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Review Article

The multifaceted role of astrocytes in regulating myelination

Hülya Kıray, Susan L. Lindsay, Sara Hosseinzadeh, Susan C. Barnett *

Institute of Infection, Inflammation and Immunity, Sir Graeme Davies Building, Glasgow Biomedical Research Centre, 120 University Place, University of Glasgow, Glasgow G12 8TA, United Kingdom.

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ABSTRACT

Astrocytes are the major glial cell of the central nervous system (CNS), providing both metabolic and physical support to other neural cells. After injury, astrocytes become reactive and express a continuum of phenotypes which may be supportive or inhibitory to CNS repair. This review will focus on the ability of astrocytes to influence myelination in the context of specific secreted factors, cytokines and other neural cell targets within the CNS. In particular, we focus on how astrocytes provide energy and cholesterol to neurons, influence synaptogenesis, affect oligodendrocyte biology and instigate cross-talk between the many cellular components of the CNS.

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1. Introduction

Astrocytes were long considered secondary to neurons in central nervous system (CNS) function, and erroneously dismissed as "brain glue" (glia is the Greek term for glue). Research over the past two decades, however, has shown astrocytic roles extending to a range of brain functions far beyond basic physical and metabolic neuronal support (Sofroniew and Vinters, 2010). Astrocytic regulation of myelination was first hypothesised by Műller in 1904, who claimed that the demyelinating disease, Multiple Sclerosis (MS), was rooted in astrocytic dysfunction (Müller, 1904; Williams et al., 2007). Evidence has since continued to grow supporting the premise that astrocytes could be important in regulating myelination (Sofroniew and Vinters, 2010; Williams et al., 2007; Barnett and Linington, 2013; Moore et al., 2011).

Glial fibrillary acidic protein (GFAP) has been used extensively in the study of astrocytes. Increased GFAP expression has been associated with astrocyte reactivity in CNS lesions and is a pathological hallmark of disease and/or injury. Fig. 1 illustrates astrocytes immunolabelled with

* Corresponding author at: Institute of Infection, Inflammation and Immunity, Sir Graeme Davies Building, Room B329, 120 University Place, University of Glasgow, Glasgow G12 8TA, United Kingdom.
E-mail address: Susan.Barnett@Glasgow.ac.uk (S.C. Barnett).

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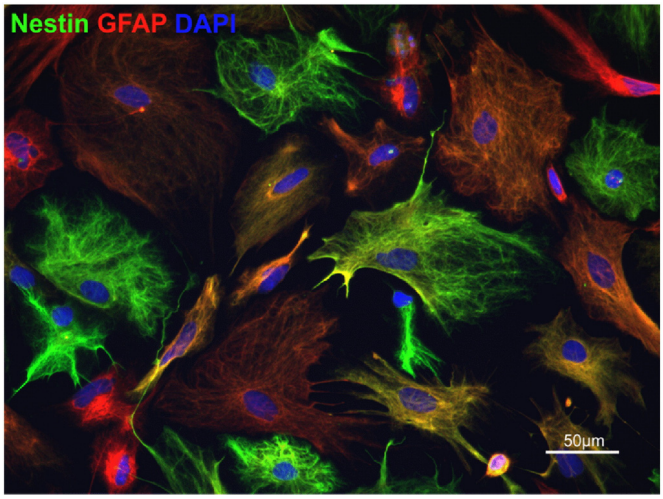
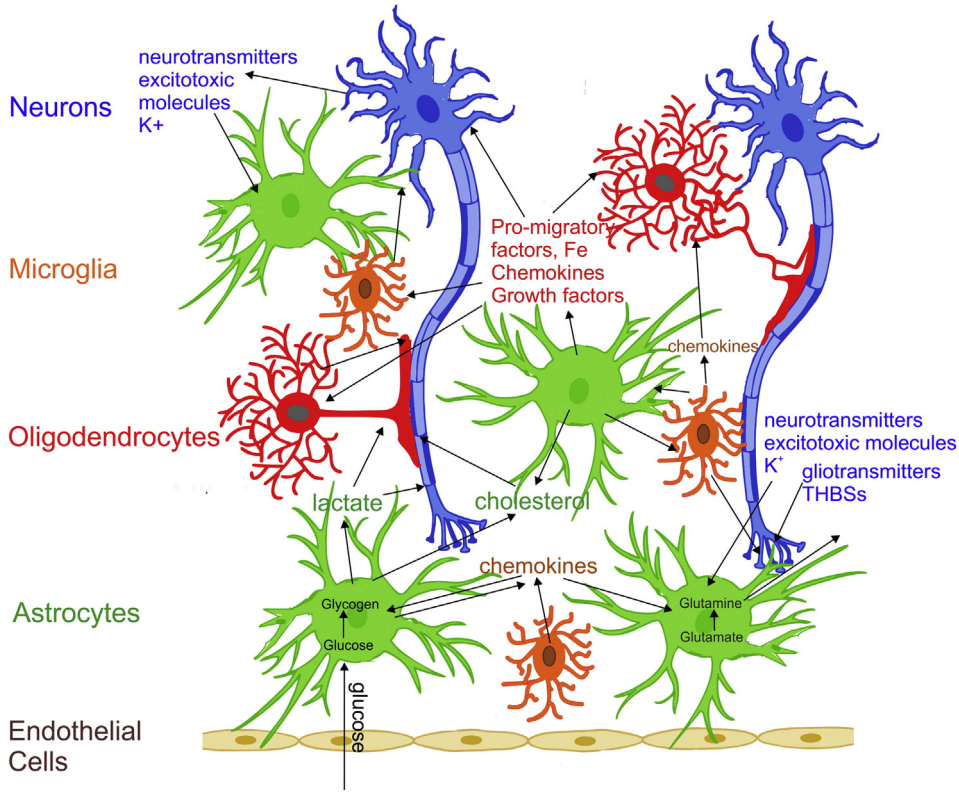


