immunofluorescence. Brain Res, 1972, 43(2):429–435. https://doi.org/10.1016/0006-8993(72)90398-8 PMID: 4559710

[18] Ludwin SK, Kosek JC, Eng LF. The topographical distribution of S-100 and GFA proteins in the adult rat brain: an immunohistochemical study using horseradish peroxidase-labelled antibodies. J Comp Neurol, 1976, 165(2):197–207. https://doi.org/10.1002/cne.901650206 PMID: 1107363

[19] Zhang Z, Ma Z, Zou W, Guo H, Liu M, Ma Y, Zhang L. The appropriate marker for astrocytes: comparing the distribution and expression of three astrocytic markers in different mouse cerebral regions. Biomed Res Int, 2019, 2019:9605265. https://doi.org/10.1155/2019/9605265 PMID: 31341912 PMCID: PMC6613026

[20] Kimelberg HK. The problem of astrocyte identity. Neurochem Int, 2004, 45(2–3):191–202. https://doi.org/10.1016/j.neuint.2003.08.015 PMID: 15145537

[21] Soares ES, Mendonça MCP, Rocha T, Kalapothakis E, da Cruz-Höfling MA. Are synchronized changes in connexin-43 and caveolin-3 a bystander effect in a *Phoneutria nigriventer* venom model of blood-brain barrier breakdown? J Mol Neurosci, 2016, 59(4):452–463. https://doi.org/10.1007/s12031-016-0749-0 PMID: 27067308

[22] Nagy JI, Patel D, Ochalski PA, Stelmack GL. Connexin30 in rodent, cat and human brain: selective expression in gray matter astrocytes, co-localization with connexin43 at gap junctions and late developmental appearance. Neuroscience, 1999, 88(2):447–468. https://doi.org/10.1016/s0306-4522(98)00191-2 PMID: 10197766

[23] Cahoy JD, Emery B, Kaushal A, Foo LC, Zamanian JL, Christopherson KS, Xing Y, Lubischer JL, Krieg PA, Krupenko SA, Thompson WJ, Barres BA. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. J Neurosci, 2008, 28(1):264–278. https://doi.org/10.1523/JNEUROSCI.4178-07.2008 PMID: 18171944 PMCID: PMC6671143

[24] de Pablo Y, Marasek P, Pozo-Rodrigálvarez A, Wilhelmsson U, Inagaki M, Pekna M, Pekny M. Vimentin phosphorylation is required for normal cell division of immature astrocytes. Cells, 2019, 8(9):1016. https://doi.org/10.3390/cells8091016 PMID: 31480524 PMCID: PMC6769829

[25] Rosu GC, Mateescu VO, Simionescu A, Istrate-Ofiteru AM, Curcă GC, Pirici I, Mogoanta L, Mindrila I, Kumar-Singh S, Hostiuc S, Pirici D. Subtle vascular and astrocytic changes in the brain of coronavirus disease 2019 (COVID-19) patients. Eur J Neurol, 2022, 29(12):3676–3692. https://doi.org/10.1111/ene.15545 PMID: 36056566 PMCID: PMC9539405

[26] Trillo-Contreras JL, Ramírez-Lorca R, Villadiego J, Echevarría M. Cellular distribution of brain aquaporins and their contribution to cerebrospinal fluid homeostasis and hydrocephalus. Biomolecules, 2022, 12(4):530. https://doi.org/10.3390/biom12040530 PMID: 35454119 PMCID: PMC9025855

[27] Ikeshima-Kataoka H. Neuroimmunological implications of AQP4 in astrocytes. Int J Mol Sci, 2016, 17(8):1306. https://doi.org/10.3390/ijms17081306 PMID: 27517922 PMCID: PMC5000703

[28] Filippov V, Kronenberg G, Pivneva T, Reuter K, Steiner B, Wang LP, Yamaguchi M, Kettenmann H, Kempermann G. Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. Mol Cell Neurosci, 2003, 23(3):373–382. https://doi.org/10.1016/s1044-7431(03)00060-5 PMID: 12837622

[29] Perez-Catalan NA, Doe CQ, Ackerman SD. The role of astrocyte-mediated plasticity in neural circuit development and function. Neural Dev, 2021, 16(1):1. https://doi.org/10.1186/s13064-020-00151-9 PMID: 33413602 PMCID: PMC7789420

