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Editorial

Targeting astrocytes in brain injuries: A translational research approach

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ABSTRACT

In the brain, the astrocentric view has increasingly changed in the past few years. The classical and old view of astrocytes as "just supporting cells" has assigned these cells some functions to help neurons maintain their homeostasis. This neuronal supportive function of astrocytes includes maintenance of ion and extracellular pH equilibrium, neuroendocrine signaling, metabolic support, clearance of glutamate and other neurotransmitters, and antioxidant protection. However, recent findings have shed some light on the new roles, some controversial though, performed by astrocytes that might change our view about the central nervous system functioning. Since astrocytes are important for neuronal survival, it is a potential approach to favor astrocytic functions in order to improve the outcome. Such translational strategies may include the use of genetically targeted proteins, and/or pharmacological therapies by administering androgens and estrogens, which have shown promising results *in vitro* and *in vivo* models. It is noteworthy that successful strategies reviewed in here shall be extrapolated to human subjects, and this is probably the next step we should move on.

Although the brain represents only about 2% of body mass, it consumes more than 20% oxygen and 25% of glucose supply (Allaman et al., 2011; Magistretti and Allaman, 2015), which represents a high rate to meet its metabolic needs. Such cerebral functions include synaptic activity, maintenance of ion transport, membrane potentials and recycling of neurotransmitters are altogether part of the main functions of nervous cells on which the brain mostly demands energy (Allaman et al., 2011; Wiesinger et al., 1997). In this context, an increase in brain activity in turn increases energy consumption and therefore the use of glucose as substrate (Allaman et al., 2011). According to the above, the model of astrocyte-neuron lactate shuttle (ANLS) was proposed (Pellerin and Magistretti, 1994, 1997), and it states that there is a tight crosstalk between neurons and astrocytes (Pellerin and Magistretti, 1994), suggesting that alterations in this metabolic coupling might lead to a neurodegenerative event.

Currently it is known that astrocytes actively participate in the development and maintenance of the blood brain barrier (BBB), favor the neurovascular coupling, attract other cells by releasing cytokines and chemokines (Barreto et al., 2011a; Posada-Duque et al., 2014), are responsible for regulating potassium levels in neuronal environment, and participate in brain pH control. Astrocytes also release growth factors, antioxidants, gliotransmitters and glutamate, which are regulated by calcium (Cabezas et al., 2012; Giffard and Ouyang, 2004). For example, astrocytes may determine the CNS architecture (Bushong et al., 2002, 2004), respond to neuronal signals by increasing intracellular calcium (Ding et al., 2007), and release signals that regulate the strength and function of synapses (Araque et al., 2002), thus modulating the synaptic activity (Perea and Araque, 2005, 2007) and cognitive functions (Dallerac and Rouach, 2016). Astrocytes also control microvascular function and this role is tightly associated to neuronal metabolism (Anderson and Nedergaard, 2003; Cabezas et al., 2014; Posada-Duque et al., 2014; Zonta et al., 2003), and can serve as precursors and regulators of neuronal turnover in the adult brain (Alvarez-Buylla and Lim, 2004; Hong et al., 2008; Magnus et al., 2007). Moreover, astrocytes store glycogen (Dringen et al., 1993), which can be used to fuel neurons upon energy/glucose withdrawal, and actively participate in neuroendrocrine and metabolic signaling, as nicely shown by Chowen et al. (2016). On the other hand, astrocytes are able to form a network through gap junction that is essential for substances transportation, trophic and antioxidant support and clearance of cellular metabolism products from extracellular space (Eddleston and Mucke, 1993; Medina et al., 1999; Takuma et al., 2004).

