Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain Research Reviews 48 (2005) 211–219

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Neural stem cells and their use as therapeutic tool in neurological disorders

Stefano Pluchino, Lucia Zanotti, Michela Deleidi, Gianvito Martino*

Department of Neuroscience, San Raffaele Scientific Institute, Neuroimmunology Unit-DIBIT, Via Olgettina 58, 20132 Milano, Italy

Accepted 9 December 2004
Available online 20 January 2005

Abstract

Spontaneous neural tissue repair occurs in patients affected by inflammatory and degenerative disorders of the central nervous system (CNS). However, this process is not robust enough to promote a functional and stable recovery of the CNS architecture. The development of cell-based therapies aimed at promoting brain repair, through damaged cell-replacement, is therefore foreseen. Several experimental cell-based strategies aimed at replacing damaged neural cells have been developed in the last 30 years. Although successful in promoting site-specific repair in focal CNS disorders, most of these therapeutic approaches have failed to foster repair in multifocal CNS diseases where the anatomical and functional damage is widespread. Stem cell-based therapies have been recently proposed and might represent in the near future a plausible alternative strategy in these disorders. However, before envisaging any human applications of stem cell-based therapies in neurological diseases, we need to consider some preliminary and still unsolved issues: (i) the ideal stem cell source for transplantation, (ii) the most appropriate route of stem cell administration, and, last but not least, (iii) the best approach to achieve an appropriate, functional, and long-lasting integration of transplanted stem cells into the host tissue.

Theme: Development and regeneration
Topic: Transplantation

Keywords: Stem cell; Neural stem cell; Demyelination; Remyelination; Neurodegeneration; Neuroprotection; Inflammation; Axonal damage

Contents

* Corresponding author. Fax: +39 02 2643 4855.
E-mail address: g.martino@hsr.it (G. Martino).

0165-0173/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2004.12.011

1. Introduction

Neural stem cells (NSCs) are considered a heterogeneous population of mitotically active, self-renewing, multipotent, immature progenitor cells of both the developing and the adult nervous system showing complex patterns of gene expression that vary in space and time [47,72]. Early in the 1960s, neural cells behaving as stem entities were isolated from the embryonic mammalian central as well as peripheral nervous system [23,51,75,87,94]. Since then, stem cells have been isolated virtually from the entire mammalian adult central nervous system (CNS) and regions such as the subventricular zone (SVZ) of the lateral ventricles, the hippocampus and the cerebral cortex have been shown to contain stem-like cellular elements [10,40,76,77,80,82]. During development, the number of uncommitted endogenous NSCs decreases over time, while the activation of cellular programs of differentiation into lineage (neuronal or glial)-restricted precursors increases [7,71]. In the adult CNS, stem-like cells–although showing modest proliferation characteristics–are capable of driving neurogenesis in specialized regions of the brain (i.e., the olfactory bulb, the hippocampus, the SVZ, the central canal of the spinal cord) which behave as highly specialized tissue niches [5,6,26,33,66,92,107]. On the other hand, cycling progenitor cells of apparent glial lineage, dispersed throughout the whole brain parenchyma, drive adult gliogenesis [42].

Whatever the terminology accepted–stem cells, precursors or progenitors–the origin of this discrete population of undifferentiated neural cells is still being debated. So far, two principal theories have been put forward. One theory claims that the true NSCs of the adult SVZ differentiate from ependymal cells expressing the intermediate filament protein nestin [49], while the other theory–recently supported by human data–identifies NSC as slowly dividing astrocyte-like (type B) subependymal cells expressing glial fibrillary acidic protein (GFAP) and nestin [30,64,82]. These multipotent, type B, NSC–which reside within the SVZ–are believed to generate in vivo at least three different populations of lineage-committed transit-amplifying progenitors [type C, type D cells and white matter progenitor cells (WMPC)] of both neuronal and glial phenotype. Proliferating type C neuroblasts migrate from the SVZ to the olfactory bulb trough the rostral migratory stream (RMS) of the adult brain and give rise to type A neurons. Mitotically active type D cells remain confined to the subgranular zone (SGZ) of the dentate gyrus and give rise to neuronal progenitors, whereas WMPC derived from SVZ-resident multipotent adult NSC reside within the subcortical parenchyma and give rise to astrocytes and oligodendrocytes. Neuronal and glial progenitors persist in both gray and white matter and their frequency within the adult CNS is maintained during adult life. Signals driving either glio- or neurogenesis in the adult brain are redundantly expressed over time, thus contributing to either physiological stem cell asymmetrical division or finalistic lineage-restricted differentiation for tissue replacement [29,42]. However, the relationship between these pools of endogenous progenitors and the identified endogenous stem cells of the CNS still remains to be elucidated.

