Astrocyte Functions

Subjects: Cell Biology

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Astrocytes are stellated glial cells that interface with nearly every functional element of the brain. They are the most abundant glial cells in the brain and can comprise up to 50% of the tissue volume in some regions. Their branch-like processes surround neurons, axons, synapses, and blood vessels, and perform numerous functions that are essential for brain homeostasis and neural functioning.

Keywords: astrocytes ; senescence ; blood–brain barrier

1. Introduction

Age-onset neurodegenerative disorders such as Alzheimer's disease (AD) and related dementias (ADRD) are debilitating conditions that progressively impair the memory, cognition, and daily functioning of afflicted individuals. As the average lifespan has increased in developed nations, so has the prevalence of symptomatic AD. An estimated 6.2 million adults aged 65 and older are living with Alzheimer's dementia, presenting a substantial societal burden [1]. However, despite decades of research, negligible progress has been made in developing effective disease-modifying treatments capable of halting or reversing AD progression and associated cognitive decline. The unsatisfactory clinical trial outcomes of experimental AD therapies indicate the need for a greater understanding of the age-related processes that drive neurodegenerative diseases.

2. Astrocyte Functions

Astrocytes are stellated glial cells that interface with nearly every functional element of the brain. They are the most abundant glial cells in the brain and can comprise up to 50% of the tissue volume in some regions [2]. Their branch-like processes surround neurons, axons, synapses, and blood vessels, and perform numerous functions that are essential for brain homeostasis and neural functioning [3]. Therefore, astrocytes play a pivotal role in preserving brain health, as well as driving pathogenic processes [4][5]. The understanding of astrocyte functions is continually growing as researchers study this heterogenous population of cells under different conditions, and it is increasingly evident that astrocytes perform unique functions, depending on their temporal and regional location within the brain [6][7][8][9]. Here, the researchers briefly review the astrocyte functions related to neuronal support, immune modulation, and regulation of the blood–brain barrier (BBB), as three factors that go awry in aging and disease.

2.1. Neuronal Support

At the macrostructural level, astrocytes help form a functional glial network that extends from the ependyma to the pial surface via gap junctions [10][11]. The perivascular feet of astrocytes associate with the parenchymal basal lamina to form a plexus called the glia limitans. This thin, but dense, structure surrounds the pia mater, subpial space, and perivascular spaces, and plays an essential role in controlling the movement of substances from the blood or cerebrospinal fluid (CSF) into the brain parenchyma, where neurons are located [12].

In addition to their role in barrier function, astrocytes maintain the optimal conditions required for neurotransmission within the cerebral microenvironment. To transmit a signal, neurotransmitters are released from an axon terminal into the synaptic cleft, where they interact with post-synaptic receptors. Ending the transmission requires neurotransmitter uptake from the synaptic cleft by neurons and astrocytes. While neurons primarily uptake the inhibitory transmitter, gamma-amino butyric acid (GABA), astrocytes are responsible for the uptake and metabolism of the excitatory amino acid, glutamate [13][14][15]. Additionally, the propagation of nerve impulses involves cellular depolarization, which causes local extracellular changes in ion concentration. Astrocytes contain ion channels, enzymes, and receptors that enable them to modify extracellular ion concentrations and pH following depolarization to restore the surrounding milieu to its resting state [16][17][18][19]. Astrocytes are also critical in removing harmful metabolites and waste products from the brain. They can directly

metabolize some soluble waste products, such as ammonia; alternatively, they collect and shuttle unwanted metabolites and soluble proteins, such as amyloid beta (Aβ) to the vasculature for elimination via the glymphatic system [15][20][21].

In addition to maintaining the cerebral microenvironment, astrocytes also participate in neurotransmission and are critical in shaping the complex circuitry of the brain [22]. Astrocytes form tripartite complexes with presynaptic and postsynaptic nerve terminals, through which they help define synaptic connections. Astrocytes are the major source of extracellular matrix proteins, cell adhesion molecules, and neurotrophic factors in the central nervous system (CNS), which are essential in promoting neurite growth and elongation [23][24][25][26][27]. Additionally, astrocytes physically associate with neuronal synapses via perisynaptic astrocytic processes (PAPs) that regulate many aspects of their formation, maturation, and function [22][28]. For example, astrocytes regulate synaptogenesis via the secretion of thrombospondins (TSP) [29] and TGFβ1 [30][31], and can specifically control the maturation and plasticity of certain circuits via the secretion of Hevin and SPARC [32][33].

2.2. Immune Modulation

Compared to other tissues, the brain is a relatively immune-privileged site because it lacks a significant resident lymphoid population, and the BBB substantially restricts the entry of circulating immune cells into the CNS. Astrocytes are not immune cells per se, but are capable of many immune functions, including phagocytosis, antigen presentation, and facilitating immune-cell trafficking [34][35]. Therefore, astrocytes may produce pro- or anti-inflammatory cytokines, such as IL-1β, IL-6, TNF, IL-10, IL-27, and TGF-β in response to disease, stress, or injury [34][36]. Within the CNS, they communicate bidirectionally with microglia to coordinate defense responses [37]. Along with microglia, astrocytes phagocytose neuronal material including synapses, apoptotic neurons, and degenerating axons, as well as toxic proteins, such as Aβ plaques in AD and α-synuclein in Parkinson's disease [38][39]. Consistent with their ability to present antigens, astrocytes express major histocompatibility complex (MHC) antigens that are upregulated in response to disease [40]. For example, high levels of astrocytic MHC-II were found in the brains of patients with Parkinson's disease (PD), which correlated with the load of pathological, phosphorylated alpha synuclein (αSYN) [41]. Notably, perivascular and infiltrated CD4+ T cells were surrounded by MHC-II expressing astrocytes, indicating astrocyte–T-cell cross-talk in the PD brain [41]. Astrocytic MHC-I is upregulated during aging, which appears to be protective, since it is associated with preserved cognitive function [42].

