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Astrocyte functions in health and disease

Elly M Hol, Erwin A van Vliet and Eleonora Aronica

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INTRODUCTION

Astrocytes are essential for the development and function of the brain.^{56,141,188,189} These homeostatic cells are involved in processes ranging from the establishment and maintenance of neuronal synapses, regulation of synaptic transmission and blood flow, to the control of both neuroprotective and regenerative responses in the brain.^{56,141} Astrocytes are in direct contact with synapses, axons, blood vessels and each other (Figure 2.1). They have a central role in many brain diseases and are a major factor in the maintenance of brain health.^{138,141,186}

MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL IDENTIFICATION

Historical perspective and morphological identification

The word ‘glia’ was introduced in 1856 by the neuropathologist Rudolf Virchow. Virchow was responsible for major advances in our understanding of the heterogeneous cellular composition of the central nervous system (CNS), and in his classic text of 1858, *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*, Virchow represented glia as homogeneous round-shaped cells (spheres), supporting the initial concept of glia as ‘brain glue’ or ‘interstitial brain tissue’.^{167,201} He did not mention the type of preparation used to highlight

these cells and did not provide details of how the glia were related to neuronal cells and blood vessels. Deiters in 1865 was the first to show branched glial cells, teased out from poorly fixed (or in some cases unfixed) tissue, which he called ‘connective tissue cells’ (later called ‘Deiters’ cells’) in line with the initial concept of a mesodermal origin of neuroglial cells.⁴⁷

Camillo Golgi’s studies provided a fundamental contribution to the morphological identification of glia.^{167,201} A major technical advance was his discovery and application of the black chrome–silver reaction which still bears his name, and using this method Golgi provided the first detailed description of cells with multiple processes, describing different types of glia,⁶⁹ including cells termed ‘protoplasmic and fibrous glial cells’.⁷ However, he still regarded these cells as part of the connective tissue, using Virchow’s definition of neuroglia. The term astrocyte was introduced later by Lenhossek, referring to their stellate morphology.¹⁰³

Ramon y Cajal introduced the gold-sublimate method in 1913 and, using it, provided a detailed description of two types of astrocyte: protoplasmic astrocytes in the grey matter, with many finely branching processes; and fibrous astrocytes in the white matter, with long fibre-like processes. In his drawings he showed astrocytic processes embracing neurons, as well as contacting blood vessels. From their first description it was evident that the morphology of astrocytes varied, supporting the concept of astrocyte heterogeneity.⁶⁶

The development of the silver carbonate method by del Río-Hortega (Cajal’s student) allowed a more detailed analysis of nervous system tissue and revealed distinct types of glia, including astrocytes, oligodendrocytes and

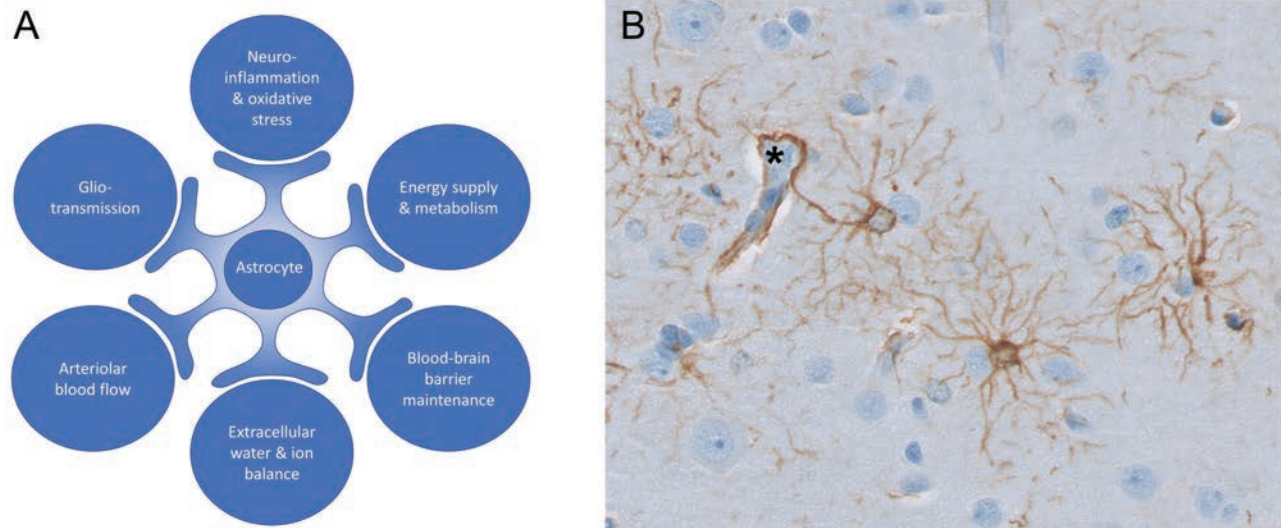


Figure 2.1 Astrocytes. (A) Overview of the versatile functions of astrocytes, from Verhoog *et al.*¹⁸⁶ (B) Astrocytes immunostained for GFAP (brown) and counterstained with haematoxylin. The asterisk shows a clear interaction of an astrocyte with a blood vessel.