[30] Allen NJ, Eroglu C. Cell biology of astrocyte–synapse interactions. Neuron, 2017, 96(3):697–708. https://doi.org/10.1016/j.neuron.2017.09.056 PMID: 29096081 PMCID: PMC5687890

[31] Blanco-Suárez E, Caldwell ALM, Allen NJ. Role of astrocyte–synapse interactions in CNS disorders. J Physiol, 2017, 595(6): 1903–1916. https://doi.org/10.1113/JP270988 PMID: 27381164 PMCID: PMC5350444

[32] Allaman I, Bélanger M, Magistretti PJ. Astrocyte–neuron metabolic relationships: for better and for worse. Trends Neurosci, 2011, 34(2):76–87. https://doi.org/10.1016/j.tins.2010.12.001 PMID: 21236501

[33] Morgello S, Uson RR, Schwartz EJ, Haber RS. The human blood-brain barrier glucose transporter (GLUT1) is a glucose transporter of gray matter astrocytes. Glia, 1995, 14(1):43–54. https://doi.org/10.1002/glia.440140107 PMID: 7615345

[34] Reichenbach A, Wolburg H. Astrocytes and ependymal glia. In: Kettenmann H, Ransom BR (eds). Neuroglia. 2nd edition, Oxford University Press, New York, NY, USA, 2005, 19–35. https://www.worldcat.org/title/314216228

[35] Brown AM, Ransom BR. Astrocyte glycogen and brain energy metabolism. Glia, 2007, 55(12):1263–1271. https://doi.org/10.1002/glia.20557 PMID: 17659525

[36] Haydon PG, Carmignoto G. Astrocyte control of synaptic transmission and neurovascular coupling. Physiol Rev, 2006, 86(3):1009–1031. https://doi.org/10.1152/physrev.00049.2005 PMID: 16816144

[37] Gourine AV, Kasparov S. Astrocytes as brain interoceptors. Exp Physiol, 2011, 96(4):411–416. https://doi.org/10.1113/expphysiol.2010.053165 PMID: 21257664

[38] Pivoriūnas A, Verkhratsky A. Astrocyte–endotheliocyte axis in the regulation of the blood-brain barrier. Neurochem Res, 2021, 46(10):2538–2550. https://doi.org/10.1007/s11064-021-03338-6 PMID: 33961207

[39] Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid *β*. Sci Transl Med, 2012, 4(147): 147ra111. https://doi.org/10.1126/scitranslmed.3003748 PMID: 22896675 PMCID: PMC3551275

[40] Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. Physiol Rev, 2019, 99(1):21–78. https://doi.org/10.1152/physrev.00050.2017 PMID: 30280653 PMCID: PMC6335099

[41] Steardo L Jr, Steardo L, Scuderi C. Astrocytes and the psychiatric sequelae of COVID-19: what we learned from the pandemic. Neurochem Res, 2023, 48(4):1015-1025. https://doi.org/10.1007/s11064-022-03709-7 PMID: 35922744 PMCID: PMC9362636

[42] Florian C, Vecsey CG, Halassa MM, Haydon PG, Abel T. Astrocyte-derived adenosine and A1 receptor activity contribute to sleep loss-induced deficits in hippocampal synaptic plasticity and memory in mice. J Neurosci, 2011, 31(19):6956–6962. https://doi.org/10.1523/JNEUROSCI.5761-10.2011 PMID: 21562257 PMCID: PMC3140051

[43] Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron, 2009, 61(2):213–219. https://doi.org/10.1016/j.neuron.2008.11.024 PMID: 19186164 PMCID: PMC2673052

[44] Gibbs ME, Hutchinson D, Hertz L. Astrocytic involvement in learning and memory consolidation. Neurosci Biobehav Rev, 2008, 32(5):927–944. https://doi.org/10.1016/j.neubiorev.2008.02.001 PMID: 18462796

[45] Phatnani H, Maniatis T. Astrocytes in neurodegenerative disease. Cold Spring Harb Perspect Biol, 2015, 7(6):a020628. https://doi.org/10.1101/cshperspect.a020628 PMID: 25877220 PMCID: PMC4448607

