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

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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.

Keywords

Oligodendrocyte; NG2 glia; Myelin; Brain repair; Demyelinating disease; Oligodendrocyte precursors; Epidermal growth factor

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

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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- α receptor (**PDGFR α**) (Pringle et al., 1992). These NG2+ / GD3+ / PDGFR α + 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) (Figure 1) (Doetsch et al., 1997; Doetsch et al., 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 corpus callosum, fimbria fornix and striatum (Menn et al., 2006).

The epidermal growth factor (**EGF**) is an important regulator of proliferation, migration and cell fate of adult NSCs (Reynolds and Weiss, 1992; Vescovi et al., 1993; Gritti et al., 1995; Craig et al., 1996). Increasing evidence indicates that overstimulation of EGF signaling pathway in the adult SVZ significantly increases the number of OPCs (Aguirre et al., 2007; Gonzalez-Perez et al., 2009). These SVZ-derived OPCs can migrate long distances and contribute to re-myelination of white matter tracks. High migratory ability and remyelination capacity are two fundamental properties in the design of cell repair therapies for demyelinating diseases (Blakemore and Franklin, 2000). Here, we describe the role of the SVZ as a source of migratory OPCs and discuss the important oligodendrogenic effect of EGF on adult NSCs to promote myelination and white matter repair.

2. Neural stem cells in the adult brain

As mentioned above, NSCs are multipotent self-renewing progenitors residing in the SVZ that continually replace local interneurons (Reynolds and Weiss, 1992; Lois and Alvarez-Buylla, 1993, 1994). Adult NSCs have been demonstrated in many vertebrate species

including birds, reptiles, mice, rats, rabbits, voles, dogs, cows, monkeys and humans (Lewis, 1968; Blakemore, 1969; Blakemore and Jolly, 1972; McDermott and Lantos, 1990; Eriksson et al., 1998; Huang et al., 1998; Gould et al., 1999; Kornack and Rakic, 2001; Garcia-Verdugo et al., 2002; Rodriguez-Perez et al., 2003; Sanai et al., 2004). In adult humans, NSCs have been isolated from the SVZ (Sanai et al., 2004) and the subcortical white matter (Nunes et al., 2003).

3. The subventricular zone

As indicated above, the SVZ generates young neurons that migrate tangentially to the olfactory bulb where they mature into different types of local interneurons. In parallel, SVZ neural progenitors also generate OPCs that migrate radially to the neighboring white matter tracts of corpus callosum, septum and fimbria fornix and differentiate into myelinating oligodendrocytes (Nait-Oumesmar et al., 1999; Picard-Riera et al., 2002; Jackson et al., 2006; Menn et al., 2006; Gonzalez-Perez et al., 2009). The SVZ NSCs, also known as Type-B cells, are a subpopulation of astrocytes that express the intermediate filament component glial fibrillary acidic proteic (**GFAP**) (Doetsch et al., 1999; Garcia et al., 2004), LeX (Capela and Temple, 2002) and Nestin (Rietze et al., 2001). Interestingly, young astrocytes, isolated from multiple brain regions before postnatal day 10, can function as neural stem cells *in vitro* (Laywell et al., 2000). After that time, only the SVZ astrocytes appear to retain this NSC capacity (Lim and Alvarez-Buylla, 1999). Remarkably, Type-B stem cells are not homogeneous, but are restricted in their neurogenic potential (Merkle et al., 2007). Thus, Type-B cells in different locations appear to generate different types of neurons.

