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Review

Astrocyte transplantation for spinal cord injury: Current status and perspective

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ABSTRACT

Spinal cord injury (SCI) often causes incurable neurological dysfunction because axonal regeneration in adult spinal cord is rare. Astrocytes are gradually recognized as being necessary for the regeneration after SCI as they promote axonal growth under both physiological and pathophysiological conditions. Heterogeneous populations of astrocytes have been explored for structural and functional restoration. The results range from the early variable and modest effects of immature astrocyte transplantation to the later significant, but controversial, outcomes of glial-restricted precursor (GRP)-derived astrocyte (GDA) transplantation. However, the traditional neuron-centric view and the concerns about the inhibitory roles of astrocytes after SCI, along with the sporadic studies and the lack of a comprehensive review, have led to some confusion over the usefulness of astrocytes in SCI. It is the purpose of the review to discuss the current status of astrocyte transplantation for SCI based on a dialectical view of the context-dependent manner of astrocyte behavior and the time-associated characteristics of glial scarring. Critical issues are then analyzed to reveal the potential direction of future research.

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1. Introduction

Spinal cord injury (SCI) results in not only tremendous suffering for individuals, but also an enormous financial burden for families and society. As one of the most devastating injuries, the treatment has always been a difficult problem for the medical field, and victims usually encounter varying degrees of permanent impairment, including sensory loss, para- and tetra-paralysis, and autonomic dysfunction (Cao and Dong, 2013; Donovan, 2007; Pickelsimer et al., 2010). The major reason for the incurable nature of functional impairment is that it is rare for axonal regeneration to occur in the injured adult spinal cord. This is mainly ascribed to extensive inflammation and cell death, loss of supportive substrates, the inhibitory growth components outweighing the stimulating ones, and glial scars that are mainly the product of astrocytes and are historically recognized as obstacles to axonal regrowth (Cao and Dong, 2013; Maier and Schwab, 2006; Oyinbo, 2011; Smith et al., 1986).

Astrocytes, also called astroglia, are the most abundant glial cells in the central nervous system (CNS). They exert pivotal structural and physiological functions in the healthy spinal cord (Kimelberg and Nedergaard, 2010; Sofroniew and Vinters, 2010). These include essential roles in synaptic transmission, provision of suitable glial

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substrates (Fallon, 1985; Noble et al., 1984), blood flow regulation and blood–spinal barrier (BSB) formation (Abbott, 2002; Gordon et al., 2007; Haseloff et al., 2005; Koehler et al., 2006), and production of multiple neurotrophic factors (Bozoyan et al., 2012; Perea and Araque, 2006; Powell and Geller, 1999). Astrocytes respond to injuries through reactive astrogliosis, a pathologic hallmark of SCI that in severe cases results in the formation of glial scars (Seifert et al., 2006; Sofroniew, 2009; Sofroniew and Vinters, 2010). The traditional view is that the glial environment is a major cause of the failure of axonal regeneration. This sees the astrocyte as no more than a supportive accessory and deleterious component of glial scars (Anders and Hurlock, 1996; Bahr et al., 1995; Fawcett et al., 1989; McKeon et al., 1991; Nieto-Sampedro, 1999; Reier and Houle, 1988). Nevertheless, astrocytes are gradually being identified as a population of heterogeneous cells that are necessary for the repair of SCI with the crucial functions required for axonal outgrowth. The complex time-dependent characteristics of glial scarring are finally becoming understood (Karimi-Abdolrezaee and Billakanti, 2012; Rolls et al., 2009; Silver and Miller, 2004; Sofroniew, 2009). These functions show that ignorance or inappropriate manipulation of astrocytes and reactive astrogliosis could greatly reduce the chances of restoring neurological function. It is noteworthy that studies now reveal the potential of astrocyte transplantation in promoting axonal regeneration and functional recovery after SCI (Davies et al., 2006, 2008, 2011; Fan et al., 2013; Haas and Fischer, 2013; Kliot et al., 1990). However, controversy still exists in the choice of astrocyte subpopulations, the variable outcomes of the studies, the underlying mechanisms, and the adverse effects (Bernstein and Goldberg, 1991; Haas et al., 2012; Hayashi et al., 2011; Jin et al., 2011; Joosten et al., 2004; Noble et al., 2011b; Olby and Blakemore, 1996). The sporadic nature of the studies and the lack of a comprehensive overview of astrocyte transplantation for the repair of SCI need addressing, so that this area of research can be developed further. However, the dominance of the traditional neuron-centric view in studying CNS diseases, as well as the concerns that the formation of glia scars could block axonal regrowth both *in vitro* (Ard et al., 1993; Canning et al., 1996; McKeon et al., 1999; Rudge and Silver, 1990) and *in vivo* (Bundesen et al., 2003; Hagino et al., 2003; McKeon et al., 1991; Reier and Houle, 1988), has led to the neglect of astrocytes in terms of their positive roles after injury. Therefore, there is an urgent need to summarize the progress in astrocyte transplantation for SCI, and evaluate the current controversial issues in terms of the characteristics of astrocytes and reactive astrogliosis.