2. Endogenous neural stem cells for brain repair

There is compelling evidence showing that ontogenetic processes governing NSC maintenance, fate, and specification occur in brain repair strategies during adult life. Notably, it has been recently shown that endogenous NSCs may sustain neurogenesis and gliogenesis in response to several different injuries such as those occurring during inflammatory, ischemic, or traumatic events [15,31,44,65,68,91]. These pathogenic events might trigger a cascade of cellular and molecular signals–possibly via the release of soluble mediators (e.g., cytokines, chemokines, metalloproteases, adhesion molecules, etc.)–capable of supporting neurogenesis and gliogenesis that, in turn, drive brain repair.

In chronic experimental autoimmune encephalomyelitis (EAE), the animal model for multiple sclerosis (MS), mitotically active progenitor cells, residing either in the SVZ of the brain or in the subependymal layer of central canal of the spinal cord, change their physiological destiny–which is basically that of migrating along the RMS to the olfactory bulb or to the laterals columns of the spinal cord [5,92], respectively–and migrate specifically into CNS areas of demyelination where they differentiate mostly into glial cells [15,68]. In experimental models of spinal cord injury (SCI) or ischemic stroke, neurogenesis of endogenous NSCs–residing close to the traumatized or ischemic regions and surviving to the injury–occurs within 1 week after the pathogenic event. Nestin-reactive proliferating progenitor cells have been, in fact, found at the border of the ischemic and traumatized areas while supporting post-injury neurogenesis within a zone comprised between the damaged tissue and the surrounding intact cerebral parenchyma [31,65,91].

There is accumulating evidence indicating that endogenous neurogenesis and gliogenesis may occur as part of an "intrinsic" brain self-repair process during adulthood, which supports the idea of developing therapeutic strategies for brain disorders based on the use of NSC transplantation.

3. Neural stem cell transplantation in CNS disorders

In CNS disorders characterized by neuronal or glial loss–e.g., stroke, Parkinson's disease, MS, SCI–cell-based replacement therapies may represent a promising alternative therapeutic approach. However, there are some preliminary questions that need to be solved before envisaging any potential human application of such therapies: (i) the ideal cell source for transplantation; (ii) the route of cell administration; and (iii) the differentiation and persistence of NSC

into the targeted tissue. Last but not least, functional and long-lasting integration of transplanted cells into the host tissue has to be achieved.

3.1. The source of cells

Whatever the organ or tissue requirements, the ideal cell for replacement therapies has to be plastic in its essence. Stem cells can meet this criterion since they are intrinsically able to adapt their fate to different environmental needs. Both embryonic stem cells (ES) and adult NSC (aNSC) might represent the ideal cell source for cell replacement-based therapies in CNS disorders. Embryo-derived neural cells, although representing a promising source of NSC, have not been consistently used so far for transplantation purposes [38,90,99].

3.1.1. Embryonic stem (ES) cells

ES cells, derived from the inner cell mass of blastocyst-stage embryos, are totipotent cells able to give rise to a differentiated progeny representative of all three embryonic germ layers as well as of the extra-embryonic tissues supporting development. ES cell lines can be established from virtually all mammals [35,79]. In humans, blastocysts for the establishment of renewable human ES cell lines may be obtained from either supernumerary embryos (from in vitro fertilization procedures) or from embryos specifically created by research purposes (i.e., nuclear transfer, parthenogenetic activation of egg) [25,85,101,103]. ES cells can be propagated indefinitely under certain in vitro conditions while maintaining a normal karyotype and totipotency, as has been recently shown by culturing ES cell lines in presence of leukemia inhibitory factor (LIF) [86]. ES cells can also be induced to differentiate in vitro into almost all cell types of the body [74,79] including neural cells that can be obtained by growing cells in the presence of neurotrophic factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF)-α, and fibroblast growth factor (FGF)-2 [11,36,37,50,54,75,112]. However, while totipotent ES cells have been used for transplants [57,78], there are no consistent data on the use of ES-derived lineage restricted neural cells.