3.1 Cytoarchitecture in the SVZ

In the adult human brain, SVZ astrocytes are not found adjacent to the ependymal layer. Instead, human SVZ astrocytes accumulate in a band or ribbon separated from the ependyma by a gap that is largely devoid of cells (Sanai et al., 2004; Quinones-Hinojosa et al., 2006). A recent work has revealed a unique center-surround organization, denominated as 'pinwheel', for ependymal cells and Type-B cells within ventricular walls (Mirzadeh et al., 2008). Pinwheel's cores contain the apical endings of Type-B cells and in its periphery two types of ependymal cells: multiciliated (Type-E1 cells) and bi-ciliated (Type-E2 cells) (Figure 1). Interestingly, SVZ Type-B cells extend a minute apical ending to directly contact the ventricle and a long basal process ending on blood vessels (Figure 1)(Mirzadeh et al., 2008; Shen et al., 2008). These contacts are important because it has been suggested that extracellular matrix (Mercier et al., 2002) or soluble factors (Leventhal et al., 1999; Shen et al., 2008; Tavazoie et al., 2008) secreted by blood vessels play an important role in regulating adult neurogenesis. Recently, it has been demonstrated that transplanted NSCs integrate into the SVZ and associate preferentially with the vasculature by a differential interaction between the stromal-derived factor 1, secreted by endothelial cells, and the CXC chemokine receptor 4 expressed by SVZ cells (Kokovay et al., 2010). However, it is not known whether these contacts and the pinwheel organizations may play a role in the regulation of oligodendrogenesis in the SVZ. Although, the signals underlying regulation of the SVZ progenitors and their activation remain unknown, epidermal (**EGF**), fibroblast (**FGF**) and platelet-derived (**PDGF**) growth factors are important mitogenic regulators for multipotent stem cells in the SVZ (Reynolds and Weiss, 1992; Vescovi et al., 1993; Gritti et al., 1995; Craig et al., 1996; Gritti et al., 1999; Jackson et al., 2006).

4. Oligodendrogenesis in the SVZ

NSCs from the adult SVZ can be grown as a cell suspension in the presence of growth factors. Under these *in vitro* conditions, NSCs form spherical structures called *neurospheres* containing cells that are not only be able to self-renew (forming more neurospheres), but

also to differentiate into neurons, astrocytes and oligodendrocytes (Reynolds and Weiss, 1992; Vescovi et al., 1993; Gritti et al., 1996). Evidence indicates that neurospheres grafted into the brain can produce a number of myelinating oligodendrocytes (Pluchino et al., 2003). However, under normal conditions, the production of oligodendrocytes in the SVZ is scarce (Menn et al., 2006). Interestingly, demyelinating lesions in the neighboring white matter can significantly increase the generation of OPCs from SVZ progenitors (Nait-Oumesmar et al., 1999; Picard-Riera et al., 2002; Menn et al., 2006). Chordin appears to be one of the responsible signals, which re-directs GAD65 and doublecortin SVZ progenitors from neuronal to glial fates, generating new oligodendrocytes in a demyelinated corpus callosum (Jablonska et al., 2010). In patients suffering from multiple sclerosis, the human SVZ shows an increase in the number of PSA-NCAM+ / Sox10+ / Olig2+ progenitors, which suggests that human SVZ respond to demyelinating lesions by increasing the production of OPCs (Nait-Oumesmar et al., 2007).

4.1 SVZ astrocytes give rise to oligodendrocytes

Type-B cells in the SVZ are also the primary progenitors of new oligodendrocytes (Menn et al., 2006). This was demonstrated by labeling SVZ astrocytes in transgenic mice (GFAP-tva mice) that express the receptor for an avian retrovirus (RCAS) under control of the GFAP promoter (Holland and Varmus, 1998). Using these transgenic mice, the lineage derivatives of dividing astrocytes can be traced using engineered avian RCAS retroviruses carrying an inheritable reporter gene (Figure 2). The SVZ astrocytes and their progeny are permanently labeled with this method and generate oligodendrocytes, which migrate to the corpus callosum and the white matter tracts in the striatum and fimbria fornix (Menn et al., 2006). Interestingly, SVZ astrocytes, but not parenchymal astrocytes can generate oligodendrocytes *in vivo* (Menn et al., 2006; Gonzalez-Perez et al., 2009) or *in vitro* (Gonzalez-Perez and Quinones-Hinojosa, 2010).

