Neurobiology of Disease 85 (2016) 254–261

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Astrogliopathology in neurological, neurodevelopmental and psychiatric disorders

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ARTICLE INFO

Article history:
Received 19 January 2015
Revised 20 March 2015
Accepted 26 March 2015
Available online 3 April 2015

Keywords:
Neuroglia
Astrocyte
Reactive astrogliosis
Neurological diseases
Hepatic encephalopathy
Psychiatric diseases
Neurodegeneration

ABSTRACT

Astroglial cells represent a main element in the maintenance of homeostasis and providing defense to the brain. Consequently, their dysfunction underlies many, if not all, neurological, neurodevelopmental and neuropsychiatric disorders. General astrogliopathy is evident in diametrically opposing morpho-functional changes in astrocytes, i.e. their hypertrophy along with reactivity or atrophy with asthenia. Neurological disorders with astroglial participation can be genetic, of which Alexander disease is a primary sporadic astrogliopathy, environmentally caused, such as heavy metal encephalopathies, or neurodevelopmental in origin. Astroglia contribute to neurodegenerative processes seen in amyotrophic lateral sclerosis, Alzheimer's and Huntington's diseases. Furthermore, astroglia also play a role in major neuropsychiatric disorders, ranging from schizophrenia to depression, as well as in addictive disorders.

Astroglia as a main element of brain homeostasis and defense

The brain and the spinal cord (which constitute the central nervous system or CNS) are composed of several types of cells that are derived from the ectoderm, i.e., the neuroepithelium (neurons and macroglia) and from other germ layers (microglia, cells of blood vessels, fibroblasts, endothelial cells etc.) (Fig. 1) (Burda and Sofroniew, 2014; Verkhratsky and Butt, 2013). These many types of cells, that differ in their structure and function, are assembled in highly complex networks coordinated by signaling molecules either released into the extracellular space (neurotransmitters, neurohormones, neuromodulators, growth factors, cytokines, trophic factors, etc.) or translocated between cells using intercellular diffusion channels formed by gap junctions (Verkhratsky, 2009; Verkhratsky, 2010).

Macroglial cells of the CNS are represented by astroglia, oligodendroglia and NG2 glia, of which the latter two types are lineage-related and are mainly responsible for myelination and various forms of axonal support. Astrocytes represent cells highly heterogeneous in structure and function, which provide for fundamentals of overall homeostasis of the CNS. Conceptually, astrocytes are responsible for virtually every conceivable homeostatic task that occurs in developing and functional CNS. Astroglia are the central elements of neurogenesis and the development of the CNS (the radial glia being the pluripotent neural precursor and the scaffold for newborn neural cells migration (Kriegstein and Alvarez-Buylla, 2009)). Astrocytes are important for the structural organization of the nervous tissue (they organize the grey matter into a series of relatively independent neurovascular units), and for synaptogenesis and synaptic maturation (astroglial cells are obligatory for the formation of at least 50% of CNS synapses. They also control synapses through the secretion of multiple factors (such as thrombospondins, cholesterol or neuregulins) and play a role in the formation and regulation of brain–blood and brain–cerebrospinal fluid barriers. Moreover, astrocytes regulate neurotransmitter turnover (astrocytes take up glutamate, γ-aminobutyric acid (GABA), glycine and adenosine by specific transporters, catabolize glutamate and adenosine by glutamine synthetase and adenosine kinase, expressed almost

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Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.03.025
0969-9961/

