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Review

The glial perspective of autism spectrum disorders

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ABSTRACT

The aetiology of autism spectrum disorders remains unclear although a growing number of associated genetic abnormalities and environmental factors have been discovered in recent decades. These advancements coincided with a remarkable increase in the comprehension of physiological functions and pathological potential of neuroglia in the central nervous system that led to a notion of fundamental contribution of glial cells into multiple neuropathologies, including neuropsychiatric and developmental disorders. Growing evidence indicates a role for deregulation of astroglial control over homeostasis and plastic potential of neural networks as well as microglial malfunction and neuroinflammatory response in the brains of autistic patients. In this review, we shall summarize the status and pathological potential of neuroglia and argue for neuroglial roots of autistic disorders.

Contents

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"*This very interstitial tissue of the brain and spinal marrow is one of the most frequent seats of morbid change*"

(Rudolf Virchow, discussing about neuroglia; taken from "Cellular Pathology", 1858)

1. Introduction

1.1. Neuroglia as homeostatic cells of the nervous system

Conceptually, plasticity of the brain is controlled at three different levels: subcellular compartments, single cells, and cellular networks. In the neural circuitry, intercellular connections are established by synapses operating in both chemical (mainly between neurones) and gap-junctional or electrical (mainly connecting astrocytes) varieties (Kettenmann and Ransom, 2013). Genesis, development, and functional remodelling of the highly complex neural cellular networks require precise homeostatic control executed at all these levels of organization. This homeostatic control is accomplished by neuroglia. Neuroglial cells, initially defined by Virchow as a connective tissue that "*. . .lies between the proper nervous parts, holds them together and gives the whole its form in a greater or less degree*" (Virchow, 1858), are represented by highly heterogeneous cells of neural (macroglia) and myeloid (microglia) origins (see Fig. 1). Macroglia in turn are classified into astroglia, oligodendroglia, and NG2 cells (Nishiyama et al., 2005; Verkhratsky, 2010; Verkhratsky and Butt, 2013). The common function of all these diverse cell types is to maintain homeostasis of the central nervous system (CNS), and therefore neuroglia can be defined as homeostatic cells of the CNS.

Astrocytes are arguably the most diverse neuroglial cells, being represented by protoplasmic astrocytes of the grey matter and fibrous astrocytes of the white matter, by the radial glia localized in the retina (Müller glia) and cerebellum (Bergmann glia), by the velate astrocytes of the cerebellum, by the interlaminar and polarized astrocytes of the primate cortex, by tanycytes and pituicytes, by perivascular and marginal astrocytes, etc. Astroglia also include several types of cells (ependymocytes, choroid plexus cells, and retinal pigment epithelial cells) that line the ventricles or the subretinal space (Verkhratsky and Butt, 2013). Astrocytes exert many functions, and these embrace almost every conceivable homeostatic task, from isolating the brain from the rest of the body (astrocytes control emergence and function of the blood brain barrier) to controlling neurogenesis (astrocytes in the neurogenic niches are the pluripotent stem cells), regulating ion homeostasis, supporting synaptogenesis, maintaining synaptic transmission through removing neurotransmitters and providing neurones with glutamate and GABA precursor glutamine, supplying neurones with energy substrates, and secreting scavengers of reactive oxygen species (ROS) (for comprehensive account on astroglial functions see Alvarez-Buylla and Lim, 2004; Giaume et al., 2010; Hertz et al., 1999; Iadecola and Nedergaard, 2007; Kimelberg, 2010; Kriegstein and Alvarez-Buylla, 2009; Nedergaard et al., 2003; Parpura and Verkhratsky, 2012; Verkhratsky and Butt, 2013; Wang and Bordey, 2008).