This review will start with the multifaceted roles and context-dependent nature of astrocytes in the normal and injured spinal cord, followed by the suggested time-dependent nature of reactive astrogliosis. Next, we summarize the current progress in astrocyte transplantation for the repair of SCI and discuss the unresolved issues that underlie the inconsistent outcomes reported by different studies. Finally, lessons are learnt from the achievements of astrocyte transplantation, and constructive suggestions are made to improve regeneration after SCI. As the ultimate goal is to ameliorate the inability of spinal cord to regenerate after injury, this review also discusses several crucial issues that need to be addressed in future clinical trials.

2. Physiological functions of astrocytes

Astrocytes are a population of heterogeneous cells that exhibit a diversity of phenotypes and functions, yet until recently they were neglected as no more than supportive brain glue (Allen and Barres, 2009; Haas et al., 2012; Molofsky et al., 2014). It is noteworthy that astrocytes are a major type of glial cells in the human CNS where nearly 90% of the cells are glia, and they play an essential role both structurally and physiologically (Kimelberg and Nedergaard, 2010; Oberheim et al., 2006; Sofroniew and Vinters, 2010). Each astrocyte extends processes that cover eight neuronal cell bodies, five blood vessels and more than 100,000 synapses (Bushong et al., 2002, 2004; Halassa et al., 2007b; Oberheim et al., 2006), and regulate the homeostasis of the CNS in various ways (Dong and Benveniste, 2001; Nicoll and Weller, 2003). Fundamentally, astrocytes support neurons by providing adherent substrates for axonal outgrowth and filling the neural network (Fallon, 1985; Noble et al., 1984). These astrocytic-neuronal interactions are considered to be largely mediated by the surface properties of astrocytes, showing their crucial roles in determining neuronal movement and structure of the CNS. Moreover, astrocytes regulate blood flow and induce the formation of the blood–brain barrier (BBB) and blood–spinal barrier (BSB) (Abbott, 2002; Gordon et al., 2007; Haseloff et al., 2005; Koehler et al., 2006). The BBB and BSB are diffusion barriers that are principally composed of microvascular endothelial cells that form tight junctions, surrounded by basal lamina, perivascular pericytes, and astrocyte end-feet (Ballabh et al., 2004). Through this structural connection, astrocytes regulate the barriers by releasing various soluble factors that mediate the role of endothelial tight junctions (Abbott et al., 2006; Rubin and Staddon, 1999). Astrocytes also form extensive connections to blood vessels *via* the end-feet and regulate vasoconstriction and vasodilation by producing molecules like arachidonic acid (AA), prostaglandins (PGE), and nitric oxide (NO) in response to changes in neuronal and synaptic activity (Gordon et al., 2007; Iadecola and Nedergaard, 2007; Koehler et al., 2009; Schummers et al., 2008). Of note, astrocytes communicate with neurons and modulate synaptic activity directly and bidirectionally through "tripartite synapses", which hypothesizes that synapses are composed of not only the pre- and postsynaptic terminal of neurons, but also the processes of astrocytes that envelope them (Halassa et al., 2007a; McKeon et al., 1995) The rich supply in receptors, channels, and proton shuttling on the astrocyte membranes guarantee its pivotal role in maintaining the pH, fluid, ion and neurotransmitter homeostasis of the synaptic interstitial fluid and in releasing active molecules in response to changes of synaptic activity (Fellin, 2009; Fiacco and McCarthy, 2006; Haydon and Carmignoto, 2006; Mauch et al., 2001; Oliet et al., 2001; Perea et al., 2009; Simard and Nedergaard, 2004; Ullian et al., 2001). A delicate balance of pH, fluids, and ions within the synapses is achieved with aquaporin 4 (AQP4) water channels and diverse proton shuttling methods, such as Na^+/K^+ pumps, Na^+/H^+ exchangers, and bicarbonate transporters that are expressed on astrocyte membranes (Kimelberg and Nedergaard, 2010; Obara et al., 2008; Sofroniew and Vinters, 2010; Zador et al., 2009). Astrocytes also maintain the transmitter balance by terminating and recycling back neurotransmitters within the extracellular space, which is mediated by neurotransmitter transporters like glutamate, γ-aminobutyric acid (GABA), and glycine (Sattler and Rothstein, 2006; Seifert et al., 2006). Moreover, when astrocytic receptors are stimulated by neurotransmitters released from the presynaptic region of a neuron, the intracellular calcium ions of the astrocyte are increased, and active gliotransmitters, such as purines (ATP and adenosine), glutamate and GABA, are secreted to respond back and alter neuronal activity (Halassa et al., 2007a; Nedergaard et al., 2003; Perea and Araque, 2010; Perea et al., 2009; Shigetomi et al., 2008).

Besides, astrocytes also participate in developmental and postnatal events, despite their tendency to be generated after neurons (Qian et al., 2000). Astrocytes not only orchestrate the development and differentiation of neurons by secreting multiple neurotrophic factors (Bozoyan et al., 2012; Powell and Geller, 1999), but also facilitate the formation and function of developing synapses by producing molecules like thrombospondin (Barres, 2008; Christopherson et al., 2005; Ullian et al., 2001). Astrocytes also release vascular endothelial growth factor (VEGF) to modulate the generation of parallel blood vessels in the rostral