4.2 Role of Olig2 transcription factor in SVZ oligodendrogenesis

Oligodendrogenesis in the SVZ appears to be mediated by a transit-amplifying progenitor (Type-C cell) that expresses the transcription factor Olig2 (Hack et al., 2005; Menn et al., 2006), which encodes basic helix-loop-helix transcription factor proteins that are crucial in the generation of OPCs (Rowitch, 2004). In the ventral embryonic forebrain, Olig2 expression and OPC formation are negatively regulated by Dlx homeobox transcription factors (Dlx1 and Dlx2) that determine neuronal cell fate acquisition (Petryniak et al., 2007). In the adult brain, Olig2 expression has been reported in OPCs and mature oligodendrocytes in the white matter (Ligon et al., 2004; Rowitch, 2004). Olig2-expressing Type-C cells may give rise to highly migratory OPCs that leave the SVZ and populate the corpus callosum, striatum and fimbria fornix, where they differentiate into NG2 glia and myelinating oligodendrocytes (Figure 2). Nevertheless, the number of SVZ-derived oligodendrocytes is limited as compared to the large number of new neurons generated by Type-B astrocytes. However, as mentioned above, the amount of oligodendrocytes produced in the SVZ can be increased by a demyelinating lesion. This suggests that external signals promote the gain-of-function of Olig2 in the SVZ (Maire et al., 2010), which stimulates oligodendrogenesis and myelination (Nait-Oumesmar et al., 1999; Picard-Riera et al., 2002; Menn et al., 2006; Gonzalez-Perez et al., 2009). Intracerebroventricular infusion of Noggin, an endogenous antagonist of bone morphogenic protein 4 (BMP4), increases the number of SVZ-derived oligodendrocytes (Colak et al., 2008; Cate et al., 2010). Endothelin-1, an astrocyte-derived signal, also regulates the migration and differentiation of OPCs (Gadea et al., 2009). A recent study indicates that glutamatergic inputs from demyelinated axons in the corpus callosum appears to signal OPCs migration from the SVZ and promotes axonal remyelination (Etxeberria et al., 2010). Thus, adult SVZ actively responds to demyelinating

lesions and increases the number of OPCs generated, which contribute to repair axonal demyelination.

5. Role of epidermal growth factor receptor (EGFR) in oligodendrocyte production

The epidermal growth factor is a small protein (6045 Da) with three intramolecular disulfide bonds and 53 amino acid residues (Cohen and Taylor, 1974; Carpenter and Cohen, 1979). The human EGF has a strong sequential and functional homology with the transforming growth factor alpha, which also binds to EGFR (Povlsen, 2008). EGF acts by binding with high affinity to the EGFR on the cell membrane that triggers the intrinsic protein-tyrosine kinase activity (Povlsen, 2008). Tyrosine kinase activity, in turn, stimulates a signal transduction cascade that increases intracellular calcium concentrations, promotes glycolysis and induces gene expression, which ultimately leads to DNA synthesis and protein production (Povlsen, 2008, 2010).

EGF can induce proliferation in a subpopulation of SVZ Type B stem cells and in the transit-amplifying Type-C cells (Doetsch et al., 2002). This appears to be mediated by the Notch and EGFR pathway interaction, which regulates the number and self-renewal of NSCs (Aguirre et al., 2010). The identity of the endogenous ligand for EGFR signaling is probably TGF- α , which is present in the choroid plexus (Seroogy et al., 1993; Tropepe et al., 1997). Overexpression of the EGFR confers migratory properties to non-migratory postnatal neural progenitors (Aguirre et al., 2005; Aguirre et al., 2007; Aguirre and Gallo, 2007; Gonzalez-Perez et al., 2009; Gonzalez-Perez and Quinones-Hinojosa, 2010). In the developing cortex and radial migration in the olfactory bulb, EGF mediates chemotactic migration (Caric et al., 2001). In the developing retina, embryonic cortical ventricular zone and early postnatal SVZ, the overexpression of EGFR results in precursors adopting a glial rather than a neuronal lineage (Lillien, 1995; Burrows et al., 1997; Petratos et al., 2004). It has been suggested that asymmetric segregation of EGFR during mitosis is responsible for glial fate restriction to a subpopulation of daughter cells (Sun et al., 2005). However, the signals underlying regulation of the primary stem cells and their activation remain to be elucidated, but it is clear that EGF plays an important role in normal cell growth, proliferation, migration and differentiation of neural cell lineages.

5.1 EGF induces SVZ astrocytes to generate oligodendrocyte precursors

Increasing evidence indicates that EGF is a key regulator of oligodendrocyte production (Aguirre et al., 2007; Aguirre and Gallo, 2007). EGFR overexpression in SVZ during early postnatal development also expands a population of NG2+Mash1+Olig2+ progenitors and enhances oligodendrocyte generation (Aguirre et al., 2005). A recent study shows that intracerebral infusion of EGF increases 300-400% the number of myelinating oligodendrocytes derived from SVZ astrocytes. Using the RCAS/GFAP-tva mouse system to label Type-B cells prior to EGF infusion, it was shown that the SVZ endogenous stem cells produce a 9.6-fold increase in the number of OPCs. Upon EGF removal these SVZ OPCs give rise to oligodendrocytes in both the normal and the injured brain (Gonzalez-Perez et al., 2009). Remarkably, this capacity appears to be restricted to SVZ astrocytes, because the labeling of astrocytes in cortex, corpus callosum or striatum with the RCA-Gtva system never resulted in labeled oligodendrocytes (Gonzalez-Perez et al., 2009). EGF increases the total number of BrdU-expressing astrocytes and Dlx-2 progenitors in the SVZ and promotes oligodendrogenesis, which occurs at the expense of neuroblast production (Doetsch et al., 2002; Gonzalez-Perez et al., 2009; Gonzalez-Perez and Quinones-Hinojosa, 2010). Instead, EGF induces the production of highly migratory cells that express Olig2 and Nestin (Figure 3 A-D). In addition, these cells also express NG2 and PDGFR α , a phenotype