When ES cells were transplanted into rodents with either genetically-determined or chemically-induced demyelination (both within the brain and the spinal cord), they differentiated into glial cells and remyelinated demyelinated axons [17,54]. However, most of the recent experimental transplantation studies involving ES cells have been complicated by the formation of heterologous tissues and teratomas within the transplantation site [16,27,104,109] suggesting that in certain circumstances cross-talk between transplanted ES cells and parenchymal cells at the site of transplantation has gone awry. To partially overcome such limitation, protocols have been developed to generate in vitro high numbers of cell type-specific neural precursors (e.g., oligodendroglial lineage cells, dopaminergic neurons) from ES cells [63,75,88,112]. A protein called stromal cell-derived inducing activity (SDIA) which promotes neural differentiation of mouse ES cells into dopaminergic neurons in vivo, has been recently identified [63]. When SDIA-induced dopaminergic neurons were transplanted into the 6-hydroxydopamine (6-OHDA)-lesioned mouse striatum, they integrated into the host tissue and remained positive for tyrosine hydroxylase (TH) expression [63]. Moreover, dopaminergic neurons have been obtained by generating stable nuclear receptor related (Nurr)1 ES cell lines. Nurr1 is a transcription factor that has been shown to have a role in the differentiation of midbrain precursors into dopamine neurons [111] and its overexpression in mouse ES cells promotes an increase in the proportion of TH^+ neurons from 5 to 50% in vitro. Once transplanted into the striatum of (6-OHDA)-lesioned hemiparkinsonian rats, Nurr1-overexpressing cells integrated into the tissue of transplantation and showed immunoreactivity for TH. They displayed electrophysiological characteristics similar to those of mesencephalic neurons and mediated a significant amelioration of amphetamine-induced behavioral tests as compared to (6-OHDA)-lesioned hemiparkinsonian rats transplanted with naive ES cells [52].

3.1.2. Adult neural stem cells (aNSC)

Mammalian aNSC support neurogenesis and gliogenesis within restricted areas of the CNS throughout adulthood. They can undergo extensive in vitro expansion upon epigenetic stimulation and possess the capacity to generate a progeny of neural cells which can integrate into and repair the tissue of origin [40,44,45,98]. These cells can be isolated from fetal and adult human brains and can be expanded and maintained safely in a chemically defined medium for years possibly providing a renewable source of uncommitted NSCs, that can be used for transplantation procedures [81,100]. These cells show: (i) growth factor (GF)-dependent proliferation and a stable growth rate; (ii) transcriptionally-regulated capacity for self-renewal; (iii) multipotentiality; and (iv) functional plasticity either over serial in vitro passaging or after several freeze–thaw cycles [40,43,62]. aNSC plasticity and functional flexibility can be modulated in vitro by the exposure to different growth factors [98]. LIF, brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), neurotrophin (NT)-3, NT-4, sonic hedgehog (Shh), and fibroblast-derived growth factor (FGF)-8 drive aNSCs trough a neuronal fate (up to 40–60% of cells in culture), whereas bone morphogenetic proteins (BMPs), CNTF, and LIF increase the number of aNSC-derived astrocytes [20,39,53].

In vivo experiments aimed at repairing injured CNS by transplanting multipotent aNSC have shown that these cells may survive to transplantation procedures within the host CNS. They display notable migratory properties from the site of grafting and maintain their multipotency. While aNSC, transplanted either intraparenchymally or intrathecally in healthy rodents show precise pathways of tissue

invasion and neuronal (i.e., dopaminergic) differentiation [32,34,110], there are data showing that these differentiation patterns change when aNSC are transplanted into rodents suffering from experimental CNS diseases. In experimental autoimmune, chemical, or traumatic CNS demyelination, aNSCs transplanted intraparenchymally, intracerebroventricularly (i.c.), or intravenously (i.v.) show ability to migrate selectively to CNS areas of tissue damage and to differentiate into axon-ensheating oligodendrocytes that promote functional recovery [2,12,18,69,108]. Similarly, site-specific dopaminergic neuronal differentiation has been obtained by intrastriatal transplantation of undifferentiated syngenic or xenogenic (human) aNSC in rats affected by experimental parkinsonism [56,89,110]. More recently, i.v.-injected human aNSC have been efficacious in promoting functional recovery in rats affected by both experimental intracerebral hemorrhage or transient cerebral ischemia via terminal differentiation into neurons (10%) and astrocytes (75%) [24,48]. Notably, aNSC transplants into both healthy and diseased rodents did not result in tumor formation in immunodeficient mice, thus strongly suggesting that the tumorigenic potential of these cells in vivo is minimal [99].

3.2. The route of cell administration

The route of cell administration represents another key issue when considering therapeutic NSC transplantation for CNS diseases.

On one hand, the anatomy of focal CNS disorders, such as Parkinson's disease or SCI, would suggest that direct intralesional cell transplantation might facilitate regeneration of dopaminergic neurons within the substantia nigra or protection of demyelinated axons within a specific segment of the spinal cord, respectively. ES-cell-derived TH^+ neuronal precursors, when focally transplanted into the striatum of 6-OHDA-lesioned rats release dopamine, extend axons, form functional synaptic connections and modulate spontaneous and pharmacologically induced behavior [13,52]. After SCI and experimental ischemia in rodents, intralesionally-transplanted aNSC integrate within the host tissue, differentiate preferentially into glial cells, release neurotrophic growth factors [e.g., BDNF, glial-derived neurotrophic factor (GDNF), nerve growth factor (NGF)], promote neurogenesis, and inhibit reactive astrogliosis thus favoring motor recovery [9,21,55,95]. Furthermore, when either neural-differentiated or fibroblast feeder-grown ES cells are engrafted into acutely injured or chemically-demyelinated spinal cords of rats, transplanted cells survive, integrate, migrate (as far as 8 mm away from the lesion edge), and finally differentiate into multiple neural cell types (i.e., astrocytes, oligodendrocytes, and neurons) [54,58,76]. However, heterotopic migration or dispersion of transplanted cells has to be viewed as a potential risk of aNSC transplants that could lower the therapeutic efficacy of aNSC-based therapies.

