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Revisiting the astrocyte–oligodendrocyte relationship in the adult CNS

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Abstract

The lineages of both astrocytes and oligodendrocytes have been popular areas of research in the last decade. The source of these cells in the mature CNS is relevant to the study of the cellular response to CNS injury. A significant amount of evidence exists to suggest that resident precursor cells proliferate and differentiate into mature glial cells that facilitate tissue repair and recovery. Additionally, the re-entry of mature astrocytes into the cell cycle can also contribute to the pool of new astrocytes that are observed following CNS injury. In order to better understand the glial response to injury in the adult CNS we must revisit the astrocyte–oligodendrocyte relationship. Specifically, we argue that there is a common glial precursor cell from which astrocytes and oligodendrocytes differentiate and that the microenvironment surrounding the injury determines the fate of the stimulated precursor cell. Ideally, better understanding the origin of new glial cells in the injured CNS will facilitate the development of therapeutics targeted to alter the glial response in a beneficial way.

Keywords: Astrocytes; Oligodendrocytes; CNS injury; Glial scar; CNS damage; Stem cell; Glial precursor

Contents

Abbreviations: ATP, adenosine triphosphate; bHLH, basic helix-loop-helix; BMP, bone morphogenic protein; BrdU, bromodeoxy uridine; CD44, cell determinant-44; CNPase, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; CNTF, ciliary neurotrophic factor; CXCR4, receptor for SDF-1; DG, dentate gyrus; EAE, experimental autoimmune encephalomyelitis; FGF, fibroblast growth factor; GDNF, glial derived growth factor; GFAP, glial fibrillary acidic protein; GFP, green fluorescent protein; GRP, glial restricted precursor; HA, hyaluronic acid; HSC, hematopoietic stem cell; IL-6, interleukin-6; JAK/STAT, janus kinase/signal transducer and activator of transcription; LIF, leukemia inhibitory factor; MAPC, multipotent adult stem cell; MAPK, ras mitogen-activated protein kinase; MNOP, motor neuron and oligodendrocyte precursor; MPTP, 1-methyl-4-phenol-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; MSC, mesenchymal stem cell; NG2, nerve/glial antigen 2; NGF, nerve growth factor; NSC, neuronal stem cell; NT3, neurotrophic factor 3; O2A, oligodendrocye precursor 2 A; O2A, oligodendrocyte-type 2 astrocyte; OPC, oligodendrocyte progenitor cell; PDGF, platelet derived growth factor; PI3K/AKT, phosphatidylinosysitol-3-kinase; PSA-NCAM, polysialylated-neural cell adhesion molecule; RTPZ, receptor tyrosine phosphatase β/ζ; SCL, stem cell leukemia factor; SDF-1, stromal-derived factor-1; SGZ, subgranular zone; Shh, sonic hedgehog; SVZ, subventricular zone; T3, triiodothyronine; VZ, ventricular zone

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1. Introduction

In mammals the process of gliogenesis, which generates both astrocytes and oligodendrocytes, begins late in embryonic development and continues into postnatal stages. It is difficult to discern the initiation of astrogliogenesis from oligodendrogliogenesis and there is evidence to suggest that this is because astrocytes and oligodendrocytes share a common glial progenitor (Rao et al., 1998; Rao and Mayer-Proschel, 1997; Mayer-Proschel et al., 1997). Other findings suggest that oligodendrocytes either derive independently or are more closely related to motor neurons and that these cell types derive from a motor neuron and oligodendrocyte precursor (MNOP), independent of astrocyte maturation (Stiles, 2003; Richardson et al., 2000; Briscoe et al., 2000). Recent studies using mice lacking transcription factors relevant for the determination of cell fate have supported the theory of different precursors for motor neurons, oligodendrocytes, and astrocytes (Wu et al., 2006). The origin of both oligodendrocytes and astrocytes is still not completely understood, though it appears that these cells derive from multiple regions of the central nervous system (CNS) rather than from a single location (Kessaris et al., 2006; Richardson et al., 2006).

Following injury in the CNS, cell replacement does occur, though it is quite slow. The cell types most commonly replaced are astrocytes and oligodendrocytes, and rarely neurons. There is a growing agreement that the appearance of new astrocytes and oligodendrocytes is largely due to the proliferation and differentiation of progenitor cells rather than the proliferation of fully differentiated cells. Following neuronal injury, bromodeoxyuridine (BrdU)-labeled dividing cells are typically observed within 24 h of injury (Alonso, 2005). Often, BrdU+ cells are observed within glial fibrillary acidic protein (GFAP) rich regions of cells indicating that new astrocytes are generated after an injury (Fawcett and Asher, 1999; Ridet et al., 1997; Norenberg, 1994).

The presence of new glial cells at the site of neuronal injury raises questions as to the origin of these cells and how they arrive at the site of an injury. It is not yet clear whether the terminal fate of progenitor cells is determined by the injury environment or by intrinsic properties of the cells themselves. Here, we discuss the potential origins of astrocytes and oligodendrocytes and offer insight into how both their origin and the injury environment can impact the fate decision of glial progenitor cells.

2. Sources of new GLIA in the mature CNS

2.1. Stem cells

Stem[c1] cells are an attractive source for new glial cells because these cells are multipotent and able to self-renew (see Fig. 1). Some neural stem cells (NSC) present in the subventricular zone (SVZ) have been shown to express the intermediate filament protein GFAP, and display characteristics of astrocytes (Doetsch et al., 1999). Culturing subependymal cells from the SVZ yields multipotent cells that can be differentiated into either neurons, oligodendrocytes, or GFAP+ astrocytes (Chiasson et al., 1999; Gage, 2000; Temple and Alvarez-Buylla, 1999). Additionally, transplantation of these cells into the CNS results in the generation of multiple cell types, including astrocytes (Gage, 2000) and oligodendrocytes (Seidenfaden et al., 2006). NSC in the injured adult CNS have also been shown to give rise to astrocytes (Picard-Riera et al., 2002) and oligodendrocytes (Nait-Oumesmar et al., 1999) indicating that the proliferation of these cells could contribute to the population of mature glial cells in the adult CNS (Fig. 2).

The extent to which NSC are involved in the response to CNS injury is limited. The number of NSC in the mature CNS is quite small, and declines with age. In addition, NSC are primarily present in confined regions of the CNS such as the SVZ and the subgranular zone (SGZ) of the dentate gyrus. Migration of progenitor cells from these stem cell niches has been associated with cell repair (Arvidsson et al., 2002; Magavi et al., 2000). However, the number of NSC-derived cells is usually small and involves the careful timing of migration and proliferation to ensure the maturation into astrocytes at the site of injury.

Furthermore, reactive/proliferating astrocytes have been observed at injury sites far from stem cell niches. The pattern of glial proliferation and response near sites of resident stem cells is similar to responses at sites very distal, such as the spinal cord. Many researchers suspect that there are a finite number of stem cells in the adult CNS and that these cells become depleted through time as mandated by regular growth and repair. Therefore, stem cell numbers are thought to attenuate in aged brains suggesting that in older individuals the chances that a progenitor response is deriving from stem cells is less likely.