consistent with OPCs (Stallcup and Beasley, 1987; Pringle et al., 1992; Nishiyama et al., 2002). The newly generated OPCs migrate extensively following white matter tracts and the blood vessels close to the SVZ (Figure 3E). Interestingly, after EGF withdrawal the SVZ-derived OPCs stop migrating and differentiate into myelinating oligodendrocytes into the corpus callosum, striatum and fimbria fornix (Figure 4 A-B). In addition, the EGF stimulation of SVZ astrocytes generates NG2+ cells in the white and gray matter (Figure 4 C). NG2-expressing cells, also known as synantocytes (Wigley and Butt, 2009) or polidendrocytes (Nishiyama et al., 2009), are involved in brain scar formation and remyelination (Zawadzka et al., 2010). NG2-expressing cells are likely functionally diverse. In fact, a subpopulation of NG2+ cells expresses AMPA receptors and plays a role in glutamatergic synaptic signaling in the hippocampus, corpus callosum and cortex (Bergles et al., 2010). To date, it is not known whether the NG2-expressing cells derived from EGF stimulation in the SVZ are a heterogeneous subpopulation of NG2-expressing glia. Thus, EGF on adult NSCs may play a significant role in the design of brain repair therapies. Interestingly, the pro-oligodendrogenic effect of EGF on SVZ astrocytes is a dose-dependent phenomenon and, even at high doses of EGF, parenchymal astrocytes are not able to produce OPCs (Gonzalez-Perez and Quinones-Hinojosa, 2010). Taken together, this evidence indicates that EGF signaling plays an important role in cell fate choice on the SVZ Type-B cells and increases the production of highly migratory OPCs, which populate white matter tracts and contribute to the repair demyelinating lesions. The effects of exogenous EGF on the cell-fate of SVZ progenitors and oligodendrocyte generation are summarized in the figure 5.

5.2 Potential pitfalls of EGFR overstimulation into the brain

EGF is a mitogenic substance used in esthetic and reconstructive medicine because it promotes proliferation, growth and regeneration of epidermal tissues, such as skin (Franklin and Lynch, 1979; Jijon et al., 1989; Mustoe et al., 1991), cornea (Petroutsos et al., 1984), nasal mucosa (Hosemann et al., 1991) and tympanic membrane (Guner et al., 2003). Experimental models have suggested a potential role of EGF as a treatment option for lung injuries (Lindsay, 2010), DNA double-strand break repair (Lindsay, 2010), stroke (Kolb et al., 2007) and demyelinating lesions (Aguirre et al., 2007; Gonzalez-Perez et al., 2009). Nevertheless, some evidence indicates that EGF stimulation may have undesirable effects. Long-lasting constitutive EGFR signaling in OPCs may lead to diffuse hyperplasia in postnatal white matter (Ivkovic et al., 2008). Other studies have found polyp-like formation after a long-lasting EGF infusion (Kuhn et al., 1997). There is also evidence that EGFR signaling plays a role in tumor progression. Approximately 50% of high-grade astrocytomas demonstrate EGFR amplification, which may drive the malignization process of glioblastomas (Maher et al., 2001; Wechsler-Reya and Scott, 2001). Olig2 and tenascin expression has been reported in brain tumors (Marie et al., 2001; Ligon et al., 2004). Interestingly, EGF infusion up-regulates the expression of tenascin (Doetsch et al., 2002) and Olig2, but did not generate glioma-like masses (Gonzalez-Perez et al., 2009). Instead, EGF-produces diffuse infiltration of SVZ progenitors that are induced to divide rapidly (Doetsch et al., 2002; Gonzalez-Perez and Quinones-Hinojosa, 2010). These cells become highly motile Olig2+ cells that travel along blood vessels and axonal tracts, an analogous behavior to that observed in brain tumor cells. Remarkably, none of these studies have reported brain tumor formation, which suggest that the genetic background plays an important role in the potential tumorigenesis of EGF infusion. In summary, it is clear that the excessive signaling of EGF on NSCs induces certain aspects of a transformed phenotype (e.g. proliferation and tissue invasion), but EGF overstimulation by itself is not enough to drive brain tumor formation.