On the other hand, the multifocality of certain CNS disorders, such as amyotrophic lateral sclerosis, MS, or Alzheimer's disease, severely limits aNSC-based therapies. However, some recent experiments have shown that in multifocal inflammatory brain disorders, these limitations can be overcome by injecting therapeutic somatic stem cells (e.g., bone marrow cells, mesenchymal cells, NSC) into the blood stream (i.v.) or into the cerebrospinal fluid circulation (i.c.). aNSC transplanted in this fashion can reach multiple inflamed areas in the brain and the spinal cord. This specific homing can be explained, at least in part, by the constitutive expression by aNSC of a wide array of inflammatory molecules such as adhesion molecules (i.e., integrins, selectins, immunoglobulins, etc.), chemokines, cytokines, and chemokine receptors [69,96]. These molecules, which mobilize precursors along patterned migration and differentiation pathways during development [70,84,96], may promote selective CNS homing because they support aNSC interactions with integrin receptor-expressing activated endothelial and ependymal cells surrounding inflamed brain tissues [19,28,70]. Thus, aNSC are very likely to follow a gradient of chemoattraction at the site of inflammatory brain lesions [73,97]. This "chemoattractive" hypothesis is strongly supported by a recent study showing that i.v.-administered mouse aNSC promote anatomical and functional recovery of the myelin sheath–in an experimental model of autoimmune demyelination (namely, EAE)–by selectively homing into inflamed brain and spinal cord areas via membrane expression of CD44 and very late antigen (VLA)-4 [69]. Since these two latter molecules are crucial for the specific homing of encephalitogenic lymphocytes into the CNS parenchyma during EAE, one might suggest that aNSC recapitulate encephalitogenic lymphocyte homing pathways for reaching areas of inflammation. As a further confirmation of this phenomenon, it has been recently shown that aNSC are capable to target both intracranial and extracranial tumors, when administered into the peripheral vasculature [1,14]. The well-characterized clonal NSC line C17.2 was injected into the tail vein of adult nude mice with established experimental intracranial and/or subcutaneous flank tumors of neural and non-neural origin and the cells were subsequently found in various tumor sites with very little accumulation in normal tissues [14].

3.3. Differentiation and persistence of neural stem cells in the targeted tissue

Ideally, once in the target organ, therapeutic NSCs should differentiate into the appropriate daughter cells and persist as long as needed at the site of engraftment. However, although very little is known about the mechanisms instructing the terminal differentiation of NSC in vivo, there is strong evidence that the local environment might dictate the fate choice of transplanted uncommitted NSC. In this respect, undifferentiated multipotent aNSC or even totipotent ES cells, transplanted in different experimental

neurological conditions, have shown considerable capacity to restrict their fate to tissue-specific cues and replace non-functioning neural cells of different lineages.

Totipotent ES cells display a preferential terminal differentiation into either myelinating oligodendrocytes or TH^+ neurons when transplanted into rodents affected by experimental acute SCI or 6-OHDA-induced Parkinsonism, respectively [13,16,50,52,54,57]. Even more efficiently, multipotent growth factor-responsive aNSCs show neuronal- or glial-restricted fate when transplanted in animal models of neuronal (e.g., Parkinson's disease, stroke) or myelin dysfunction (e.g., EAE, SCI) [21,24,32,48,55,95,108,110], respectively. Thus, the local environment may dictate the fate choice of transplanted NSC. However, transplanted NSC might exert their therapeutic effect not only by differentiating into lineage-restricted daughter cells and by functionally integrating into the host tissue. Whatever the characteristics of the model of transplantation, it has been recently shown aNSCs may also remain in an undifferentiated state in vivo. Discrete numbers of transplanted aNSCs fail to express differentiation antigens, retain a rounded morphology, as well as perivascular localization, but continue to release neurotrophic growth factors (FGF-2, BDNF, GDNF, etc.) [9,55,67,95]. This evidence suggests that aNSCs might repair brain damage even when they remain in their undifferentiated state, essentially acting as bystander regulators of neuron and/or oligodendrocyte rescue via the release of neurotrophic molecules.