Reactive astrocytes not only can exert neuroprotective effects, but also increase damage (Pekny et al., 2014; Romero et al., 2014), therefore therapeutic strategies aimed at selective astrogliosis regulation is a potential strategy to improve the outcome. In the special issue, Filous and Silver (2016), Liu and Chopp (2016) and Verkhratsky et al. (2016) have greatly discussed the role of astrocytes in brain injuries, and consequences of astrocytes dysfunctions under pathological conditions. Since activated astrocytes express GFAP (glial fibrillary acidic protein), vimentin (Barreto et al., 2007, 2009, 2012; Sofroniew, 2009) and endothelin-1, as discussed by Hostenbach et al. (2016) upon injury, inhibition of these proteins may increase tissue regeneration and induce plastic actions over time following brain injury (Wilhelmsson et al., 2004). Nevertheless, more recently, a study reports that attenuation of reactive gliosis does not affect infarct volume in neonatal

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ischemic-reperfusion injury (Jarlestedt et al., 2010), and that reactive astroglia is important for axonal outgrowth (Anderson et al., 2016), demonstrating that astrogliosis is important at some extent for CNS injury and recovery. On the other side, astrocytes mediate cellular repair through the secretion of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF; Hostenbach et al., 2016), platelet-derived growth factor (PDGF-BB), fibroblast growth factor (FGF), minimize damage by maintaining homeostatic levels of neurotransmitters, and protect neurons via synthesis of metabolic factors such as lactate (Barreto et al., 2011a,b; Cabezas et al., 2012, 2014, 2015). At a biochemical level, astroglial reactivity induces alterations in glutamate reuptake, promotes the release of pro-inflammatory cytokines and chemokines, and productions of reactive oxygen/nitrogen species (Cabezas et al., 2012, 2014).

Upon brain damage, reactive astrocytes decrease tissue damage by controlling and restoring the blood brain barrier integrity (Posada-Duque et al., 2014), thus avoiding the extension of cytotoxic edemas via upregulation of aquaporins. As discussed above, although glial scar supposes a barrier that limits tissue expansion, it may inhibit axonal regeneration and neurites outgrowth in some cases (Fawcett, 2015; Garcia-Alias et al., 2011; Kwok et al., 2014a,b). For example, MHCI molecules, such as PirB receptor and ligands Kb and Db, which are expressed by neurons, induce neuronal regeneration failure following stroke by a SHP-2 dependent pathway (Adelson et al., 2012). Moreover, numerous molecules that are known to inhibit tissue regeneration are present in glial scar (Kwok et al., 2014a; Silver and Miller, 2004). Among these molecules, proteoglycans overexpressed by reactive astrocytes turn the glial scar into a dense barrier impeding the sprouting of axonal cones (Kwok et al., 2012, 2014a). In this context, previous studies have shown that inhibition of astrogliosis stimulates axonal regeneration and neurites growth, not only by reducing glial scar density, but also decreasing the production of inhibitory molecules by activated astrocytes (Fawcett and Asher, 1999; Gates and Dunnett, 2001; Sandvig et al., 2004; Silver and Miller, 2004). In *in vitro* cocultures of astrocytes and neurons, inhibition of gliosis induces neuronal survival and increase neurites extension and ramifications length, while in *in vivo* studies, this experimental strategy allows an improved motor recovery in rats following medullary hemidissection (Menet et al., 2001). Also, disruption of glial scar has been shown to promote a better anatomical and functional integration of transplanted neurons into nervous tissue (Kinouchi et al., 2003).