Due to their proximity to blood vessels, astrocytes play a critical role in mediating reciprocal communication between CNS-resident cells and the immune system. Depending on the subsets involved, astrocytes respond to T-cell signals to either boost or limit CNS inflammation. For instance, pathogenic Th17 cells signal to astrocytes via GM-CSF and IL-17 to boost neurotoxic astrogliosis [43][44][45]; however, FOXP3+ regulatory T cells secrete amphiregulin to suppress astrogliosis and promote recovery after ischemic stroke [46]. Conversely, they can also produce chemokines, such as CCL2, CXCL10, and CXCL12, which are involved in leukocyte recruitment into the CNS [47]. During aging, there is an increase in the production of astrocytic CXCL10, which serves as a chemoattractant for peripheral immune cells and aids in T-cell adhesion to endothelial cells [48]. In summary, astrocytes are critical regulators of immune responses in the CNS, as they may promote or dampen neuronal damage and inflammation, depending on the context and stimuli.

2.3. Blood–Brain Barrier Regulation and Maintenance

The BBB is a highly selective semipermeable barrier that restricts the entry of blood cells and plasma components into the brain parenchyma, facilitates the influx of essential nutrients, and mediates the efflux of neurotoxic products. Together, these tasks maintain an optimal environment for neuronal survival and function. The anatomical BBB consists of a continuous monolayer of endothelial cells (ECs) connected by tight junctions (TJ) and adherens junctions (containing claudin, occludin, and zonula occludens proteins). TJ proteins restrict paracellular permeability and also segregate the apical and basal domains of the cell membrane, which enables endothelial polarization [49]. The regulation of the BBB is accomplished by the neurovascular unit (NVU), a multicellular unit that functionally connects the brain and the cerebral vasculature. The NVU is composed of specialized ECs, pericytes, and perivascular astrocytes, whose end-feet sheath all cerebral blood vessels [50].

In addition to the paracellular pathway, several transcellular pathways across the BBB are carefully regulated by the NVU. Due to large surface areas of the lipophilic membranes in ECs, small gaseous molecules, such as O_2 and CO_2, and small lipid-soluble agents can diffuse freely though the endothelium. Specialized EC transporter proteins, such as glucose transporter 1 (GLUT1) and L-type amino acid transporter 1 (LAT1), supply the brain with glucose and amino acids, respectively. Additional transporters supply the brain with nucleosides, nucleobases, and other substances [51]. Some transporters, such as P-glycoprotein (Pgp), are energy-dependent and act as efflux transporters for neurotoxic molecules [52]. Other proteins, such as insulin and transferrin, are taken up by ECs via receptor-mediated endocytosis and then

transported across the BBB in vesicles, in a process called receptor-mediated transcytosis (RMT) [53]. Native plasma proteins, such as albumin, are typically excluded from the healthy adult brain, but can cross the BBB via adsorptive-mediated transcytosis (AMT) under specific conditions [54]. AMT is also vesicle-mediated, but it involves nonspecific binding to the membrane surface charges before internalization and transport through EC cell bodies.

The perivascular end feet of astrocytes show several specialized features, including a high density of K+ transporters and aquaporin (AQP4) water channels, which are involved in ion recycling and brain-volume regulation, respectively [55]. Through a combination of cell–cell interactions and soluble factors, perivascular astrocytes regulate the expression of TJ proteins and directly modify the transport properties of the cerebral endothelium [55][56][57]. Compared with ECs cultured alone, ECs co-cultured with astrocytes or astrocyte-conditioned media were found to exhibit increased TJ formation, transporter expression, and overall improved barrier function [58]. Subsequent studies have identified the molecular mechanisms responsible for the astrocytic regulation of the BBB. For example, the astrocyte secretion of factors such as angiopoietin 1 (ANG1) and sonic hedgehog (SHH) cause ECs to upregulate TJ proteins, thus enhancing barrier tightness [59][60][61].

Beyond BBB regulation, a recent research showed that astrocytes perform a necessary and nonredundant function in adult BBB maintenance [62]. The research used a genetic DTA ablation system to conditionally and selectively ablate astrocytes from the adult mouse brain and observed significant BBBD, indicated by the leakage of cadaverine (~900 Da) and fibrinogen (340 kDa) into the parenchyma. The blood vessels within the regions of astrocyte loss had a lower expression of the TJ protein zonula occludens-1 (ZO-1), while the expression of the endothelial transporter GLUT1 remained undisturbed. BBBD persisted for several weeks following ablation, suggesting a lack of barrier repair [62].

Other roles of astrocytes in BBB function have been studied in the context of disease. For example, the E4 variant of apolipoprotein E (APOE), the main susceptibility gene for AD, leads to accelerated BBBD and cognitive decline in humans and animals [63][64]. APOE is primarily synthesized and secreted in the CNS by astrocytes and is required for BBB formation and maintenance [65]. A recent study used allele-specific knock-in mice with the human E4, E3, and E2 APOE variants and showed that the humanized APOE4, but not APOE2 or APOE3, mice exhibited BBBD, increased matrix metalloproteinases-9 (MMP9), impaired TJs, and reduced the astrocyte end-foot coverage of blood vessels [66]. This is a seminal example of how astrocyte dysfunction can directly lead to BBBD and subsequent neurological disease. Additional mechanisms through which astrocytes contribute to BBBD in aging and disease continue to be explored.

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