6. Concluding remarks

NSCs transplantation has been tested as a cell replacement therapy in several experimental demyelination models with promising results (Keirstead, 2005; Pluchino and Martino, 2005), but delayed rejection of grafted precursor cells is a common event (Barker and Widner, 2004; Ashton-Chess et al., 2006). Therefore, recruitment of oligodendrocytes by stimulation of endogenous NSCs derived from the SVZ may be a feasible alternative for the remyelination of white matter tracts (D'Intino et al., 2006). SVZ oligodendrocyte production increases in response to demyelination, yet cell recruitment into the lesion is not extensive. Remarkably, EGF administration can significantly increase the number of oligodendrocytes derived from Type-B SVZ stem cells, which migrate long distances and contribute to myelin repair. High migration potential and the ability to differentiate into myelin-forming cells have been described as crucial properties in cell repair therapies for demyelinating diseases (Blakemore and Franklin, 2000). Therefore, endogenous stimulation of adult NSCs by EGF may represent a feasible alternative for these degenerative disorders. Nevertheless, future research will be needed to elucidate the role of SVZ progenitors in functional repair after demyelination. In addition, experimental tracking of SVZ stem cells in animals that lack myelin basic protein would be useful to clarify the role of SVZ in remyelination. Understanding the optimal conditions for oligodendrocyte production in the SVZ is a crucial step for designing a stem cell-based therapy.

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Figure 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.

Figure 2. Origin of oligodendrocytes in the SVZ

At the top, a schematic representation of the RCAS/GFP-tva system. After injection of the RCAS-GFP virus, a proliferating astrocyte incorporates into their genome the GFP gene that is inherited to its progeny.

Type-B cells can also generate oligodendrocyte precursor cells possibly via intermediate precursors similar to Type-C cells that express Olig2. Oligodendrocyte precursor cells derived from the SVZ migrate long distances and differentiate in NG2+ cells and oligodendrocytes in the corpus callosum, striatum and fimbria fornix.

Figure 3. EGF increases the production of Oligodendrocyte precursors in the SVZ

Immunofluorescence for Olig2 (red) on a coronal section of mouse brain after a 7-day infusion of vehicle (A) or EGF (B) into the lateral ventricle (V). EGF induces an important expansion of Olig2+ cells and nestin+ cells around the SVZ (C - D). E: Semi-thin section stained with cresyl violet showing elongated cells with heterogeneous chromatin and light cytoplasm (arrowheads) that leave the SVZ and migrate into the brain parenchyma using axonal tracts and blood vessels (BV). Scale bars: A - B = 50 μ m; C - D = 200 μ m; E = 10 μ m.

Figure 4. EGF removal induces SVZ-derived OPCs to differentiate into oligodendrocyte lineage NSCs in the SVZ were first labeled with RCAS-GFP virus. SVZ-derived oligodendrocytes extensively populate axonal tracts into the brain after a 7-day infusion of EGF (A) into the lateral ventricle. RCAS-GFP-labeled oligodendrocytes (B) and NG2 glia (C) found the corpus callosum. Green fluorescent protein was detected by immunohistochemistry. Scale bars: A = 200 μ m; B - C = 10 μ m.

Figure 5. Hypothetical model of EGFR stimulation in the SVZ

Under physiological conditions, Type-B NSCs in the SVZ generate many new neurons and few oligodendrocytes. However, the exposure to EGF (represented by the pink arrows) greatly reduces the number of neuroblasts. Instead, SVZ astrocytes proliferate and give rise to a type of intermediate progenitor or transit amplifying cell committed to the lineage of oligodendrocytes. These Type-C-like cells give rise to Olig2+NG2+PDGFRα+ progenitors that migrate long distances via axonal tracts and blood vessels. Upon EGF removal (represented by the orange arrows), Olig2+ progenitors stop migrating and many of them differentiate into myelinating oligodendrocytes and NG2-expressing cells. Some of the NG2+ cells may in turn give rise to oligodendrocytes.