microglia (of mesodermal origin).^{167,201} The distinction between the two main classes of astrocyte (protoplasmic and fibrous) detected using these classical histological techniques is still used today, although several additional human subtypes have now been identified, such as varicose projection astrocytes and interlaminar astrocytes.¹³⁶ In addition, a variety of highly specialised glial cells have been described, such as Bergmann glia of the cerebellum (described by Golgi and Cajal as epithelial glia), velate astrocytes in the cerebellar cortex, Müller glia in the retina, tanyocytes at the base of the third ventricle, and pituicytes in the neurohypophysis. Their morphology reflects the cytoarchitecture and function of specific brain regions.¹⁶⁷ Pituicytes and tanyocytes are discussed in more detail below. Pituicytes express astroglial markers consistent with their identities as astroglial cells of the pituitary,¹⁹³ and recent studies have provided new insights into their physiological functions, and both their molecular and cellular features, which in part resemble that of tanyocytes.^{6,35} Tanyocytes are specialised, non-ciliated ependymoglia cells (classified as astroglia) with a peculiar morphology and neural stem/progenitor cell properties, and which act as key players in the hypothalamic regulation of energy homeostasis.^{53,65,100} Recent advances in their gene expression dynamics highlight the complex molecular and functional heterogeneity of tanyocytes.¹⁰⁰ The revolution of single-cell RNA sequencing is expected to lead to the discovery of more astrocytic subtypes within the human brain, as has already been demonstrated in rodent brains.¹⁴

The classical histological techniques (including their many variants)^{93,131,154} can be inconsistent and therefore may lead to variable results and interpretation. In addition, they generally do not work well on formalin-fixed, paraffin-embedded sections, limiting their use for routine and practical procedures. While astrocytes can be identified and distinguished from neurons and other glia by using routine tinctorial stains, such as haematoxylin and eosin (H&E), based on their nuclear morphology (oval or round vesicular nucleus that usually lacks a prominent nucleolus),

under normal physiological conditions their intricate pattern of cytoplasmic processes cannot be appreciated.¹

With the advent of transmission electron microscopy (EM), additional features of both protoplasmic and fibrous astrocytes were revealed, including clear evidence of the close contact of astrocytic processes to the pre- and postsynaptic compartments, and the presence of gap junctions in both types,^{99,143,160} resulting in a highly interconnected astrocytic network. The major identifying ultrastructural features of astrocytes are their clear cytoplasm, abundant glycogen granules and the presence of bundles of approximately 10 nm fibrils which belong to the class of intermediate filaments (IF) of the cytoskeleton.^{68,143,197} They are more prominent in fibrous astrocytes than in protoplasmic astrocytes. The identification of glial fibrillary acidic protein (GFAP) as the major component of IF in mature astrocytes represented an important breakthrough in the identification of astrocytes both *in situ* and in cell culture.^{55,124,148}

Immunohistochemical identification

Astrocytes express four types of IF proteins: GFAP, vimentin, synemin, and nestin.^{54,82,86} Nestin and vimentin are the main IF proteins in immature astroglial cells, whereas mature astrocytes contain GFAP.⁵⁴ GFAP has become the most common marker for the immunohistochemical detection of astrocytes in both normal and pathological brain tissue,^{56,166} although it is not expressed in all astrocytes.^{81,176} Using antibodies raised against GFAP, several morphological subtypes of protoplasmic and fibrous astrocytes have been described in the primate cortex, including marginal astrocytes with processes extending to the pial surface (glia limitans), perivascular astrocytes that encircle the endothelial cells with their end-feet, interlaminar astrocytes, and the more recently identified human-specific astrocytes, designated as varicose projection astrocytes.^{119,204} However, it is important to recognise the limitations of GFAP as an astrocytic marker. GFAP is not an absolute marker of all astrocytes in healthy CNS tissue, and GFAP

immunohistochemistry reveals only part of the total volume of the astrocytes, thus underestimating the complexity of astrocytic arborisation, which can be better detected with a Golgi stain, filling with fluorescent dyes, or using transgenic reporter proteins.^{92,119,166} Accordingly, GFAP immunostaining often only visualises the structure of primary branches and end-feet. In addition, not all the mature astrocytes display detectable levels of GFAP, and different levels of expression can be observed between white and grey matter astrocytes, as well as in astrocytes from different brain regions.^{70,75,88}

Differences in the GFAP staining pattern are also related to the use of different GFAP antibody clones (recognising different GFAP epitopes), which may account for discrepancies between studies, including the interpretation of results using GFAP immunohistochemistry in human tissue.^{77,124,125} In addition, the technical aspects of tissue preparation and immunohistochemistry (different fixatives and methods of antigen retrieval) are critical (particularly when using human post-mortem tissues), as these may significantly influence the detectability of antigens.^{109,162} When using GFAP as a cell-specific marker for astrocytes, it is important to note that GFAP is expressed by highly specialised astroglial cells (Bergmann glia, Müller cells, tanycytes, pituicytes), by ependymal cells (which are also derived from radial glia),^{110,171} as well as by a variety of ‘astrocyte-related’ cells in different organs outside the CNS.^{29,107,166,207}

The GFAP gene is known to generate several splice variants, including α , β , γ , δ (also referred to as GFAP ϵ) κ , λ , μ , $\Delta 164$ and Δ exon6.^{19,40,60,64,80,83,132,179,203} The predominant splice form is GFAP- α , which is expressed by a majority of astrocytes. In addition, the expression of the minor isoforms has been also described in subpopulations of astrocytes under physiological and pathological conditions.^{19,26,41,83,132,151,179,180,203} In particular, GFAP- δ has been identified as a potentially useful marker to identify a specific subpopulation of astrocytes located in the subpial layer, the subgranular zone (SGZ) of the hippocampus, and along the length of the lateral ventricles (subventricular zone [SVZ]), the latter two regions containing multipotent neural stem cells in the adult mammalian brain.^{117,123,151} By using an antibody against $\Delta 164$ and Δ exon6 (referred to as GFAP⁺¹), a subpopulation of astrocytes has been detected in normal human brain and spinal cord tissue, and brain sections of Alzheimer’s disease (AD), Parkinson’s disease (PD) and epilepsy patients.^{20,83,125} The systematic use of antibodies directed against different GFAP isoforms may further contribute to the identification of astrocytic subtypes, potentially related to activation states in specific brain regions in both health and disease.

