Perivascular Astrocyte Endfeet

Subjects: Anatomy & Morphology
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Astrocytes (ACs) are the most abundant cells in the brain and, importantly, are the master connecting and communicating cells that provide structural and functional support for brain cells at all levels of organization. Further, they are recognized as the guardians and housekeepers of the brain. Protoplasmic perivascular astrocyte endfeet and their basal lamina form the delimiting outermost barrier (glia limitans) of the perivascular spaces in postcapillary venules and are important for the clearance of metabolic waste. They comprise the glymphatic system, which is critically dependent on proper waste removal by the pvACef polarized aquaporin-4 water channels. Also, the protoplasmic perisynaptic astrocyte endfeet (psACef) are important in cradling the neuronal synapses that serve to maintain homeostasis and serve a functional and supportive role in synaptic transmission. Enlarged perivascular spaces (EPVS) are emerging as important aberrant findings on magnetic resonance imaging (MRI), and are associated with white matter hyperintensities, lacunes, and aging, and are accepted as biomarkers for cerebral small vessel disease, increased obesity, metabolic syndrome, and type 2 diabetes. Knowledge is exponentially expanding regarding EPVS along with the glymphatic system, since EPVS are closely associated with impaired glymphatic function and waste removal from the brain to the cerebrospinal fluid and systemic circulation.

Keywords: enlarged perivascular spaces ; neurovascular unit ; perivascular spaces ; perivascular astrocyte endfeet (rpvACef)

1. Introduction

Perivascular spaces (PVS) are fluid filled spaces that ensheathe pia vessels as they dive into the cortical grey and white matter of the central nervous system (CNS). The pia arteries and precapillary arterioles PVS are known to deliver cerebrospinal fluid (CSF) to the interstitium, while the postcapillary venules and veins are known to deliver primarily interstitial fluid (ISF), metabolic waste (MW), and some residual admixed CSF to the subarachnoid space (SAS) for eventual disposal from the brain to the systemic circulation [1][2][3][4].

Protoplasmic perivascular astrocyte endfeet (pvACef) adhere tightly to the basement membrane (BM) of the neurovascular unit (NVU) shared by both the brain endothelial cell(s) (BECs) and pericyte(s) (Pcs) via their pvACef basal lamina, also termed the glia limitans (GL). PvACef are responsible for integrating the vascular mural cells (BECs and Pcs) of the NVU to nearby regional neurons [1][2][3][4]. PvACef allow for NVU coupling, which is fundamental for the regulation of regional capillary cerebral blood flow (CBF) by both astrocyte and neuron-derived chemical messengers that provide for functional hyperemia that is known as neurovascular coupling [1][5][6]. PvACef are surrounded by the neuropil, which is comprised primarily of dendritic synapses and unmyelinated neurons—interneurons with traversing myelinated neurons and an extracellular matrix (ECM) interstitial space (ISS) between these cellular structures.

PvACef with their basal lamina form the delimiting outermost nanosized membrane barrier of perivascular spaces (PVS), which is also referred to as the glia limitans (GL), while the innermost barrier is the basement membrane (BM) of the neurovascular unit (NVU) brain endothelial cell(s) (BECs) and pericytes (Pcs) [2][3][7].

The glia limitans (GL) also consists of the pvACef basal lamina—BM in the peri-meningeal barrier that is known as *glia limitans superficialis* or *externa*, whereas this barrier surrounding the NVU is defined as *glia limitans perivascularis and further, any* substance entering the central nervous system (CNS) from the blood or cerebrospinal fluid (CSF) must cross the GL [8].

There are three basic types of astrocytes (ACs) that consist of (1) protoplasmic ACs found primarily in the grey matter cortex and are responsible for pvACef and perisynaptic astrocyte endfeet (psACef); (2) fibrous ACs found primarily in the white matter that are important for myelin maintenance and remyelination with interaction among oligodendrocytes and oligodendrocyte precursor cells; (3) peripheral astroglial processes (PAPs) ACs that are responsible for AC cytoplasmic extensions to the pvACef of the NVU and psACef that are known to cradle the synapses [8][9].