4. Bone marrow stem cell therapies for brain repair

Bone marrow stem cells (BMSCs) have recently been shown to have the capacity to differentiate into other specific cell lineages (e.g., muscle, skin, liver, lung), including neural cells, when transplanted in both rodents and humans [59,60,106]. Although it is not yet clear which fraction of BMSCs is more prone to differentiate into cell types of a different embryonic origin in vivo (e.g., haematopoietic vs. mesenchymal cells), transdifferentiation of BMSCs into neural cells deserves special attention due to the potential importance of this biological event in cell-based regenerative therapies for brain disorders.

The first and most challenging example of a possible contribution of BMSCs to the cytoarchitecture of the brain comes from a recent report showing Y-chromosomes in cerebellar Purkinje neurons of women who had received bone marrow transplants from male donors [106]. Along with this evidence of BMSC plasticity, there are other reports that collectively suggest that these cells could contribute to generate new neurons in the adult brain by means of (i) transdifferentiation (direct conversion of transplanted cells into neurons) [59,60,105,106]; (ii) transdetermination (direct conversion of transplanted stem cells into a stem cell of a different embryonic origin) [105]; and/or (iii) cell fusion (assimilation of transplanted cells or their progeny into existing neurons and formation of heterokaryons) [8].

The demonstration that BMSCs are developmentally plastic has encouraged many attempts to use BMSCs for brain repair. BMSCs have recently been injected into animals affected by experimental demyelination, ischemic stroke, amyotrophic lateral sclerosis (ALS), and SCI [3,4,41,46,83,113]. In rats with focal chemical demyelination of the spinal cord, collagen type I^+/fibronectin$^+$/$CD44^+$ mouse BMSCs gave rise to new myelin forming cells in vivo and determined improvement of axonal conduction velocity, when transplanted i.v. or by direct microinjection into the demyelinated spinal cord of immunosuppressed rats [3,4,46]. When injected into adult mice in which focal cerebral ischemia had been induced, transplanted Tie2-lacZ-positive BMSCs–immunoreactive for von Willebrand factor endothelial antigenic marker–were found in areas of neovascularization at the border of the infarct [113]. Human umbilical cord blood cells and hematopoietic stem cells–directly transplanted into the spinal cord of rodent models of SCI–survived within the host tissue, expressed specific markers for astrocytes, oligodendrocytes, and neural precursors and promoted functional recovery [3,4,83]. Human umbilical cord blood cells delivered i.v. into mice with experimental ALS survived 10–12 weeks after infusion, delayed disease progression and increased lifespan of diseased mice. They entered regions of motor neuron degeneration–both in the brain and in the spinal cord–and expressed neural and astrocytic markers [41].

Although the abovementioned studies demonstrate that BMSCs differentiating into brain cells might support functional CNS repair, the real "brain repair" potential of this cell source has been recently challenged by the demonstration that transdifferentiation in vivo of BMSCs into mature, and properly functioning, neural cells is a very rare event (e.g., 1 out of 500,000 cells) and may depend on cell fusion rather than on "real" transdifferentiation [22,61,102].

5. Conclusions

The identification and isolation of a discrete population of uncommitted self-renewing NSCs both in embryos and in specialized areas of the adult mammalian CNS–along with the demonstration of their therapeutic potential in several experimental models of human CNS diseases (e.g., SCI, Parkinson's disease, EAE, stroke, brain tumors)–has represented a milestone in the field of regenerative medicine [77,87,93,94]. However, this is still a baby science suffering from growing pain, and before envisaging any therapeutic application of such cells in humans with brain disorders, we need to confront with several, and still unsolved, problems: (i) the ideal "stem" cell source for transplantation; (ii) the most appropriate in vivo and/or in vitro manipulations to obtain the appropriate cells to transplant; (iii) a clinically

applicable transplantation strategy (e.g., route of cell transplantation in focal and multifocal CNS disorders); (iii) the right timing for cell transplantation; and, finally, (iv) the appropriate number of cells to transplant.

Acknowledgments

This work is supported in part by the Minister of Health, Italian Multiple Sclerosis Foundation (FISM) and MIUR. S.P. is receiving a fellowship from the Italian Multiple Sclerosis Foundation (FISM); L.Z. is receiving a fellowship from The Myelin Project (TMP).

References

[1] K.S. Aboody, A. Brown, N.G. Rainov, K.A. Bower, S. Liu, W. Yang, J.E. Small, U. Herrlinger, V. Ourednik, P.M. Black, X.O. Breakefield, E.Y. Snyder, Neural stem cells display extensive tropism for pathology in adult brain: evidence from intracranial gliomas, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 12846–12851.

[2] Y. Akiyama, O. Honmou, T. Kato, T. Uede, K. Hashi, J.D. Kocsis, Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord, Exp. Neurol. 167 (2001) 27–39.

[3] Y. Akiyama, C. Radtke, O. Honmou, J.D. Kocsis, Remyelination of the spinal cord following intravenous delivery of bone marrow cells, Glia 39 (2002) 229–236.