In addition to GFAP, glutamine synthetase (GS), aquaporin 4, connexin-43 and S100 β have also been used to detect astroglial cells in brain tissue, although these are not all exclusively confined to astrocytes.⁹¹ ALDH1L1 is a promising new, highly specific marker for astrocytes,³⁴ however, reliable immunostaining is challenging. ALDH1L1 mRNA is present in human astrocytes as shown with fluorescent *in situ* hybridisation (FISH),¹³⁵ but this is not a technique used in routine diagnostic pathology. The combined use of different antibodies specifically directed against different astroglial markers is a useful approach to increase astroglial detection and can be particularly helpful when identifying

populations of astrocytes with low levels of GFAP immunoreactivity.^{70,133} It is therefore essential to use different cell type-specific markers when evaluating the potential loss of astrocytes in pathological conditions, as some routinely used markers are not expressed by all astrocytes.

HETEROGENEITY OF ASTROCYTES

Large-scale gene expression studies (including more recently RNA-sequencing-based transcriptomes from region-specific brain samples and specific cell types) provide a global characterisation of the astrocyte transcriptome and the identification of cell-type-specific markers of the rodent and human brain.^{137,205} These studies have identified several genes that are highly enriched in astrocytes, compared with other neuronal and neuroglial cells (neurons, oligodendrocytes and microglia), including, in addition to GFAP, a variety of extracellular secreted proteins, glutamate transporters (e.g. *Slc1a3*, GLAST), enzymes, receptors/membrane proteins (e.g. connexin43) and transcription factors.^{34,52,101,112,137} One gene encodes for the protein Aldh1L1, and detection of this protein by immunohistochemistry suggests that it is a highly specific astrocytic marker, with a broader and more homogeneous expression pattern than GFAP,³⁴ although routine immunohistochemistry for this marker can be challenging.¹³⁵ *Pbxip1* (another astrocyte-enriched gene detected with the same approach)³⁴ identifies a specific subpopulation of astrocytes located in the subpial layer and the SVZ. Moreover, astrocyte subpopulations and cortical layer-specific gene signatures have been identified,^{43,87,101} further supporting the importance of astrocyte morphological, molecular and functional heterogeneity. Single-cell transcriptomic studies provide additional strong evidence of the spatial and temporal heterogeneity of astrocytes, revealing morphologically and physiologically distinct astrocytic subtypes between and within brain regions.^{14,202} A single-cell study using human neocortex identified two astrocytic subtypes: *FGFR3* and *GFAP* express astrocytes in layer 1 and 2 of the cortex, and *FGFR3* and *SLC14A1* express astrocytes in all layers of the neocortex.⁸¹ Moreover, the use of recently developed spatial transcriptomic techniques allows quantification of single-cell gene expression *in situ*, revealing distinct neuronal and astroglial organisation in lineage-associated laminae and divergent astrocyte layer patterns between cortical regions in the mouse brain.¹⁵ Single nucleus RNA sequencing (snRNAseq) using droplet technology has been applied to frozen brain tissue to elucidate cellular heterogeneity in the human brain,⁷⁴ achieving a more detailed understanding of the heterogeneous and dynamic astrocytic phenotypes under physiological and pathological conditions.^{4,25,56,81} This can be combined with the isolation of astrocytes from the human brain with fluorescent-assisted cell or nuclei sorting techniques.¹³⁰

Thus, the application of more sophisticated research strategies, together with a systematic evaluation and comparison of different glial markers, represent the best approach towards new advances in the identification of human astrocyte subpopulations and a better understanding of their role in brain function¹³⁶ in both physiological and pathological conditions.

ASTROCYTES AND BRAIN DEVELOPMENT

Astrogenesis starts towards the end of the neurogenic wave (shortly before gestational weeks 17–20 in humans and embryonic day [E] 18.5 in rodents).^{45,97,152,163} Astrocytes are generated from the same progenitors as neurons; the switch from a neurogenic to an astrogenic differentiation programme is regulated at the genetic and epigenetic level through different signalling pathways and results in the induction of the expression of astrocyte-specific genes, such as *GFAP*.^{57,90,126} The density of astrocytes continues to increase through the first month of life, during which time astrocytes differentiate, acquiring a mature morphology, establishing contact with neurons, and playing a critical role in the control of regulation of synapse formation and function during development.^{57,147} The use of cell fate tracking techniques has demonstrated that astrocytic heterogeneity, even within the same brain region, is determined early in development,²⁷ although the molecular and functional programs of the astrocytes are not hard-wired during development but rather adapt to neuronal cues.⁵⁹

