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Review article

Translational potential of astrocytes in brain disorders

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ABSTRACT

Fundamentally, all brain disorders can be broadly defined as the homeostatic failure of this organ. As the brain is composed of many different cells types, including but not limited to neurons and glia, it is only logical that all the cell types/constituents could play a role in health and disease. Yet, for a long time the sole conceptualization of brain pathology was focused on the well-being of neurons. Here, we challenge this neuron-centric view and present neuroglia as a key element in neuropathology, a process that has a toll on astrocytes, which undergo complex morpho-functional changes that can in turn affect the course of the disorder. Such changes can be grossly identified as reactivity, atrophy with loss of function and pathological remodeling. We outline the pathogenic potential of astrocytes in variety of disorders, ranging from neurotrauma, infection, toxic damage, stroke, epilepsy, neurodevelopmental, neurodegenerative and psychiatric disorders, Alexander disease to neoplastic changes seen in gliomas. We hope that in near future we would witness glial-based translational medicine with generation of deliverables for the containment and cure of disorders. We point out that such as a task will require a holistic and multi-disciplinary approach that will take in consideration the concerted operation of all the cell types in the brain.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; AS, α-synuclein; ASD, Autism spectrum disorder; ADK, adenosine kinase; ATP, adenosine triphosphate; AxD, Alexander disease; CD81, Cluster of Differentiation 81; CMV, cytomegalovirus; CNO, clozapine N-oxide; CNS, central nervous system; CSC, cancer stem cell; CXCL-1, chemokine (C-X-C motif) ligand 1; DISC1, Disrupted-In-Schizophrenia-1; DREADD, designer receptor exclusively activated by a designer drug; DS, Down syndrome; EAST, epilepsy – ataxia – sensorineural deafness – salt-wasting renal tubulopathy; fALS, familial ALS; FDA, The Food and Drug Administration; FTD, fronto-temporal dementia; FUS, fused in sarcoma; GABA, γ-amino butyric acid; GBM, glioblastoma multiforme; GFAP, glial fibrillary acidic protein; GS, glutamine synthetase; HD, Huntington's disease; HRAS, Harvey rat sarcoma viral oncogene homolog; hSOD1, human superoxide dismutase; HSV1, herpes simplex virus 1; $InsP_3$, inositol 1,4,5 trisphosphate; IL, interleukin; iNOS, inducible nitric oxide synthetase; JNK, c-Jun N-terminal kinase; L-AAA, L-alpha-aminoadipic acid; mGluR, metabotropic glutamate receptor; mhtt, mutant huntingtin protein; MAO-B, monoamine-oxidase B; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSA, multiple system atrophy; NFAT, immune/inflammatory calcineurin/nuclear factor of activated T-cells; NAcore, the nucleus accumbens core; NMDA, N-methyl D-aspartate; NOD2, nucleotide-binding oligomerization domain containing protein 2; PD, Parkinson's disease; PS, presenilin; Ras, rat sarcoma; ROS, reactive oxygen species; SeSAME, seizures – sensorineural deafness – ataxia – mental retardation – electrolyte imbalance; SNARE, soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor; TARDBP, TAR DNA binding protein; TNF-α, tumor necrosis factor α; TRP, transient receptor potential.

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1. Astrogliopathology: reactivity, atrophy with loss of function and pathological remodeling

Fundamentally, all diseases, including neurological disorders can be broadly defined as homeostatic failures within tissue, organ or a system. For a long time neuropathology was dominated by the neuron-centric views with all conceptualization of brain pathology being focused on neurons, on their survival or death. The neuron-centricity is now being challenged and neuroglia begins to be regarded as a central element of neuropathology (Burda and Sofroniew, 2014; Giaume et al., 2007; Nedergaard et al., 2010; Parpura et al., 2012; Sofroniew, 2009).