[4] Y. Akiyama, C. Radtke, J.D. Kocsis, Remyelination of the rat spinal cord by transplantation of identified bone marrow stromal cells, J. Neurosci. 22 (2002) 6623–6630.

[5] J. Altman, Autoradiographic and histological studies of postnatal neurogenesis. 3. Dating the time of production and onset of differentiation of cerebellar microneurons in rats, J. Comp. Neurol. 136 (1969) 269–293.

[6] J. Altman, G.D. Das, Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats, J. Comp. Neurol. 124 (1965) 319–335.

[7] A. Alvarez-Buylla, J.M. Garcia-Verdugo, A.D. Tramontin, A unified hypothesis on the lineage of neural stem cells, Nat. Rev., Neurosci. 2 (2001) 287–293.

[8] M. Alvarez-Dolado, R. Pardal, J.M. Garcia-Verdugo, J.R. Fike, H.O. Lee, K. Pfeffer, C. Lois, S.J. Morrison, A. Alvarez-Buylla, Fusion of bone-marrow-derived cells with Purkinje neurons, cardiomyocytes and hepatocytes, Nature 425 (2003) 968–973.

[9] G. Andsberg, Z. Kokaia, A. Bjorklund, O. Lindvall, A. Martinez-Serrano, Amelioration of ischaemia-induced neuronal death in the rat striatum by NGF-secreting neural stem cells, Eur. J. Neurosci. 10 (1998) 2026–2036.

[10] Y. Arsenijevic, J.G. Villemure, J.F. Brunet, J.J. Bloch, N. Deglon, C. Kostic, A. Zurn, P. Aebischer, Isolation of multipotent neural precursors residing in the cortex of the adult human brain, Exp. Neurol. 170 (2001) 48–62.

[11] G. Bain, D. Kitchens, M. Yao, J.E. Huettner, D.I. Gottlieb, Embryonic stem cells express neuronal properties in vitro, Dev. Biol. 168 (1995) 342–357.

[12] T. Ben-Hur, O. Einstein, R. Mizrachi-Kol, O. Ben-Menachem, E. Reinhartz, D. Karussis, O. Abramsky, Transplanted multipotential neural precursor cells migrate into the inflamed white matter in response to experimental autoimmune encephalomyelitis, Glia 41 (2003) 73–80.

[13] L.M. Bjorklund, R. Sanchez-Pernaute, S. Chung, T. Andersson, I.Y. Chen, K.S. McNaught, A.L. Brownell, B.G. Jenkins, C. Wahlestedt, K.S. Kim, O. Isacson, Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 2344–2349.

[14] A.B. Brown, W. Yang, N.O. Schmidt, R. Carroll, K.K. Leishear, N.G. Rainov, P.M. Black, X.O. Breakefield, K.S. Aboody, Intravascular delivery of neural stem cell lines to target intracranial and extracranial tumors of neural and non-neural origin, Hum. Gene Ther. 14 (2003) 1777–1785.

[15] L. Brundin, H. Brismar, A.I. Danilov, T. Olsson, C.B. Johansson, Neural stem cells: a potential source for remyelination in neuroinflammatory disease, Brain Pathol. 13 (2003) 322–328.

[16] O. Brustle, A.C. Spiro, K. Karram, K. Choudhary, S. Okabe, R.D. McKay, In vitro-generated neural precursors participate in mammalian brain development, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 14809–14814.

[17] O. Brustle, K.N. Jones, R.D. Learish, K. Karram, K. Choudhary, O.D. Wiestler, I.D. Duncan, R.D. McKay, Embryonic stem cell-derived glial precursors: a source of myelinating transplants, Science 285 (1999) 754–756.

[18] J.W. Bulte, T. Ben-Hur, B.R. Miller, R. Mizrachi-Kol, O. Einstein, E. Reinhartz, H.A. Zywicke, T. Douglas, J.A. Frank, MR microscopy of magnetically labeled neurospheres transplanted into the Lewis EAE rat brain, Magn. Reson. Med. 50 (2003) 201–205.

[19] E.C. Butcher, L.J. Picker, Lymphocyte homing and homeostasis, Science 272 (1996) 60–66.

[20] M.A. Caldwell, X. He, N. Wilkie, S. Pollack, G. Marshall, K.A. Wafford, C.N. Svendsen, Growth factors regulate the survival and fate of cells derived from human neurospheres, Nat. Biotechnol. 19 (2001) 475–479.

[21] Q.L. Cao, Y.P. Zhang, R.M. Howard, W.M. Walters, P. Tsoulfas, S.R. Whittemore, Pluripotent stem cells engrafted into the normal or lesioned adult rat spinal cord are restricted to a glial lineage, Exp. Neurol. 167 (2001) 48–58.

