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Review article

Functional dissection of astrocyte-secreted proteins: Implications in brain health and diseases

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ABSTRACT

Astrocytes, which are homeostatic cells of the central nervous system (CNS), display remarkable heterogeneity in their morphology and function. Besides their physical and metabolic support to neurons, astrocytes modulate the blood-brain barrier, regulate CNS synaptogenesis, guide axon pathfinding, maintain brain homeostasis, affect neuronal development and plasticity, and contribute to diverse neuropathologies via secreted proteins. The identification of astrocytic proteome and secretome profiles has provided new insights into the maintenance of neuronal health and survival, the pathogenesis of brain injury, and neurodegeneration. Recent advances in proteomics research have provided an excellent catalog of astrocyte-secreted proteins. This review categorizes astrocyte-secreted proteins and discusses evidence that astrocytes play a crucial role in neuronal activity and brain function. An in-depth understanding of astrocyte-secreted proteins and their pathways is pivotal for the development of novel strategies for restoring brain homeostasis, limiting brain injury/inflammation, counteracting neurodegeneration, and obtaining functional recovery.

Contents

Abbreviations: ACM, astrocyte-conditioned media; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; ApoE, apolipoprotein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CCN, CYR61/connective tissue growth factor/nephroblastoma; ECM, extracellular matrix; GFAP, glial fibrillary acidic protein; LCN2, lipocalin-2; MMP, matrix metalloproteinases; NRG, neuregulin; AD, Alzheimer's disease; PD, Parkinson's disease; Sema, semaphorin; SPARC, secreted protein acidic and rich in cysteine; TN-C, tenascin C; TSP, thrombospondin; VEGF, vascular endothelial growth factor.

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1. Introduction

Neurons and glia are the primary cellular components of the central nervous system (CNS). The ratio of glia to neurons is 1:1 in the entire human brain (von Bartheld et al., 2016). Multiple studies have been conducted to investigate the contributions of glial cells. In the CNS, oligodendrocytes make up 45–75% of glial cells and are therefore the most prevalent. Astrocytes represent about 19–40% of the glial population, while microglia contribute 10% or less (Pelvig et al., 2008). Similarly, NG2 cells make up 5–10% of the glia in the CNS (Trotter et al., 2010). However, the ratio varies in different parts of the brain and with age. Glia are critical for the development and function of the CNS and are involved in diseases of the CNS. The functions of glia are not limited to providing structural and metabolic support to neurons and repairing neurons following injury, but they are also pivotal in diverse neuropathophysiologies. Growing evidence is unraveling the key roles of glial cells, especially astrocytes and microglia, in neuronal activity and complex higher brain functions and their interactions with neurons. Research performed over the last decade has changed the understanding of the role of astrocytes from passive supporters of neuronal activity to key players in brain function. Emerging evidence has established astrocytes as a crucial cell type that governs brain development, structural support, vasculature and/or blood flow (Howarth et al., 2017), blood-brain barrier (BBB) formation and function (Yamamizu et al., 2017), neurotrophic and survival factor allocation, synapse formation and elimination (Christopherson et al., 2005; Henneberger et al., 2010; Stevens et al., 2007; van Deijk et al., 2017), and brain homeostasis and that is involved in diverse neurological disorders (Barca-Mayo et al., 2017).

Glia communicate with neuron via signals, including ion fluxes, neurotransmitters, cell adhesion molecules, and several specialized signaling molecules that are released from synaptic and non-synaptic regions of neurons (Fernandes et al., 2017; Fields and Stevens-Graham, 2002). Neurotransmitters and other extracellular signaling molecules that are released from glia affect neuronal excitability and synaptic transmission and coordinate activity across neuronal networks. Emerging evidence defines astrocytes as CNS secretory cells (Verkhratsky et al., 2016a). In addition, astrocytes secrete neuroactive substances when in close contact with synapses (Paixao and Klein, 2010). During brain injury, astrocytes secrete factors that generate various regulatory signals and initiate intracellular signal transduction to stimulate glial cells located far away from the lesion center to migrate to the lesion. However, multiple astrocytic functions, including ionostasis, the uptake and regulation of neurotransmitters, and shuttling glutamate–glutamine, are not directly associated with the secretory nature of the astrocytes. Accumulating evidence has identified astrocytes as a primary component in the pathogenesis of many, if not all, neurological, neurodevelopmental, and psychiatric disorders (Verkhratsky et al., 2015, 2013, 2014, 2017). Neurological disorders with astrocytic participation can be genetic (e.g., Alexander disease, which is a primary sporadic astrogliopathy), environmental (e.g., heavy metal encephalopathies), or neurodevelopmental in origin. Astrocytes are crucial contributors to the neurodegenerative processes underlying Alzheimer's disease (AD), Huntington's disease, and amyotrophic lateral sclerosis. In addition, astrocytes contribute to neuropsychiatric disorders, including schizophrenia, depression, and addictive disorders (Verkhratsky and Parpura, 2016; Verkhratsky et al., 2014). Hypertrophy, gliosis, loss of function, atrophy, and asthenia of astrocytes are common hallmarks of neurological diseases (Ben Haim et al., 2015; Sun et al., 2017; Verkhratsky and Parpura, 2016; Verkhratsky et al., 2014). Astrocytes release protective or neurotoxic proteins following injury or under disease conditions in the brain. Astrocyte-secreted proteins have both detrimental effects, including neuroinflammation and neuropathologies, and beneficial effects, such as neuroprotection and repair processes, including tissue remodeling, axon regeneration, glial scar formation, angiogenesis, and neural circuitry rewiring. Therefore, the identification of known and unknown factors secreted from astrocytes is necessary not only to achieve a better understanding of their neuroprotective or neurotoxic properties but also to develop astrocyte-based therapeutic strategies that prevent disease progression and promote neurological recovery.

Secretomics is a subset of proteomics in which secreted proteins are analyzed. It is a powerful tool for studying the functions of astrocytes and finding novel biomarkers and therapeutic targets. The astrocyte secretome, which is a complete