Two other classes of neuroglial cells, the oligodendrocytes and NG2 glia, are lineage related. The oligodendrocytes are critical for axon myelination, which in turn is fundamental for establishing the brain connectome and indispensable for miniaturization of the CNS (Hartline and Colman, 2007; Sporns et al., 2005; Van Essen and Ugurbil, 2012). The NG2 glia belong, from the lineage point of view, to oligodendroglial precursors, although their relatively numerous presence in the mammalian brain and their ultimate function(s) remain, to a large extend, enigmatic (Butt et al., 2005; Nishiyama et al., 2009).

Finally, microglial cells are scions of myeloid progenitors originating from the extra-embryonic yolk sac (Ginhoux et al., 2010). These myeloid progenitors enter the CNS during early embryonic development; the second wave of myeloid invasion possibly occurs in perinatal period in a form of "fountains of microglia" (Kershman, 1939), these being clearly visible around, for example, the corpus callosum. After entering the CNS, microglial cells undergo remarkable metamorphosis that converts them into surveying or "resting" microglia, which constantly scan the neighbouring neural tissue for the signs of damage (Kettenmann et al., 2011). At the same time, microglial cells have extensive array of physiological functions specifically important for the development, shaping, and fine tuning of synaptic connectivity. Of note, microglial cells are the first and only glial cells populating early embryonic brain, because astro- and oligodendrogliogenesis occur later in perinatal period. Physiological functions of microglia are many; in particular, they include (i) early synaptogenesis in which microglia can provide growth factors and thrombospondins, (ii) elimination of redundant synapses, (iii) direct modulation of synaptic transmission by secreting diverse factors such as, for example, BDNF or TNF-α; microglial cells also (iv) provide trophic support, and (v) regulate neurogenesis (for further details, see Kettenmann et al., 2013; Tremblay et al., 2010, 2011; Tyler and Boulanger, 2012).

1.2. Neuroglia in neuropathology

Neurological diseases are, by definition, failures of nervous system homeostasis in response to environmental (e.g. trauma, infection or toxic poisoning), systemic (e.g. ischaemia) or endogenous factors. Glial cells, being the central element of brain homeostasis, are ultimately involved in the pathogenesis of several neurological disorders. In addition to controlling homeostasis, neuroglia form the defensive system of the brain activated in response to every kind of lesion. Neuroglial defence defines, to a very large extend, the progression and outcome of neuropathology. The role of neuroglia in neuropathology can be primary; for instance, in Alexander disease when astroglial expression of mutated GFAP gene results in profound alterations to white matter, or in toxic assaults that render astrocytes incapable to contain glutamate load and hence trigger massive excitotoxicity; the examples of these include toxic encephalopathies such as Minamoto disease or Wernicke-Korsakoff encephalopathy. It can also be secondary; these latter being represented by variants of reactive gliosis, which is typical for virtually every type of neuropathology (Giaume et al., 2007; Verkhratsky et al., 2013).

Conceptually, gliotic reaction, which is further classified into reactive astrogliosis and activation of microglia, can be regarded as a complex, multistage, and disease specific defensive response to neuropathology (see Fig. 2). Reactive astrogliosis represents an evolutionary conserved (astrogliotic response is already in operation in arthropods) and highly versatile remodelling of astroglia aimed at neuroprotection and trophic support of stressed neurones, at isolation of the damaged area, and at reconstruction of damaged tissue after resolution of the pathology (Sofroniew, 2009; Sofroniew and Vinters, 2010; Verkhratsky and Butt, 2013). Insults of different severity and aetiology induce distinct astrogliotic programmes classified as isomorphic (i.e. preserving morphology and usually fully reversible) and anisomorphic (i.e. changing the morphology, in which astrocytes loose their domain organization and form the gliotic scar) astrogliosis. Similarly, activation of microglia is an intrinsically defensive reaction that produces multiple phenotypes, depending on severity and specificity of the pathological process, providing neuroprotection and elimination of pathogens, dead cells, or cellular debris (Hanisch and Kettenmann, 2007; Kettenmann et al., 2011; Ransohoff and Perry, 2009).

Besides reactive remodelling, numerous neurological diseases are associated with astroglial atrophy and/or functional asthenia. Atrophic and functionally weakened astrocytes are observed at the