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Review

Heterogeneous astrocytes: Active players in CNS

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ABSTRACT

Astrocytes, the predominant cell type that are broadly distributed in the brain and spinal cord, play key roles in maintaining homeostasis of the central nerve system (CNS) in physiological and pathological conditions. Increasing evidence indicates that astrocytes are a complex colony with heterogeneity on morphology, gene expression, function and many other aspects depending on their spatio-temporal distribution and activation level. In pathological conditions, astrocytes differentially respond to all kinds of insults, including injury and disease, and participate in the neuropathological process. Based on current studies, we here give an overview of the roles of heterogeneous astrocytes in CNS, especially in neuropathologies, which focuses on biological and functional diversity of astrocytes. We propose that a precise understanding of the heterogeneous astrocytes is critical to unlocking the secrets about pathogenesis and treatment of the mazy CNS.

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1. Introduction

Astrocytes are the most abundant cell type that broadly distributed throughout the mammalian central nervous system (CNS). For a long time, astrocytes have been considered to be a homogeneous and non-excitable cell type in the CNS, which just support neuronal survival. However, increasing evidences show that astrocytes located in separate territories display diverse active properties and play essential roles in physiological or pathological CNS (Volterra and Meldolesi, 2005). For decades, a variety of physiological functions of astrocytes have constantly been reported, such as supporting the CNS metabolism, regulating the cerebral blood flow, maintaining the blood-brain barrier, clearing the neurotransmitters between synapses (Freeman, 2010, 2013; Rose and Karus, 2013; Sofroniew and Vinters, 2010), and specific effects on neural circuit development and synaptic plasticity (Han et al., 2013). In addition, astrocytes also perform critical functions in pathological CNS, including traumatic brain injury (TBI), spinal cord injury (SCI), stroke, Parkinson's disease (PD), Alzheimer disease (AD), and amyotrophic lateral sclerosis (ALS) (Sofroniew and Vinters, 2010; Zlokovic, 2008).

As the numerous morphologies and functions of astrocytes were documented, the heterogeneity of astrocytes is beginning to be appreciated (Anderson et al., 2014; Matyash and Kettenmann, 2010; Oberheim et al., 2012; Zhang and Barres, 2010). With the development of experiment technology including transgenic animals, gene chip, and two-photon imaging, more and more secrets about the astroglial heterogeneity were unlocked. Recent evidences show that the heterogeneity of astrocytes exists in not only the morphologies and functions but also many other aspects, including the development (Bayraktar et al., 2014), genomes (Darmanis et al., 2015; Doyle et al., 2008; Hawrylycz and Guillozet-Bongaarts, 2012; Yeh et al., 2009), astrogliosis (Sofroniew, 2014) and cell-cell interaction (Gabor and Petzold, 2011). In the past few years, there are some excellent review articles on the heterogeneous astrocytes in development and in physiological conditions (Bayraktar et al., 2014; Chaboub and Deneen, 2012; Khakh and Sofroniew, 2015; Matyash and Kettenmann, 2010; Oberheim et al., 2012; Sofroniew and Vinters, 2010; Zhang and Barres, 2010). Here, this review will focus on the heterogeneous astrocytes in response to CNS injury or disease. The insight into astrocyte diversity will undoubtedly contribute to understanding of the astroglial function, dissection of the CNS pathology, and identification of potential strategies for CNS injury and diseases therapy.

2. Astrocyte, an active and versatile cell in CNS

Recently, the importance of astrocytes in the CNS is brought to our attention. In addition to providing metabolic and trophic support for neurons, astrocytes are shown to perform many essential functions in healthy CNS, including synaptic transmission, information processing and maintaining homeostasis (Sofroniew and Vinters, 2010).

2.1. Heterogeneous populations

Astrocytes have been viewed as a homogeneous group of cells in the CNS for a long time. However, a growing body of evidences shows the significant heterogeneity in many aspects of astrocytes, including developmental origin, morphology, gene expression profile, physiological properties, and function (Zhang and Barres, 2010). The astroglial heterogeneity is displayed in a spatio-temporal manner.

The heterogeneous astrocytes may arise from distinct groups of progenitors. Based on the expression level of Pax6/Nkx6.1/Nkx2.2, glial cells originated from ventricular zone (VZ) migrate to relevant ventral white matter domains, subsequently differentiating into mature astrocytes (Muroyama et al., 2005). The regional diversity of astrocytes in the white matter is controlled by several key genes expressed along the dorsal-ventral axis in VZ which is identified as p1-3 domains. Of note, three distinct subpopulations of astrocytes are identified in different domains of white matter in spinal cord (Hochstim et al., 2008). In adult mammals, two main types of astrocytes, radial astrocytes (rAs) and horizontal astrocytes (hAs) are identified in the subgranular zone (SGZ) (Seri et al., 2004). They show differences in morphology, ultrastructure and function (Romero-Aleman Mdelet al., 2003; Seri et al., 2004). Interestingly, once astrocytes in the ventral spinal cord finish their migration, they will never restart secondary tangential migration, even after acute CNS injury (Tsai et al., 2012), hinting that the fate of various kinds of astrocytes might be determined by the distinct developmental origins of the glial cells.

The most intuitionistic aspect of astroglial heterogeneity should be their morphologies. They were mainly classified as two types, protoplasmic and fibrous astrocytes, respectively in gray matter and white matter of CNS (Andriezen, 1893). The astrocyte morphology is distinct among different species. Four types of astrocytes with distinct morphologies, protoplasmic, interlaminar, polarized and fibrous astrocytes, are identified in human cortex (Table 1). Compared with rodent astrocytes, the primate astrocytes, particularly human astrocytes, have more complicated and multiple phenotypes (Oberheim et al., 2009, 2006). An additional line of evidence showed that regional heterogeneity contributes to a variety of astroglial morphologies (Reichenbach, 1989, 2005; Valverde and Lopez-Mascaraque, 1991; Yuasa, 1996). Several regional-specific astrocytes present distinct morphologies, including tanycytes, Müller glia, Bergmann glia, velate glia, marginal glia, and radial astrocytes (Table 2) (Reichenbach, 1989, 2005; Valverde and Lopez-Mascaraque, 1991; Yuasa, 1996). For example, tanycytes are special ependymal cells found in the third ventricle of brain and play active roles in regulating energy homeostasis and metabolism (Gao et al., 2014; Lee and Blackshaw, 2014). They are characterized by long stretched peripheral processes connecting the ventricular wall with the pial surface or with blood vessels (Wittkowski, 1998). Despite of the common character with a radial appearance, tanycytes are subdivided into alpha (α) and beta (β) subtypes in dependent of their differential location, morphology and marker gene expression (Goodman and Hajihosseini, 2015). Müller glia are the principal macroglial cells in the retina and span the entire thickness of the neuroretina where their perikarya are localized in the inner nuclear layer (INL) and funnel-shaped endfeet form the inner surface of the retina. Müller glia are responsible for the homeostatic and metabolic support of retinal neurons via their processes ensheathing the blood vessels and the somata and processes of each retinal neuron (Reichenbach and Bringmann, 2013). Recently, Müller glia were also reported to possess the potential as neurogenic retinal progenitor cells to provide a source of neural regeneration (Fischer and Reh, 2003). Of note, morphological diversity among Müller glia was observed in distinct region of retina. In central retina, Müller glia quickly morphological maturated from a single ventricular