Astroglia is the name for a highly heterogeneous population of neural cells, populating the grey and white matter of the central nervous system (CNS), which are chiefly responsible for the homeostasis of the neural tissue and contribute to its defense in pathology (Kettenmann and Ransom, 2013; Verkhratsky and Butt, 2013). Astroglial expression of a wide array of receptors for neurotransmitters and neurohormones is regulated by the neurochemical environment and, as a rule, astrocytes possess receptors allowing them to sense neighboring neuronal transmission (Parpura and Verkhratsky, 2012a). Activation of these receptors triggers dynamic changes of concentration of ions (mainly Ca^{2+} and Na^{+}) in the astroglial cytoplasm, which regulate astroglial functions and serve as a substrate for astroglial excitability (Agulhon et al., 2008; Kirischuk et al., 2012; Parpura and Verkhratsky, 2012b, 2013; Rose and Karus, 2013; Verkhratsky et al., 2014c; Zorec et al., 2012). The functions of astrocytes are highly diverse and are regionally specialized (Anderson et al., 2014; Chaboub and Deneen, 2012; Matyash and Kettenmann, 2010; Oberheim et al., 2012; Parpura et al., 2012; Schitine et al., 2015). In the gray matter astrocytes divide (through the process known as tiling that starts in the late embryogenesis) the parenchyma into relatively independent units, traditionally known as neurovascular units and recently often called astroglio-vascular units, that integrate, within an individual astroglial territorial domain, neural and vascular elements (Bushong et al., 2002; Iadecola and Nedergaard, 2007; Nedergaard et al., 2003). By employing a variety of molecular mechanisms (exocytosis, membrane transporters or diffusion through plasmalemmal channels) astrocytes secrete numerous neurotransmitters, neurohormones and trophic factors (Malarkey and Parpura, 2008; Parpura et al., 2011) that regulate synapse formation and maintenance, modulate synaptic transmission and synchronization of neuronal networks and signal to other (in addition to neurons) cellular elements (e.g., microglia, oligodendroglia, pericytes, and endothelial cells). At the level of the whole brain, astrocytes form the glia limitans (i.e., a thin barrier surrounding the brain and spinal cord and containing astrocytic end-feet associated with the parenchymal basal lamina) and regulate emergence and function of brain-blood and brain-cerebro-spinal fluid barriers and contribute to overall brain metabolism being the sole producers and repository of glycogen (Kettenmann and Ransom, 2013; Verkhratsky and Butt, 2013).

Cellular pathophysiology of the CNS involves all cells that constitute brain tissue, with each cell type playing its defined function (Burda and Sofroniew, 2014). Astrocytes contribute to virtually all neuropathological conditions. First and foremost, astrocytes maintain CNS homeostasis; the homeostatic function of astroglia is linked to their neuroprotective capabilities. Insults to the CNS regardless of their etiology put the strain on the organ homeostasis and it is astrocytes that through dedicated molecular cascades protect neurons against glutamate excitotoxicity, extracellular K^{+} overload, and reactive oxygen species (ROS). Astrocytes also supply stressed neurons with energy substrates. The loss of these critical astroglial functions permits and exacerbates progression of various diseases, from which amyotrophic lateral sclerosis, toxic encephalopathies and neurodegeneration are prominent examples (Verkhratsky et al., 2014a). In addition, astrocytes are capable of mounting a specific defensive response, generally known as reactive astrogliosis (Fig. 1), a multicomponent and complex remodeling of astroglia triggered by lesions to the CNS (Burda and Sofroniew, 2014; Pekny et al., 2014; Sofroniew, 2009; Verkhratsky et al., 2014b). Astrogliotic phenotypes are yet to be investigated in detail, although the context specificity becomes increasingly clear. Transciptomes of reactive astrocytes activated by two distinct stimuli, the ischemic stroke and injection of bacterial lipopolysaccharide, showed remarkable difference, indicating that the stress signal defines characteristic of astrogliotic program (Zamanian et al., 2012). Astrogliosis is an important component of cellular pathophysiology and its suppression generally aggravates neuropathology.