ACs are the most abundant cells in the brain and, importantly, are the master connecting, communicating, continuing, and creating cells (in the case of the creation of the perivascular unit (PVU) and its normal PVS and pathologic enlarged perivascular spaces (EPVS) in the postcapillary venule) of the brain. The ACs connect with the NVU via pvACef, and synapses via the perisynaptic astrocyte endfeet (psACef); the fibrous ACs connect to the myelinated neurons in the white matter, and connect to communicate with one another to create the AC syncytium via gap junction connexins [7][8][9][10][11][12][13].

ACs are capable of enacting most housekeeping and guardian homeostatic functions in the brain, from structural support to controlling molecular homeostasis and regulation of CBF, synaptogenesis, neurogenesis, and additionally development of the nervous system [11]. A brief summary of the homeostatic functions of ACs (via pvACef and perisynaptic ACef) include molecular homeostasis, which includes ion homeostasis (of potassium, chloride, and potassium), regulation of pH, water transport and homeostasis via aquaporin-4 (AQP4), and neurotransmitter homeostasis (including glutamate, gamma-aminobutyric acid (GABA), adenosine, and monoamines); systemic homeostasis, including chemosensing (O_2, CO_2, pH, Na+, and glucose), regulation of energy balance and food intake, and sleep homeostasis; cellular and network homeostasis, including neurogenesis, neuronal guidance, synaptogenesis, synaptic maintenance, elimination, and plasticity; metabolic homeostasis, including NVU formation and maintenance, support of NVU, CBF, metabolic support and maintenance, and glycogen synthesis and storage. Additionally, ACs act as a major supplier of energy via glycogen storage and glycolysis, as well as supplying antioxidant reserves such as glutathione (GSH) and superoxide dismutase (SOD), and growth factors such as brain-derived growth factor transforming growth factor-β (TGFβ). ACs also define many aspects of synapse formation, plasticity, protective function, synaptic maintenance, and elimination [11][12]. It is very important to note that human studies may not always conform to the findings of rodent models because pvACs in the neocortex are much larger in diameter (2.6-fold), have longer extending cellular extensions (10-fold), and have greater complexity and diversity than in rodent models [11][14].

The large AC cellular presence in the brain and their vast cell–cell communication via gap junction connexins may be viewed as the brain's functional syncytium [8]. The relationships among the pvACef and the NVU (including ECs, Pcs, and their shared outer basement membrane, as well as the cell–matrix attachments via dystroglycans and integrins of the pvACef to NVU BMs) are essential for proper homeostasis and function [7][13][15][16].

2. Perivascular Astrocyte Endfeet (pvACef)

One might refer to the NVU as the "neuro-glial-vascular unit" (NGVU), since the pvACs endfeet play such a critical role in connecting ACs to the NVU to accomplish NVU coupling with regional neurons to increase regional cerebral blood flow to neural activity [17][18]. Early on in researchers' studies of the diabetic *db/db* mouse models at 20 weeks of age, the group found multiple ultrastructure remodeling changes including the reactive pvACef that were tightly adherent to the basement membrane in the control models and depicted ultrastructural detachment and retraction of the pvACef in the diabetic *db/db* models [7][19]. This detachment and retraction created a void electron lucent fluid-filled space around the NVU between the NVU BM and the pvACef glia limitans [7][19].

This detachment and retraction are currently felt to be a result of the degradation and/or loss of function of the extracellular matrix receptors beta-dystroglycan (β-DG) and integrin alpha 6 beta 4 (α6β4) proteins localized to the plasma membrane of the pvACef due to oxidative stress via ROS that induce the proteolytic matrix metalloproteinases (MMP-2, 9) [20][21][22][23][24][25]. Importantly, the β-DG and α6β4 integrin receptors of the pvACef secure it to the BM via its connections that adhere to the laminin and other cytoskeletal components of the ECM BM of the NVU [20], and the α-dystroglycan form is responsible for the linkage to the basement membrane proteins [23], whereas β-dystroglycan links α-dystroglycan to the actin cytoskeleton [25]. Also, DG proteins are known to be present on dendritic spines [24].

It is a fascinating perspective that among the billions of neuroglia and neurons, the mammalian brain has interlaced an elaborate network of blood vessels that are enwrapped specifically by pvACef and connected to the neuronal synapses by psACef processes (80–90%) to provide a plentiful blood supply.

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