ASTROCYTES AND THE REGULATION OF BLOOD–BRAIN BARRIER FUNCTION AND BLOOD FLOW

The blood–brain barrier (BBB) constitutes an elaborate structure formed by brain capillary endothelial cells that are connected via tight junctions (forming the primary barrier), ensheathed by astrocytes forming the second line of defence and surrounded by mural cells, pericytes and neurons, together referred to as the neurovascular unit (NVU)² (Figure 2.2). The BBB develops during embryonic angiogenesis and tight junctions in brain endothelial cells appear early in gestation (9–15 weeks' gestation in humans). However, at this early developmental stage, the microvasculature is still leaky because of an abundance of blood vessels in the germinal matrix together with the immaturity of the basal lamina, paucity of pericytes and a deficiency of

GFAP in the ensheathing astrocytic end-feet.^{13,127} Several studies have highlighted the importance of astrocytes in the development and maintenance of physiological BBB functions through different mechanisms, including the production of a variety of factors that influence the formation of tight junctions and the expression of transporter proteins, and the modulation of enzymatic pathways.^{5,102,198}

The intimate anatomical relationship between astrocytes and cerebral blood vessels, as suggested by Cajal in the late 1800s, supports the role of these cells in the regulation of local CNS blood flow. Over the past decades, several studies have provided clear evidence that astrocytes are capable of eliciting both vasoconstriction and vasodilation through different mechanisms, involving the calcium-dependent release of various vasoactive substances, accompanying neuronal activity, and activation of ionotropic and metabotropic glutamate receptors.^{63,84,115,155} These vasoactive substances include metabolites of arachidonic acid, such as prostaglandin E2 (PGE2) and epoxyeicosatrienoic acids (EETs), which dilate blood vessels, and 20-hydroxyeicosatetraenoic acid (20-HETE), which constricts vessels. Additionally, nitric oxide (NO) and local potassium signalling have been shown to contribute to the functional coupling between local blood perfusion and neuronal activity. For a more detailed discussion, please refer to Verhoog *et al.*¹⁸⁶

ASTROCYTES AND WATER/ION TRANSPORT

Astrocytes are important for maintaining the homeostatic extracellular water and ion balance in the brain. As the brain is encapsulated within the cranium, it has very limited space for volume enlargement during brain oedema (see Chapter 7). Therefore, mechanisms for efficient and quick redistribution of water within the brain parenchyma are essential for normal neuronal function. Since astrocytes can tolerate rapid changes in volume,¹⁴⁵ they play an important role in homeostasis. Changes in ion or water balance also affect local synaptic activity by modifying the concentration gradient upon which the electrochemical

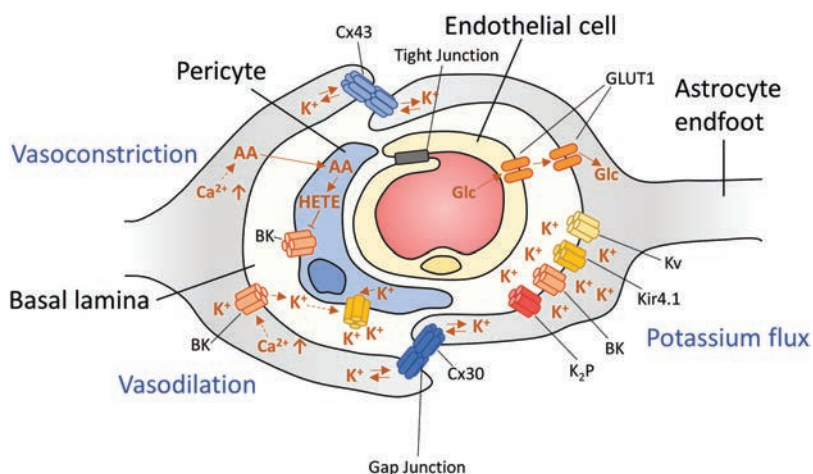


Figure 2.2 Astrocytes and blood vessels. Overview of the interaction between astrocytes and blood vessels, forming the blood–brain barrier (BBB) and the neurovascular unit (NVU), as well as regulating vasoconstriction and vasodilatation. From Verhoog *et al.*¹⁸⁶

potential is based. Utilising a variety of transporter proteins and channels that are present in astrocytes, water as well as potassium, sodium, calcium and chloride can be regulated. Water transport is mainly regulated via aquaporins, a diverse protein family that are mostly permeable to water. Three aquaporin types have been described in astrocytes: aquaporins AQP1 and AQP4, which are permeable to water, and the aquaglyceroporin AQP9, which is permeable to water and to small solutes, such as glycerol and urea.¹⁴⁵ Astrocytes also express an array of different voltage-dependent and voltage-independent channels to help with ion regulation (e.g. K^+ and Na^+ channels) but also Ca^{2+} and Cl^- transporters.¹²⁰ The mechanisms underlying ion regulation may vary between and within brain regions and the precise effects of regional differences in the composition of astrocytic channels and transporters on network activity are not, at this stage, fully understood.

homeostasis.^{48,116,200} In addition to the intrinsic neuronal energy supply, astrocytes are also equipped with a glucose-metabolism pathway to meet the local energy demands. Indeed, in times of hypoglycaemia and during periods of high neuronal activation, astrocytes take over the energy supply completely.^{28,172} Moreover, several studies support the ability of astrocytes (in addition to their high glycolytic capacity yielding lactate) to produce ketone bodies, and astrocytes are a major site of fatty acid oxidation.^{170,173} In addition, astrocytes are key players in the uptake and degradation of excess neurotransmitters (e.g. glutamate, gamma-aminobutyric acid [GABA]) and other neuromodulators. Thus, energy dynamics and homeostasis in the brain relies on strict cooperation between neurons and astrocytes, and astrocytes are essential in the control of energy homeostasis and metabolism in the CNS.^{16,48,170,173}

