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Review

Lineage, fate, and fate potential of NG2-glia

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ABSTRACT

NG2 cells represent a fourth major glial cell population in the mammalian central nervous system (CNS). They arise from discrete germinal zones in mid-gestation embryos and expand to occupy the entire CNS parenchyma. Genetic fate mapping studies have shown that oligodendrocytes and a subpopulation of ventral protoplasmic astrocytes arise from NG2 cells. This review describes recent findings on the fate and fate potential of NG2 cells under physiological and pathological conditions. We discuss age-dependent changes in the fate and fate potential of NG2 cells and possible mechanisms that could be involved in restricting their oligodendrocyte differentiation or fate plasticity.

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1. Introduction

NG2 cells represent a fourth resident glial cell population in the mammalian central nervous system (CNS) that is distinct from astrocytes, mature oligodendrocytes, and microglia. They are defined as non-neuronal, non-vascular glial cells in the CNS parenchyma that express the NG2 antigen and the alpha receptor for platelet-derived growth factor (Pdgfra) (Nishiyama et al., 2009; Hill and Nishiyama, 2014). They are distributed widely throughout both gray and white matter. They generate oligodendrocytes in culture and in vivo and hence are often equated with oligodendrocyte precursor cells (OPCs). Cells with similar properties have been reported in earlier ultrastructural studies as satellite cells apposed to principal neurons in gray matter (Penfield, 1924; Mugnaini and Walberg, 1964), small glioblasts (Vaughn, 1969), oligodendroglioblasts (Skoff, 1982), and β-astrocytes (Reyners, 1982, 1986). However, it was not until the 1990s when immunolabeling for NG2 became feasible on routinely processed tissue sections and revealed their multi-processed morphology with their striking coverage of the entire CNS parenchyma that their existence as a resident glial cell population in the CNS was appreciated (Stallcup et al., 1983; Levine et al., 1993; Nishiyama et al., 1996; Peters, 2004) (Fig. 1). The morphology and distribution of these cells were not what one expected of immature precursor cells destined to become oligodendrocytes, and the lineage of NG2 cells was intensely debated over the following two decades. The term polydendrocytes has been proposed as an inclusive substitute and synonym for NG2 cells or NG2-glia to avoid using a marker for the name of a cell type and to avoid using the term OPCs when discussing their properties that are not directly related to their ability to generate oligodendrocytes (Nishiyama et al., 2009; Hill and Nishiyama, 2014). Here we summarize our current understanding of the lineage commitment and fate of NG2 cells in normal and pathological states in vivo and discuss some unanswered questions regarding their fate and fate potential.

2. Origin of NG2 cells during development

2.1. *Olig2 specifies NG2 cells and the oligodendrocyte lineage*

In the mammalian CNS, neurons, astrocytes and oligodendrocytes arise from the neuroepithelium according to a temporally and spatially regulated program. In the rodent spinal cord, oligodendrocyte lineage cells first become specified within a discrete domain in the ventral ventricular zone called pMN domain, which is marked by the expression of the basic helix-loop-helix transcription factor Olig2 (bHLH) induced by the ventral morphogen Sonic hedgehog (Shh). Olig2+ progenitor cells in this domain first give rise to motor neurons at E9–10 and subsequently switch to produce oligodendrocyte lineage cells after E12 (Kessaris et al., 2001). In the forebrain, oligodendrocyte lineage cells are also generated initially ventrally from Olig2+ cells in the medial and lateral ganglionic eminences (MGE and LGE, respectively) that also generate interneurons concomitant with oligodendrocyte lineage cells (Nery et al., 2001; Spassky et al., 2001; Tekki-Kessaris et al., 2001). During neuronal differentiation in both regions, Olig2 expression is downregulated while the expression of neurogenic transcription factors is sustained. Conversely in cells that become committed to the oligodendrocyte lineage and begin to express NG2, Olig2 expression is sustained while neuronal genes are repressed (Novitch et al., 2001; Petryniak et al., 2007).

2.2. *Appearance of NG2 cells shortly after oligodendrocyte lineage specification*

Since Olig2 expression is shared by neuronal and oligodendrocyte lineage cells, further specification must occur for the Olig2+ cells in the germinal zone (ventricular zone, VZ) to become committed to NG2 cells. Sox10 is a member of the high-mobility group (HMG) transcription factor family and is expressed throughout the oligodendrocyte lineage. The onset of its expression follows that of Olig2 and precedes that of NG2 cell markers such as NG2 and Pdgfra (Fig. 2A), suggesting that Olig2 induces Sox10. Indeed, Olig2 binds to the U2 enhancer sequence in the 5′-flanking region of the mouse Sox10 gene and activates its transcription (Kuspert et al., 2011). Development of Pdgfra+ cells is severely compromised in mice lacking both Sox10 and a related transcription factor Sox9, and Sox9 binds to specific sites in the proximal 5′-flanking region of the Pdgfra gene (Stolt et al., 2002; Finzsch et al., 2008). Pdgfra transcription is also reduced in mice lacking Sox10 (Stolt et al., 2002). Since Sox10 expression is restricted to oligodendrocyte lineage cells in the CNS, the induction of Sox10 transcription by Olig2 marks the first step in the commitment of neuroepithelial cells to the oligodendrocyte (NG2 cell) lineage (Fig. 2A).

Shortly after the onset of Pdgfra transcription in the VZ, cells begin to migrate out into the parenchyma where they undergo extensive dispersion and PDGF-dependent proliferation (Pringle et al., 1992; Calver et al., 1998). NG2 is not