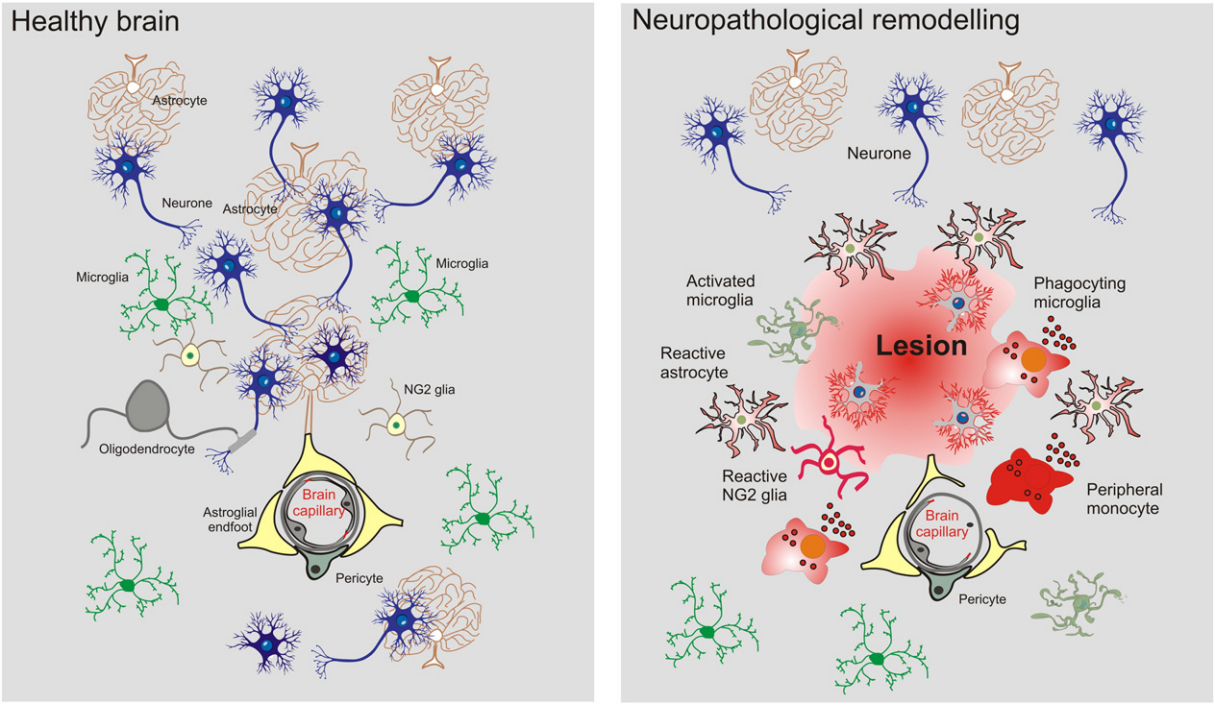

Fig. 1. Multicellular nature of the pathological response of the CNS tissue. The brain and the spinal cord cellular networks are composed of various cell types that include the posterity of ectodermal neuroepithelial cells represented by neurons, astrocytes, oligodendrocytes and NG2 glia, and cells derived from other germ layers (microglial cells, smooth muscle cells of the blood vessels, endothelial cells, blood cells, fibroblasts and pericytes, although the precise origin of the latter remain somewhat controversial). Pathological responses of the CNS involve all these cell types in a disease-specific fashion and may be manifested in reactive responses of astrocytes, NG2 cells and microglia, in pathological remodeling of oligodendrocytes, in atrophic changes of all these cells, in CNS tissue invasion by peripheral monocytes, etc. The specificity of cellular response defines the evolution, progression and resolution of neuropathological conditions. See details in the text.

solely in astroglia, and supply neurons with glutamine which appears as a compulsory precursor for glutamate and GABA). They contain numerous transporters that control ion homeostasis in the CNS. Astrocytes are intimately involved in sensing brain hyperthermia and are the main component of heat stress response; they specifically upregulate the expression of the 70 kDa heat shock proteins (Hsp70). These chaperones are the primary components of the heat shock response which are expressed exclusively in neuroglia and not in neurons (Sharma, 2011). Finally, these cells are indispensable for water transport and for scavenging reactive oxygen species (as astroglia is the major source of glutathione and ascorbic acid). All these homeostatic functions of astroglia are well known and have been overviewed in numerous papers published in the past decade to which we do refer our reader (see (Clarke and Barres, 2013; Iadecola and Nedergaard, 2007; Kettenmann and Ransom, 2013; Kimelberg and Nedergaard, 2010; Nedergaard and Verkhratsky, 2012; Oberheim et al., 2012; Parpura et al., 2012; Zhang and Barres, 2010)).

Homeostatic capabilities of astroglia are of paramount importance for CNS function in physiological conditions, and naturally they are critical for brain response to pathological insults of any etiology. The disease being homeostatic failure develops when homeostatic reserves are exhausted, and neurological diseases critically depend on the capability of astrocytes to maintain homeostasis of the CNS. Furthermore, astrocytes are endowed with evolutionarily conserved program, which is activated in pathological conditions, the program of reactive astrogliosis which remodels cellular biochemistry, structure and function in an attempt to contain the pathological developments. The pathological potential of astrocytes is not, however, limited to their reactivity; in many types of neuropathology astrodegeneration and loss of astroglial function bear serious pathological significance.

General gliopathology: reactivity and atrophy

Pathological changes in the CNS affect all cell types (Fig. 1) and lead to a complex and disease-specific remodeling of cellular networks. Already in early histopathological studies, performed at the beginning of the 20th century, both progressive (which we now refer to as reactive) and regressive (atrophic and degenerative) remodeling changes have been documented (for the early history of gliopathology see for example (Glees, 1955; Kettenmann and Verkhratsky, 2008)). All types of neuroglial cells affected by the insult undergo complex and multifaceted changes leading to an appearance of numerous new "reactive" phenotypes. The reactive gliotic response is represented by reactive astrogliosis, reactive activation of NG2 cells, reactive remodeling of oligodendroglia (which is partly manifested as Wallerian degeneration) and the activation of microglia. Neuropathology is also associated with glial atrophy, loss of function or pathological remodeling, which generally reduces homeostatic and defensive capabilities of these cells and may permit or mediate various forms of neurotoxicity. Complex neuropathological changes that occur in glial cells inspired a reassessment of neurono-centrism in neuropathology (Barres, 2008; Molofsky et al., 2012; Nedergaard et al., 2010; Thrane et al., 2014; Verkhratsky et al., 2012, 2014b,c).

Reactive astrogliosis has been regarded as a purely pathological, detrimental reaction that exacerbates the neuropathological progression, although this point of view gradually yields to a modern concept that regards astrogliotic response as an intrinsically defensive and protective metamorphosis aimed at the preservation and regeneration of the neural tissue (Pekna and Pekny, 2012; Pekny et al., 2014; Sofroniew, 2009; Sofroniew and Vinters, 2010; Verkhratsky et al., 2012). Generally, astroglial reactivity is defined as astrocytic hypertrophy and proliferation that goes along with an up-regulation of cytoskeletal components such as glial fibrillary acidic protein (GFAP), vimentin