ASTROCYTES AND METABOLIC CONTROL

There is increasing evidence supporting the role of astrocytes as metabolic sensors of the CNS microenvironment, rapidly detecting and responding to changes in the brain parenchymal levels of metabolic substrates such as oxygen and glucose, as well as metabolic waste products, including carbon dioxide, to maintain brain metabolic

NEURON–ASTROCYTE AND INTERGLIAL CROSSTALK

Much progress has been made recently in understanding the role of neuronal-glia crosstalk (Figure 2.3). The concept of the ‘tripartite synapse’ was introduced in the 1990s,⁸ based on the mounting evidence of bidirectional communication between neurons and astrocytes. The central role of astrocytes, beyond their homeostatic functions, in information processing in the brain has emerged as a rapidly

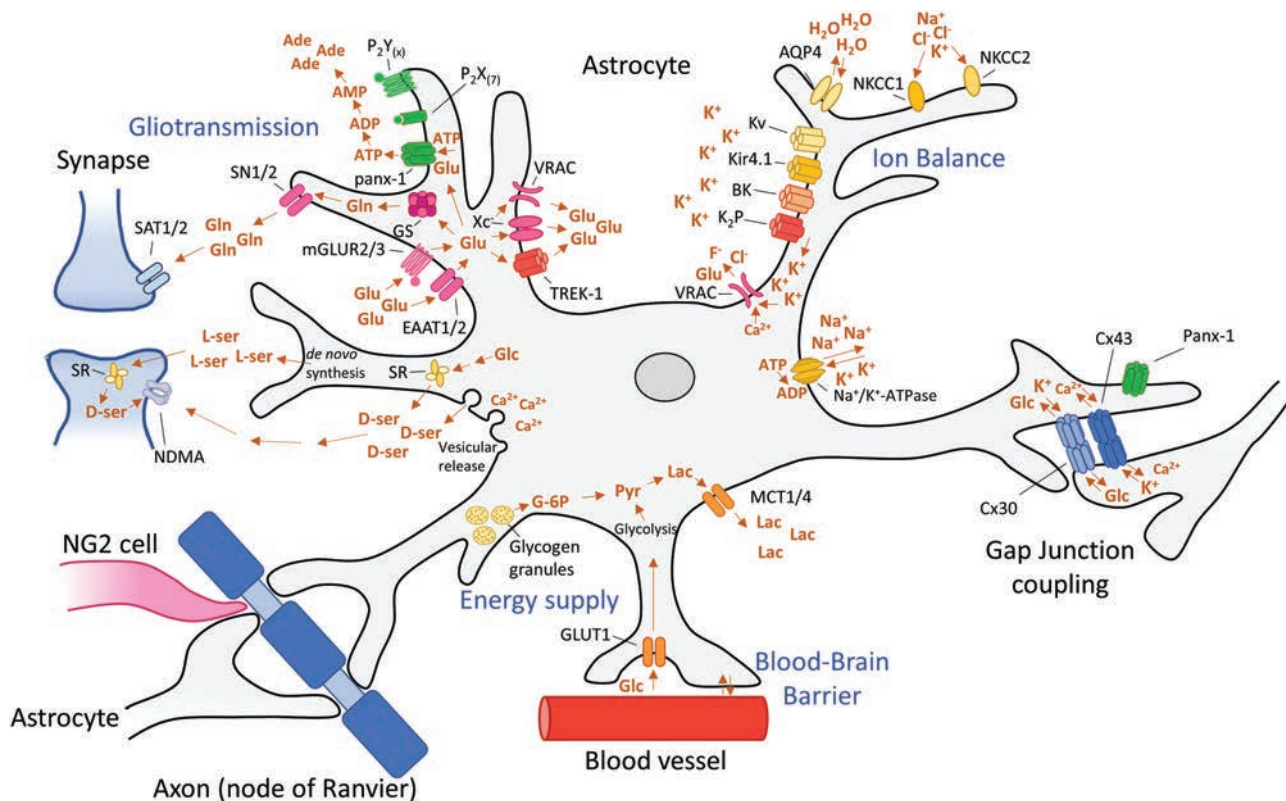


Figure 2.3 Astrocytes interact with synapses, axons, blood vessels and each other. They are involved in energy metabolism and gliotransmission, keep the extracellular ion concentrations in balance and regulate the blood–brain barrier function and blood flow. From Verhoog et al.¹⁸⁶

expanding field of neuroscience research. Accumulating evidence supports the existence of a neuronal–astrocytic network, in which astrocytes can modulate the function of both excitatory and inhibitory synapses.^{10,76,111,142,156} The concept of ‘gliotransmission’ remains one of the most controversial topics in astrocyte biology. The term gliotransmitter is loosely defined as a chemically active transmitter that originates from glial cells and which may participate in or affect the excitatory or inhibitory network of neurons.¹⁸⁶ In addition to communicating with neurons, astrocytes are interconnected via gap junctions, which allow the rapid intercellular exchange of ions, second messengers and metabolites between astrocytes, creating an organised intercellular network that contributes to the dynamic regulation of neurons by astrocytes.^{31,73,140} More recently, a quadripartite view of synapses has emerged pointing to the dynamic roles of microglia, together with astrocytes, at both developing and mature synapses.^{158,194}

