BRAIN RESEARCH REVIEWS 67 (2011) 147–156

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BRAIN RESEARCH REVIEWS

Review

Oligodendrogenesis in the subventricular zone and the role of epidermal growth factor

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ARTICLE INFO

Article history:
Accepted 5 January 2011
Available online 12 January 2011

Keywords:
Oligodendrocyte
NG2 glia
Myelin
Brain repair
Demyelinating disease
Oligodendrocyte precursor cell
Epidermal growth factor

ABSTRACT

Demyelinating diseases are characterized by an extensive loss of oligodendrocytes and myelin sheaths from axolemma. These neurological disorders are a common cause of disability in young adults, but so far, there is no effective treatment against them. It has been suggested that neural stem cells (NSCs) may play an important role in brain repair therapies. NSCs in the adult subventricular zone (SVZ), also known as Type-B cells, are multipotential cells that can self-renew and give rise to neurons and glia. Recent findings have shown that cells derived from SVZ Type-B cells actively respond to epidermal-growth-factor (EGF) stimulation becoming highly migratory and proliferative. Interestingly, a subpopulation of these EGF-activated cells expresses markers of oligodendrocyte precursor cells (OPCs). When EGF administration is removed, SVZ-derived OPCs differentiate into myelinating and pre-myelinating oligodendrocytes in the white matter tracts of corpus callosum, fimbria fornix and striatum. In the presence of a demyelinating lesion, OPCs derived from EGF-stimulated SVZ progenitors contribute to myelin repair. Given their high migratory potential and their ability to differentiate into myelin-forming cells, SVZ NSCs represent an important endogenous source of OPCs for preserving the oligodendrocyte population in the white matter and for the repair of demyelinating injuries.

Contents

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doi:10.1016/j.brainresrev.2011.01.001

1. Introduction

Oligodendrocytes are neuroglial cells that produce a functional segmentation of the axolemma, promote axon maturation and provide an electric insulation of axons in the central nervous system (Colello et al., 1994; Mathis et al., 2001). Telencephalic oligodendrocytes derive from progenitors that migrate from medial ganglionic eminence and the anterior entopeduncular area (Nery et al., 2001; Richardson et al., 2006). In the adult brain, mature myelinating oligodendrocytes are continuously produced from local oligodendrocyte precursor cells (OPCs) residing in the brain parenchyma (Gensert and Goldman, 1997; Fancy et al., 2004), and from cell precursors located in the subventricular zone (Nait-Oumesmar et al., 1999; Picard-Riera et al., 2002; Menn et al., 2006). Parenchymal OPCs express the NG2 proteoglycan (Stallcup and Beasley, 1987; Nishiyama et al., 2002), the ganglioside GD3 (LeVine and Goldman, 1988), and the platelet-derived growth factor-alpha receptor (PDGFRα) (Pringle et al., 1992). These NG2+/GD3+/PDGFRα+ precursors actively respond to demyelinating lesion by proliferating and differentiating in mature oligodendrocytes that restore myelin sheaths, but they do not migrate extensively (Gensert and Goldman, 1997; Fancy et al., 2004).

Demyelinating diseases comprise a group of progressive disorders characterized by an extensive loss of oligodendrocytes and myelin sheaths from nerve fibers. Multiple sclerosis is the most common demyelinating disease and an important cause of disability in young adults. Women are affected about two to three times more often than men, and that is worldwide. To date, there is no effective treatment for these diseases. Nevertheless, it has been suggested that neural stem cells (NSCs) represent an endogenous source of cells for brain repair that circumvents immune rejection (Goldman and Windrem, 2006; Taupin, 2006; Lim et al., 2007). NSCs are multipotent cells that can self-renew and differentiate into all neural cell types, i.e. neurons, astrocytes and oligodendrocytes. These multipotent cells are present in the adult mammalian brain and are restricted to specialized niches (Doetsch, 2003b; Kriegstein and Alvarez-Buylla, 2009). The most extensive such niche is the subventricular zone (SVZ) located along the walls of the lateral ventricles in the forebrain (Doetsch et al., 1997; Doetsch, 2003a). The SVZ contains slowly dividing astrocytic neural progenitors also known as Type-B cells. These germinal astrocytes give rise to actively proliferating transit-amplifying cells named Type-C cells, which in turn generate immature neuroblasts (Type-A cells) (Fig. 1) (Doetsch et al., 1997, 1999). Type-A cells are ensheathed by the processes of Type B cells and form tangential chains of neuroblasts along the anterior extension of the SVZ. At the rostral region of SVZ, these chains of migrating neuroblasts merge and compose the rostral migratory stream (RMS) (Lois and Alvarez-Buylla, 1994; Lois et al., 1996). Then, Type-A cells reach the olfactory bulb and mature into distinct interneurons (Lois and Alvarez-Buylla, 1993, 1994; Merkle et al., 2007). In addition to olfactory interneurons, it has been demonstrated that Type-B cells of the SVZ are able to produce myelinating oligodendrocytes, which populate the white matter tracts of

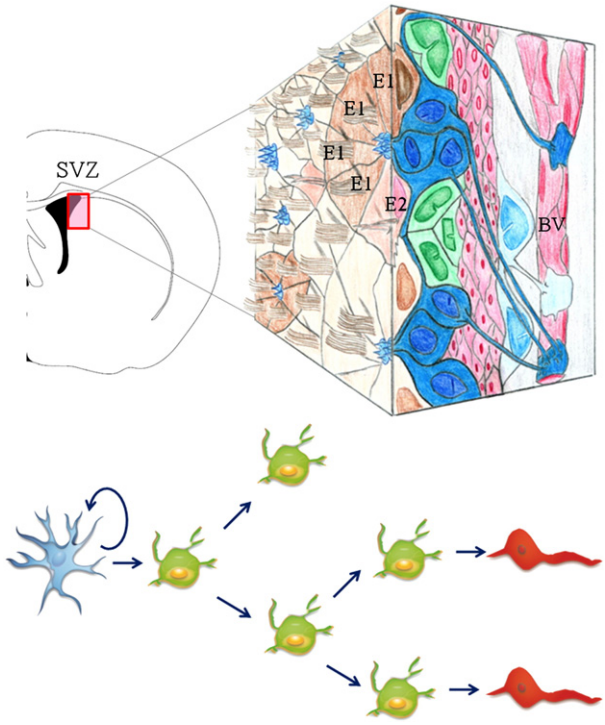

Fig. 1 – The subventricular zone (SVZ) niche. The SVZ is lining the lateral ventricles in the brain (coronal section left), which contains Type-B neural stem cells (NSCs) that have astrocytic characteristics (shown in blue). NSCs give rise to rapidly dividing Type-C cells (shown in green), intermediate progenitor cells that function as transit-amplifying progeny in the generation of neuroblasts (Type-A cells; shown in red), which migrate to the olfactory bulb and differentiate into neurons. A detail of the three-dimensional model of the adult SVZ neurogenic niche is shown to the right. Type-B cells have a long basal process that contacts blood vessels (BV) and an apical ending at the ventricle surface. Note the pinwheel-like organization composed of multiciliated (Type-E1) and bi-ciliated (Type-E2) ependymal cells encircling Type-B apical surfaces.