Fig. 1. Expression of astrocyte reactivity markers. Rat neurosphere-derived astrocytes cultured on PLL-coated glass coverslips express the reactivity markers GFAP (green) and nestin (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

GFAP and nestin, another marker thought to label reactive astrocytes (Kamphuis et al., 2012). In experimental allergic encephalomyelitis (EAE), a widely used animal model of MS, where demyelination is induced by myelin antigens, administered together with adjuvant that contains bacterial components (Traugott and Lebon, 1988; Tsukada et al., 1991; Villarroya et al., 1996), GFAP expression was seen on more numerous and much larger astrocytic processes in chronic lesions compared to normal appearing white matter (Webster et al., 1985; Eng et al., 1971). Thus, the degree of GFAP immunoreactivity appears to reflect the level of reactive astrogliosis. This was reviewed in detail by Sofroniew and Vinters (2010), who described a continuum of phenotypic changes, that range from mild to severe, the latter resulting in glial scar formation (Sofroniew and Vinters, 2010; Nash et al., 2011a). Attempts have also been made to define the astrocyte phenotype in more detail along this continuum (Liberto et al., 2004). It has been suggested that mild astrogliosis is associated with astrocyte "activation" and severe astrogliosis is associated with "reactivity", with the former promoting recovery of CNS function after injury and the latter walling off the injured area and preventing repair (Liberto et al., 2004). Although activated astrocytes have been associated with less detrimental effects on the CNS and reactive astrocytes as more damaging, it is clear that these properties are not all or nothing and reactive astrocytes can



Astrocytes provide energy and cholesterol for neurons.

Astrocytes play a role in synaptic signal transmission and can modulate synapses.

Astrocytic secreted factors effect oligodendrocyte migration, proliferation, maturation and function.

Astrocytes and microglia can modulate astrocyte reactivity by releasing chemokines.

Fig. 2. Astrocytic effects on re/myelination can be classified into 4 main groups. They contribute to re/myelination by: 1) Providing an energy source (lactate) and cholesterol for neurons. Glucose taken up by endothelial cells lining the blood brain barrier is later transferred to astrocytes which transform it to glycogen, which can then be used to produce lactate. 2) Playing a role in synaptic signal transmission by regulating the fluid, pH/ion (*e.g.* potassium, K^+), glio/neurotransmitter homeostasis and contributing to synapse modulation through secreted molecules, such as thrombospondins (THBSs). 3) Affecting the survival, proliferation and maturation of oligodendrocytes by secreting growth factors, some of which are regulated by iron homeostasis provided by astrocytes. Chemokines may also influence oligodendrocyte membrane ensheathment of axons. 4) Altering reactivity status through their release of chemokines/cytokines, which in turn affects the cross-talk between all neural cells including microglia.

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