Emerging evidence further highlights the bilateral signalling between microglia and astrocytes, supporting the fundamental role of this interglial crosstalk in health and disease.¹⁰⁶ Microglia influence the functions of reactive astrocytes, driving astrocytes from a neuroprotective to neurotoxic phenotype; conversely, astrocytes release molecules that regulate microglial functions. Together, this bidirectional crosstalk is crucial for the maintenance of a pro-inflammatory environment under pathological conditions.^{30,51,85,105,178}

An additional interaction in the context of interglial crosstalk is the role of astrocytes to directly influence oligodendrocyte progenitor migration, proliferation and differentiation, and emerging studies provide further evidence of bidirectional astrocytic–oligodendrocytic crosstalk and its significance for neurological diseases.^{104,128,134}

Although attention has been primarily focused on astrocyte interactions with other CNS cell types, there is also recent evidence that astrocyte function may be influenced by the gut microbiome and this crosstalk between gut microbiota and brain, involving astrocytes, may have implications in the development and progression of CNS disorders.^{79,114}

ASTROCYTES AND BRAIN INFLAMMATION/OXIDATIVE STRESS RESPONSE

Astrocytes have emerged as key regulators of the inflammatory response in several human CNS diseases,^{11,58,165,184,186} through their interaction with microglia and other immune cells.⁷⁸ They produce cytokines, chemokines and components of the complement pathway. In addition, they can respond to inflammatory molecules through the activation of specific receptors (including pattern-recognition receptors and related intracellular signalling pathways, such as IL-1 receptor/toll-like receptor-mediated pathways, complement receptors, etc.), which can aggravate astrogliosis and amplify pathological inflammatory signalling and thereby affect the function of neurons.^{11,165,184} Neuronal

activity per se is sufficient to trigger synthesis and release of pro-inflammatory molecules from astrocytes and microglia, a mechanism which is termed ‘neurogenic neuroinflammation’.^{184,199} Moreover, pro-inflammatory mediators may act as neuromodulators by different intracellular signalling pathways that affect neuronal function and may contribute to hyperexcitability and excitotoxicity.^{184,190}

As CNS homeostatic cells, astrocytes are also involved in the modulation of oxidative stress, which is pivotal for inducing or perpetuating astrocyte-mediated inflammation.^{9,36,209} Despite the attention given to the pro-inflammatory roles for astrocytes, there is mounting evidence highlighting the ability of these cells to mediate a wide range of compensatory responses to stress or toxic conditions. These compensatory response mechanisms promote protection and repair and include several mechanisms aiming to mitigate inflammation (anti-inflammatory response/anti-inflammatory phenotype) and to protect against redox stress (anti-oxidant response), glutamate toxicity and metabolic stress.^{33,118,209}

ASTROCYTES AND AGEING

A growing number of studies have provided evidence of age-related morphological and molecular changes in astrocytes.^{38,118,137,139} As discussed above, the use of modern transcriptomic techniques has shed light on the molecular signature of astrocytes, and this has provided information about cellular changes during the ageing process. Recent studies have shown that astrocytes can undergo region-specific age-dependent changes in gene expression, gaining a neuroinflammatory/neurotoxic phenotype that may contribute to age-related neuropathology.^{22,38,105} Although studies in the human brain are still limited,¹⁸⁷ the study of Soreq and colleagues,¹⁶⁸ showing a shift of the regional expression patterns of glial-specific genes in human brain ageing, is in line with the concept of a region-specific vulnerability linked to age-dependent changes in astrocytes. Astrocytic senescence as an important mechanism of ageing is an emerging field of study to understand the link between alterations in astrocytic phenotype and age-associated neurodegenerative diseases.^{12,39} In addition, astrocytic senescence has been reported to be involved in cognitive impairment in hepatic encephalopathy as a consequence of ammonia-induced oxidative stress.⁷¹ Of note is that the features of senescent astrocytes include inflammation, oxidative stress and mitochondrial dysfunction, features which are also associated with neurodegenerative disorders.^{12,37,39} Thus, understanding the biology of the senescence-associated astrocytic phenotype involving different mechanisms, such as a recently suggested dysregulation of alternative splicing,¹¹³ may represent an interesting topic of future research. Moreover, experimental studies support astroglial involvement in senescence-related processes that may precede tau pathology.³² Accordingly, attention has been focused on astroglial tau pathology occurring in the aged brain. The term ageing-related tau astrogliopathy (ARTAG) (see Chapter 33) has been introduced to describe a morphological spectrum of astroglial pathology

characterised by tau-positive astroglia with or without accompanying morphological features of other neurodegenerative disorders.^{94–96} Further studies are required to clarify the vulnerability of specific astrocytic subpopulations, the mechanisms underlying ageing-related astrocytic tau accumulation and propagation (independently from neuronal tau), the functional consequences of tau accumulation (loss of physiological protective functions or gain of toxic function) as well as the clinical significance of these cellular changes (cognitive decompensation and subsequent cognitive decline).^{44,94,150,161}