As widely stated, a hallmark of astrogliosis is the morphological changes and increased expression of GFAP and vimentin in astrocytes. Until nowadays, GFAP has been widely used as a marker of reactive astrocytes. Nevertheless, it does not stain distal astrocytes processes and its expression is limited to soma and cell body. It is also important to point that GFAP is not expressed in the undamaged cerebral cortex (Barreto et al., 2012; Sofroniew and Vinters, 2010), and this caveat raises the question of whether we should search for more accurate and specific astrocytic markers. Various recent studies have addressed this question by using different experimental approaches such as single cell gene expression (Rusnakova et al., 2013), genomic analysis (Zamanian et al., 2012), positron emission tomography imaging (Lavisse et al., 2012), proteomic and transcriptomic data (Jha et al., 2013; Zhang et al., 2014). As stated before, reactive astrocytes can exhibit a phenotype that may be beneficial or protective, while acquire a detrimental activated-like state. It is likely that the boundary of whether astrocyte will react and assume a more "good" or "bad" role depends on the type of brain injury, post-injury period and microenvironment factors. For example, a previous study showed a novel role for meteorin as a negative feedback effector in astrogliosis. In this study the authors observed that meteorin, a hormone induced during exercise in muscle and adipose tissue (Rao et al., 2014), silencing is directly correlated with increased expression of GFAP and S100B after photothrombotic ischemia, suggesting a positive modulation of reactive astrogliosis by meteorin (Lee et al., 2015). Similarly, reactive astrocytes-secreted molecules, such as lipocalin-2 (lcn2), have been shown to promote neuronal death in response to inflammatory stimulus, thus contributing to damage (Bi et al., 2013). For instance, lcn2 has been demonstrated to mediate immune response, induce cytokines production and is recognized as an important autocrine mediator of astrogliosis in several CNS injuries (Jha et al., 2015; Lee et al., 2011). Lcn2 knockdown attenuates inflammation-induced astrocytes activation, and improves the outcome following oxygen-glucose deprivation (Jha et al., 2015; Jin et al., 2014; Lee et al., 2011), suggesting Lcn2 as potential target in brain injuries, as quite discussed by Suk (2016). Similar effects were observed in KO animals for Ndrg2 (N-myc downstream-regulated gene 2), an early expressed stress molecule implicated in differentiation and inflammatory response upon brain injury, demonstrating that deletion of Ndrg2 regulates reactive astrocytes and diminishes neuroinflammation by a possible IL-6 signaling mediated mechanism (Takarada-Iemata et al., 2014). Similarly, it seems like that positive regulation of nicotine receptors has a beneficial impact in the inflammatory response and cognition in Alzheimer, as suggested by Echeverria et al. (2016), demonstrating that targeting the nicotinic acetylcholine receptor in astrocytes might be considered an important therapeutic translational strategy against neurodegenerative diseases (Jurado-Coronel et al., 2016).

Aging is also associated with increased astrocytes reactivity (Anderson et al., 2002; Barreto et al., 2009; Kohama et al., 1995; Osborn et al., 2016). The circulating levels of estrogens and androgens reduce with aging, and this might implicate in loss of protection induced by these gonadal hormones. As widely acknowledged, the reduction of the ovarian hormone, estradiol, is tightly associated to neurodegenerative diseases. For instance, upon a chronic neuropathological event, such as Alzheimer, some alterations in cytoskeleton and astrocytes morphology, as raised by Osborn et al. (2016), are important mechanisms that should be further addressed in a more deep context. In this regard, therapy with estrogenic compounds may be considered as a promising therapeutic approach to reduce or even delay disease onset and progression. However, undesired effects are observed under treatment with estradiol, and the design of compounds aimed to maintain the beneficial effects of estradiol in the brain and avoid side peripheral effects are being nowadays assessed. Experimental animal studies have clearly demonstrated that estradiol exerts neuroprotective actions in the adult brain (Arevalo et al., 2015; Garcia-Segura et al., 2001). Indeed, androgens and estrogens, and progesterone as well, have been shown to regulate the reactive astroglia upon cerebral injury, as deeply discussed in Acaz-Fonseca et al. (2016) and Arbo et al. (2016). Moreover, ovariectomized rats treated with estradiol significantly show reduced damage caused by hypoxic-ischemic injury (Alkayed et al., 1998; Dubal et al., 1998; Simpkins et al., 1997; Zhang et al., 1998) and injuries caused by other neurotoxic stimuli (Azcoitia et al., 1998, 1999). On the other hand, prolonged absence of ovarian hormones during adulthood may be involved in neurodegenerative events (Dubal et al., 2001) and also the time of genetic (transcription of the gene through the union of the ligand with the estrogen receptor) and cellular responses to brain insult is deregulated in old animals compared with young or middle-aged subjects (Badan et al., 2003; Popa-Wagner et al., 2007).

It seems like that estrogenic response in astrocytes involves pleiotropic effects associated with a genomic or non-genomic activation (Spence et al., 2011). For example, Spence et al showed that mediation of astrocytes is essential in the estrogenic neuronal