[46] Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci, 2009, 32(12):638–647. https://doi.org/10.1016/j.tins.2009.08.002 PMID: 19782411 PMCID: 2787735
[47] García DM, Koke JR. Astrocytes as gate-keepers in optic nerve regeneration – a mini-review. Comp Biochem Physiol A Mol Integr Physiol, 2009, 152(2):135–138. https://doi.org/10.1016/j.cbpa.2008.09.026 PMID: 18930160
[48] Hernandez MR. The optic nerve head in glaucoma: role of astrocytes in tissue remodeling. Prog Retin Eye Res, 2000, 19(3):297–321. https://doi.org/10.1016/s1350-9462(99)00017-8 PMID: 10749379
[49] Sun D, Moore S, Jakobs TC. Optic nerve astrocyte reactivity protects function in experimental glaucoma and other nerve injuries. J Exp Med, 2017, 214(5):1411–1430. https://doi.org/10.1084/jem.20160412 PMID: 28416649 PMCID: PMC5413323
[50] Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S, Price RW, Blennow K, Zetterberg H, Gisslén M. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology, 2020, 95(12):e1754–e1759. https://doi.org/10.1212/WNL.0000000000010111 PMID: 32546655
[51] Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M, Dottermusch M, Heinemann A, Pfefferle S, Schwabenland M, Sumner Magruder D, Bonn S, Prinz M, Gerloff C, Püschel K, Krasemann S, Aepfelbacher M, Glatzel M. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol, 2020, 19(11):919–929. https://doi.org/10.1016/S1474-4422(20)30308-2 PMID: 33031735 PMCID: PMC7535629
[52] Savelieff MG, Feldman EL, Stino AM. Neurological sequela and disruption of neuron–glia homeostasis in SARS-CoV-2 infection. Neurobiol Dis, 2022, 168:105715. https://doi.org/10.1016/j.nbd.2022.105715 PMID: 35364273 PMCID: PMC8963977
[53] Tavčar P, Potokar M, Kolenc M, Korva M, Avšič-Županc T, Zorec R, Jorgačevski J. Neurotropic viruses, astrocytes, and COVID-19. Front Cell Neurosci, 2021, 15:662578. https://doi.org/10.3389/fncel.2021.662578 PMID: 33897376 PMCID: PMC8062881
[54] Pirici D, Mogoantă L, Mărgăritescu O, Pirici I, Tudorică V, Coconu M. Fractal analysis of astrocytes in stroke and dementia. Rom J Morphol Embryol, 2009, 50(3):381–390. PMID: 19690763
[55] Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. Neurosci Lett, 2014, 565:30–38. https://doi.org/10.1016/j.neulet.2013.12.071 PMID: 24406153
[56] Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E; Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol, 2003, 121(1):48–56. https://doi.org/10.1001/archopht.121.1.48 PMID: 12523884
[57] Schneider M, Fuchshofer R. The role of astrocytes in optic nerve head fibrosis in glaucoma. Exp Eye Res, 2016, 142:49–55. https://doi.org/10.1016/j.exer.2015.08.014 PMID: 26321510
[58] Anderson DR, Hoyt WF. Ultrastructure of intraorbital portion of human and monkey optic nerve. Arch Ophthalmol, 1969, 82(4):506–530. https://doi.org/10.1001/archopht.1969.00990020508017 PMID: 4981187
[59] Oyama T, Abe H, Ushiki T. The connective tissue and glial framework in the optic nerve head of the normal human eye: light and scanning electron microscopic studies. Arch Histol Cytol, 2006, 69(5):341–356. https://doi.org/10.1679/aohc.69.341 PMID: 17372390
[60] Anderson DR. Ultrastructure of human and monkey *lamina cribrosa* and optic nerve head. Arch Ophthalmol, 1969, 82(6):800–814. https://doi.org/10.1001/archopht.1969.00990020792015 PMID: 4982225
[61] Dai C, Khaw PT, Yin ZQ, Li D, Raisman G, Li Y. Structural basis of glaucoma: the fortified astrocytes of the optic nerve head are the target of raised intraocular pressure. Glia, 2012, 60(1):13–28. https://doi.org/10.1002/glia.21242 PMID: 21948238