MORPHOLOGICAL AND FUNCTIONAL CHANGES OF ASTROCYTES IN CNS DISORDERS

Astrogliosis

The term astrogliosis, often referred to as reactive astrogliosis or reactive astrocytosis, was introduced in the late nineteenth century to describe structural changes in astrocytes in response to CNS insults of different aetiologies. Astrogliosis is a common feature and pathological hallmark of several CNS diseases,^{164,166} and it is used to refer to astrocytic hypertrophy and/or proliferation. Initially, attention was focused on the morphological features, with terms such as isomorphic (preserving the astroglial environment and potentially reversible) and anisomorphic (disruption of the astroglial environment, ultimately resulting in the formation of a permanent glial scar) astrogliosis¹⁴⁹ used to describe the heterogeneity of reactive astrocytes in relation to location and stage of evolution of reactive gliosis. Over the past two decades the concept of astrogliosis heterogeneity characterised by a spectrum of molecular, cellular and

functional changes, underlying subcategories ranging from mild to severe diffuse astrogliosis, with or without compact scar formation, has developed.^{164,166} As discussed above, in the context of the physiological role of astrocytes, reactive astrocytes may also exert both beneficial and detrimental functions under different pathological conditions and their phenotype may vary with different disease stages. Thus, reactive astrocytes may be initially essential for limiting tissue damage and/or preserving neurological function after injury, but later in the course of the disease may have the potential to exert detrimental effects, such as acquiring an inflammatory/neurotoxic phenotype induced by a specific local environment and signalling mechanisms.^{21,105,164,166,184} A working consensus on the nomenclature and definitions of reactive astrocytes emphasises the concept of ‘astrocyte reactivity’ as the ability of these cell types to adopt multiple states/phenotypes in response to diverse pathologies, in contrast to the simpler concept of binary phenotypes (i.e. neurotoxic–neuroprotective A1–A2).⁵⁶

Astrogliosis accompanies a large variety of pathological situations affecting the CNS, such as trauma, ischaemic damage, epilepsy, infections, autoimmune disorders, metabolic disorders and neurodegenerative diseases. Although there is a common feature across these different pathologies (upregulation of GFAP and inflammatory proteins),⁵⁶ specific molecular and functional characteristics, determined by specific signalling mechanisms, are associated with different neurological disorders.

Astrogliopathies

There is growing evidence supporting the concept of ‘astrogliopathies’, highlighting the central role of astrocytic dysfunction in the disease mechanisms of a range of neurological conditions (Figure 2.4). Astrogliopathies include reactive astrogliosis, astrodegeneration (with astroglial

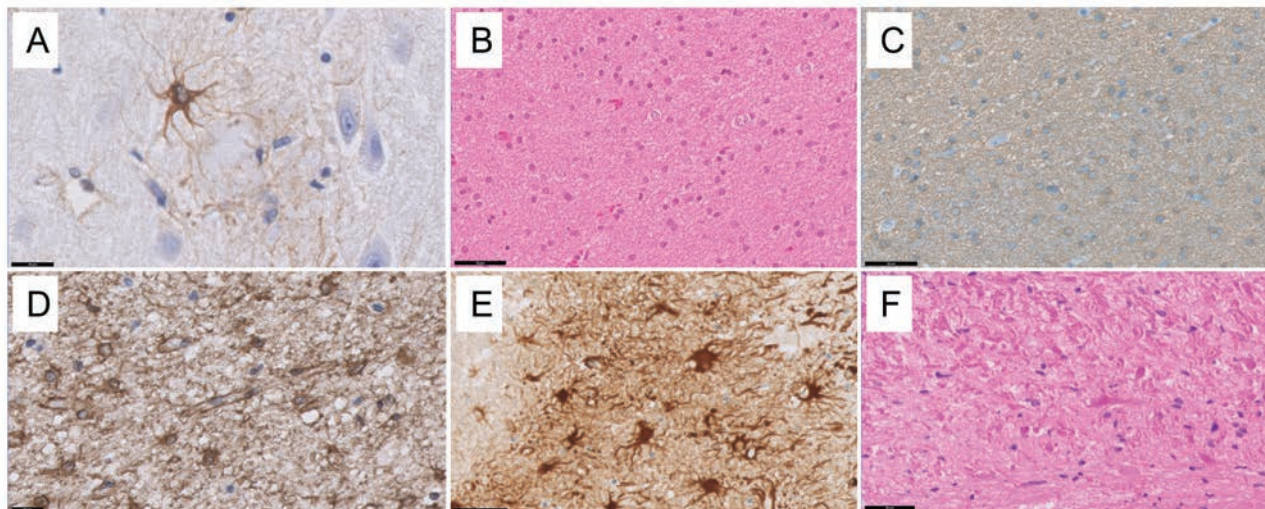


Figure 2.4 Examples of reactive gliosis. (A) Alzheimer’s disease: GFAP immunostaining showing an astrocyte embracing an A β deposit. (B,C) Chronic dense fibrillary gliosis in the hippocampus (hippocampal sclerosis in temporal lobe epilepsy): (B) H&E stain, (C) GFAP stain. (D) Neonatal hippocampus (CA1) after perinatal asphyxia: AQP4 immunostaining showing astroglial expression, particularly around the blood vessel.¹⁵⁹ (E) Glial scar surrounding an injury site: GFAP stain. (F) Rosenthal fibres in an area of chronic gliosis (H&E). Scale bars: (A) and (D) 20 μ m; (B), (C), (E) and (F) 50 μ m.

atrophy and loss of function) and astroglial pathological remodelling.^{141,188} The so-called Alzheimer type II astrocytes reflect an astroglial pathology linked to metabolic disturbance caused by hepatic or renal dysfunction.^{3,67} Astrodegeneration and reactive astrogliosis have been reported in different neurodegenerative disorders, in toxic encephalopathies as well as in neuropsychiatric diseases,^{141,188,189} although the latter is a poorly defined phenotype.^{177,183} Reactive astrogliosis and astroglial pathological remodelling are well represented in both acquired and genetic epilepsies, also including neurodevelopmental disorders, with a large spectrum of complex morphological and functional changes.^{18,21,50,141,184,186,208}