[22] R.F. Castro, K.A. Jackson, M.A. Goodell, C.S. Robertson, H. Liu, H.D. Shine, Failure of bone marrow cells to transdifferentiate into neural cells in vivo, Science 297 (2002) 1299.

[23] E. Cattaneo, R. McKay, Proliferation and differentiation of neuronal stem cells regulated by nerve growth factor, Nature 347 (1990) 762–765.

[24] K. Chu, M. Kim, S.W. Jeong, S.U. Kim, B.W. Yoon, Human neural stem cells can migrate, differentiate, and integrate after intravenous transplantation in adult rats with transient forebrain ischemia, Neurosci. Lett. 343 (2003) 129–133.

[25] J.B. Cibelli, K.A. Grant, K.B. Chapman, K. Cunniff, T. Worst, H.L. Green, S.J. Walker, P.H. Gutin, L. Vilner, V. Tabar, T. Dominko, J. Kane, P.J. Wettstein, R.P. Lanza, L. Studer, K.E. Vrana, M.D. West, Parthenogenetic stem cells in nonhuman primates, Science 295 (2002) 819.

[26] F.S. Corotto, J.A. Henegar, J.A. Maruniak, Neurogenesis persists in the subependymal layer of the adult mouse brain, Neurosci. Lett. 149 (1993) 111–114.

[27] T. Deacon, J. Dinsmore, L.C. Costantini, J. Ratliff, O. Isacson, Blastula-stage stem cells can differentiate into dopaminergic and serotonergic neurons after transplantation, Exp. Neurol. 149 (1998) 28–41.

[28] M. Deckert-Schluter, D. Schluter, H. Hof, O.D. Wiestler, H. Lassmann, Differential expression of ICAM-1, VCAM-1 and their ligands LFA-1, Mac-1, CD43, VLA-4, and MHC class II antigens in murine Toxoplasma encephalitis: a light microscopic and ultrastructural immunohistochemical study, J. Neuropathol. Exp. Neurol. 53 (1994) 457–468.

[29] F. Doetsch, The glial identity of neural stem cells, Nat. Neurosci. 6 (2003) 1127–1134.

[30] F. Doetsch, I. Caille, D.A. Lim, J.M. Garcia-Verdugo, A. Alvarez-Buylla, Subventricular zone astrocytes are neural stem cells in the adult mammalian brain, Cell 97 (1999) 703–716.