[62] Galou M, Gao J, Humbert J, Mericskay M, Li Z, Paulin D, Vicart P. The importance of intermediate filaments in the adaptation of tissues to mechanical stress: evidence from gene knockout studies. Biol Cell, 1997, 89(2):85–97. PMID: 9351189
[63] Calvo JL, Carbonell AL, Boya J. Coexpression of vimentin and glial fibrillary acidic protein in astrocytes of the adult rat optic nerve. Brain Res, 1990, 532(1–2):355–357. https://doi.org/10.1016/0006-8993(90)91784-e PMID: 2282531
[64] Varela HJ, Hernandez MR. Astrocyte responses in human optic nerve head with primary open-angle glaucoma. J Glaucoma, 1997, 6(5):303–313. PMID: 9327349
[65] Ricard CS, Pena JD, Hernandez MR. Differential expression of neural cell adhesion molecule isoforms in normal and glaucomatous human optic nerve heads. Brain Res Mol Brain Res, 1999, 74(1–2):69–82. https://doi.org/10.1016/s0169-328x(99)00264-8 PMID: 10640677
[66] Pena JD, Roy S, Hernandez MR. Tropoelastin gene expression in optic nerve heads of normal and glaucomatous subjects. Matrix Biol, 1996, 15(5):323–330. https://doi.org/10.1016/s0945-053x(96)90135-3 PMID: 8981328
[67] Hernandez MR, Ye H, Roy S. Collagen type IV gene expression in human optic nerve heads with primary open angle glaucoma. Exp Eye Res, 1994, 59(1):41–51. https://doi.org/10.1006/exer.1994.1079 PMID: 7835397
[68] Lukas TJ, Miao H, Chen L, Riordan SM, Li W, Crabb AM, Wise A, Du P, Lin SM, Hernandez MR. Susceptibility to glaucoma: differential comparison of the astrocyte transcriptome from glaucomatous African American and Caucasian American donors. Genome Biol, 2008, 9(7):R111. https://doi.org/10.1186/gb-2008-9-7-r111 PMID: 18613964 PMCID: PMC2530868
[69] Neufeld AH. Nitric oxide: a potential mediator of retinal ganglion cell damage in glaucoma. Surv Ophthalmol, 1999, 43(Suppl 1):S129–S135. https://doi.org/10.1016/s0039-6257(99)00010-7 PMID: 10416755
[70] Neufeld AH, Liu B. Glaucomatous optic neuropathy: when glia misbehave. Neuroscientist, 2003, 9(6):485–495. https://doi.org/10.1177/1073858403253460 PMID: 14678581
[71] Grohm J, Kim SW, Mamrak U, Tobaben S, Cassidy-Stone A, Nunnari J, Plesnila N, Culmsee C. Inhibition of Drp1 provides neuroprotection *in vitro* and *in vivo*. Cell Death Differ, 2012, 19(9):1446–1458. https://doi.org/10.1038/cdd.2012.18 PMID: 22388349 PMCID: PMC3422469
[72] Song W, Chen J, Petrilli A, Liot G, Klinglmayr E, Zhou Y, Poquiz P, Tjong J, Pouladi MA, Hayden MR, Masliah E, Ellisman M, Rouiller I, Schwarzenbacher R, Bossy B, Perkins G, Bossy-Wetzel E. Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nat Med, 2011, 17(3):377–382. https://doi.org/10.1038/nm.2313 PMID: 21336284 PMCID: PMC3051025
[73] Lee D, Shim MS, Kim KY, Noh YH, Kim H, Kim SY, Weinreb RN, Ju WK. Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma. Invest Ophthalmol Vis Sci, 2014, 55(2):993–1005. https://doi.org/10.1167/iovs.13-12564 PMID: 24458150 PMCID: PMC3929080
[74] Hernandez MR, Miao H, Lukas T. Astrocytes in glaucomatous optic neuropathy. Prog Brain Res, 2008, 173:353–373. https://doi.org/10.1016/S0079-6123(08)01125-4 PMID: 18929121
[75] Yang H, Downs JC, Sigal IA, Roberts MD, Thompson H, Burgoyne CF. Deformation of the normal monkey optic nerve head connective tissue after acute IOP elevation within 3-D histomorphometric reconstructions. Invest Ophthalmol Vis Sci, 2009, 50(12):5785–5799. https://doi.org/10.1167/iovs.09-3410 PMID: 19628739 PMCID: PMC2866112

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