Astroglial pathologies associated with specific genetic mutations have been described, emphasising the role of aberrant neuroglial crosstalk, as well as interglial communication, in defining the clinical phenotype. Alexander disease (see Chapter 12) represents a classic example of a primary astroglial pathology caused by a dominant mutation in the *GFAP* gene, resulting in a large number of pathological features, including changes in astrocytic morphology and astrocytic dysfunction, associated with the activation of both cell stress and inflammatory pathways and even astrocytic TDP-43 pathology.^{122,169,191} Aicardi-Goutières syndrome (see Chapter 12) is another example of a rare genetically determined infantile encephalopathy in which astrocytes, through cell-autonomous and non-cell-autonomous mechanisms, contribute to the auto-inflammatory response with increased interferon-alpha production.^{42,157,181} Tuberous sclerosis complex (TSC) represents the prototypic monogenic disorder of the mammalian target of rapamycin (mTOR) pathway dysregulation (see Chapter 15) and is characterised by morphological and functional changes in glial cells, particularly the astrocytes. Understanding mTOR-related astrocytic dysfunction may offer new insights into the common neurobiological mechanisms underlying epilepsy and the complex cognitive and behavioural comorbidities that are characteristic within the spectrum of mTOR-associated neurodevelopmental disorders.^{129,206,208}

Neurodegenerative disorders

Dominant mutations in superoxide dismutase 1 (*SOD1*) and transactive response DNA-binding protein 43 (*TARDBP* gene, TDP-43 protein) are known causes of familial amyotrophic lateral sclerosis (ALS)¹²¹ (see Chapter 29). In experimental studies, it has been shown that astrocytes expressing mutations in *SOD1* and *TARDBP* may trigger the death of motor neurons via non-cell-autonomous processes involving common pathogenic pathways.^{153,174,192} A recent study focusing on the effect of TDP-43 inclusions provides additional evidence of dysregulated astroglial metabolism and metabolic support of neurons in TDP-43-associated ALS and frontotemporal dementia (FTD).¹⁸⁵ As with other neurodegenerative diseases, ALS pathology is at least partially non-cell-autonomous, involving astrocytes and their interplay with microglia as well as peripheral immune cells.⁴⁶ In Huntington's disease (see Chapter 31), mutant huntingtin (*mHTT*) is expressed and aggregates in astrocytes. This contributes to neuronal excitotoxicity via different mechanisms involving downregulation

of glutamate transporters, decreased expression of Kir4.1 channels, leading to impaired K⁺ homeostasis, and other changes promoting oxidative stress and neuroinflammation.^{72,144,175,182,196} These genetic conditions provide a mechanistic basis of a direct link between a specific gene mutation and astrocyte dysfunction contributing to the complex clinical phenotype.

The strongest known genetic risk factor for AD is the $\epsilon 4$ allele of the apolipoprotein E (*APOE*) gene.^{17,61} Several studies indicate that *APOE* $\epsilon 4$ accelerates the shift from physiological to pathological ageing of astrocytes.¹⁸⁷ The *APOE* $\epsilon 4$ -related changes to astrocytes include reduced secretion of brain-derived neurotrophic factor (BDNF), changes in their ability to maintain neurotransmitter homeostasis, alteration of cholesterol metabolism, the acquisition of a pro-inflammatory phenotype, increased expression of matrisome-related molecules and a reduced capacity for amyloid beta ($A\beta$) clearing.¹⁸⁷ In particular, the downregulation of Na⁺/H⁺ exchanger isoform 6 (NHE6) observed in *APOE* $\epsilon 4$ astrocytes results in excessive endosomal acidification, which impairs the endocytic recycling of the low-density lipoprotein receptor-related protein 1 (LRP1), a receptor that facilitates the endocytosis of many ligands including $A\beta$.¹⁴⁶ Moreover, in astrocytes, $A\beta$ produces alterations of Ca²⁺ homeostasis via calcineurin and its downstream target NF- κ B.^{49,187} In addition, genome-wide association studies have revealed other astrocytic genes that are correlated to AD, such as clusterin,⁹⁸ and a gene cluster involved in the regulation of astrocyte activation,¹⁹⁵ emphasising the key role of astrocytes in AD.

In PD (see Chapter 27) α -synuclein released by neurons can be taken up by astrocytes and its accumulation interferes with normal physiological functions, resulting in mitochondrial damage.^{62,108} Moreover, various PD-related genes (e.g. *LRRK2*, *ATP13A2* and *GBA*) are expressed in astrocytes and have been shown to critically regulate astrocyte function.^{24,62} These may also alter the endolysosomal pathway in astrocytes, leading to impairment of clearance mechanisms and accumulation of toxic protein species, thus further contributing to glial dysfunction and disease progression.^{24,62,89} DJ-1 is a protein encoded by the parkinsonism-associated deglycase gene *PARK7*, which has been shown to have a key role in astrocyte biology (including protection against oxidative stress).^{24,89} Loss-of-function mutations in *PARK7* have been linked to early-onset familial PD.²³

CONCLUSION

Our knowledge in relation to the function of astrocytes in the brain and their role in brain disorders is rapidly increasing. Currently, there is a shift from a *neurocentric* view of neurological disorders to one that incorporates the primary role of astrocytes in disease initiation and progression through to functional outcome. The role of astrocytes in health and disease represents an exciting focus for future studies in the fields of neuropathology and basic neuroscience.

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