[31] N. Duggal, R. Schmidt-Kastner, A.M. Hakim, Nestin expression in

reactive astrocytes following focal cerebral ischemia in rats, Brain Res. 768 (1997) 1–9.
[32] U. Englund, A. Bjorklund, K. Wictorin, O. Lindvall, M. Kokaia, Grafted neural stem cells develop into functional pyramidal neurons and integrate into host cortical circuitry, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 17089–17094.
[33] P.S. Eriksson, E. Perfilieva, T. Bjork-Eriksson, A.M. Alborn, C. Nordborg, D.A. Peterson, F.H. Gage, Neurogenesis in the adult human hippocampus, Nat. Med. 4 (1998) 1313–1317.
[34] C. Eriksson, A. Bjorklund, K. Wictorin, Neuronal differentiation following transplantation of expanded mouse neurosphere cultures derived from different embryonic forebrain regions, Exp. Neurol. 184 (2003) 615–635.
[35] M.J. Evans, M.H. Kaufman, Establishment in culture of pluripotential cells from mouse embryos, Nature 292 (1981) 154–156.
[36] M.F. Finley, N. Kulkarni, J.E. Huettner, Synapse formation and establishment of neuronal polarity by P19 embryonic carcinoma cells and embryonic stem cells, J. Neurosci. 16 (1996) 1056–1065.
[37] A. Fraichard, O. Chassande, G. Bilbaut, C. Dehay, P. Savatier, J. Samarut, In vitro differentiation of embryonic stem cells into glial cells and functional neurons, J. Cell Sci. 108 (Pt 10) (1995) 3181–3188.
[38] J. Frisen, C.B. Johansson, C. Lothian, U. Lendahl, Central nervous system stem cells in the embryo and adult, Cell. Mol. Life Sci. 54 (1998) 935–945.
[39] R. Galli, S.F. Pagano, A. Gritti, A.L. Vescovi, Regulation of neuronal differentiation in human CNS stem cell progeny by leukemia inhibitory factor, Dev. Neurosci. 22 (2000) 86–95.
[40] R. Galli, A. Gritti, L. Bonfanti, A.L. Vescovi, Neural stem cells: an overview, Circ. Res. 92 (2003) 598–608.
[41] S. Garbuzova-Davis, A.E. Willing, T. Zigova, S. Saporta, E.B. Justen, J.C. Lane, J.E. Hudson, N. Chen, C.D. Davis, P.R. Sanberg, Intravenous administration of human umbilical cord blood cells in a mouse model of amyotrophic lateral sclerosis: distribution, migration, and differentiation, J. Hematother. Stem Cell Res. 12 (2003) 255–270.
[42] S. Goldman, Glia as neural progenitor cells, Trends Neurosci. 26 (2003) 590–596.
[43] A. Gritti, P. Frolichsthal-Schoeller, R. Galli, E.A. Parati, L. Cova, S.F. Pagano, C.R. Bjornson, A.L. Vescovi, Epidermal and fibroblast growth factors behave as mitogenic regulators for a single multipotent stem cell-like population from the subventricular region of the adult mouse forebrain, J. Neurosci. 19 (1999) 3287–3297.
[44] A.F. Hallbergson, C. Gnatenco, D.A. Peterson, Neurogenesis and brain injury: managing a renewable resource for repair, J. Clin. Invest. 112 (2003) 1128–1133.
[45] P.J. Horner, F.H. Gage, Regenerating the damaged central nervous system, Nature 407 (2000) 963–970.
[46] M. Inoue, O. Honmou, S. Oka, K. Houkin, K. Hashi, J.D. Kocsis, Comparative analysis of remyelinating potential of focal and intravenous administration of autologous bone marrow cells into the rat demyelinated spinal cord, Glia 44 (2003) 111–118.
[47] N.B. Ivanova, J.T. Dimos, C. Schaniel, J.A. Hackney, K.A. Moore, I.R. Lemischka, A stem cell molecular signature, Science 298 (2002) 601–604.
[48] S.W. Jeong, K. Chu, K.H. Jung, S.U. Kim, M. Kim, J.K. Roh, Human neural stem cell transplantation promotes functional recovery in rats with experimental intracerebral hemorrhage, Stroke 34 (2003) 2258–2263.
[49] C.B. Johansson, S. Momma, D.L. Clarke, M. Risling, U. Lendahl, J. Frisen, Identification of a neural stem cell in the adult mammalian central nervous system, Cell 96 (1999) 25–34.
[50] H. Kawasaki, K. Mizuseki, S. Nishikawa, S. Kaneko, Y. Kuwana, S. Nakanishi, S.I. Nishikawa, Y. Sasai, Induction of midbrain dopaminergic neurons from ES cells by stromal cell-derived inducing activity, Neuron 28 (2000) 31–40.
[51] T.J. Kilpatrick, P.F. Bartlett, Cloning and growth of multipotential neural precursors: requirements for proliferation and differentiation, Neuron 10 (1993) 255–265.
[52] J.H. Kim, J.M. Auerbach, J.A. Rodriguez-Gomez, I. Velasco, D. Gavin, N. Lumelsky, S.H. Lee, J. Nguyen, R. Sanchez-Pernaute, K. Bankiewicz, R. McKay, Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease, Nature 418 (2002) 50–56.
[53] T.E. Kim, H.S. Lee, Y.B. Lee, S.H. Hong, Y.S. Lee, H. Ichinose, S.U. Kim, M.A. Lee, Sonic hedgehog and FGF8 collaborate to induce dopaminergic phenotypes in the Nurr1-overexpressing neural stem cell, Biochem. Biophys. Res. Commun. 305 (2003) 1040–1048.
[54] S. Liu, Y. Qu, T.J. Stewart, M.J. Howard, S. Chakrabortty, T.F. Holekamp, J.W. McDonald, Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 6126–6131.
[55] P. Lu, L.L. Jones, E.Y. Snyder, M.H. Tuszynski, Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury, Exp. Neurol. 181 (2003) 115–129.
[56] C. Lundberg, A. Martinez-Serrano, E. Cattaneo, R.D. McKay, A. Bjorklund, Survival, integration, and differentiation of neural stem cell lines after transplantation to the adult rat striatum, Exp. Neurol. 145 (1997) 342–360.
[57] J.W. McDonald, M.J. Howard, Repairing the damaged spinal cord: a summary of our early success with embryonic stem cell transplantation and remyelination, Prog. Brain Res. 137 (2002) 299–309.
[58] J.W. McDonald, X.Z. Liu, Y. Qu, S. Liu, S.K. Mickey, D. Turetsky, D.I. Gottlieb, D.W. Choi, Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord, Nat. Med. 5 (1999) 1410–1412.
[59] E. Mezey, K.J. Chandross, G. Harta, R.A. Maki, S.R. McKercher, Turning blood into brain: cells bearing neuronal antigens generated in vivo from bone marrow, Science 290 (2000) 1779–1782.
[60] E. Mezey, S. Key, G. Vogelsang, I. Szalayova, G.D. Lange, B. Crain, Transplanted bone marrow generates new neurons in human brains, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 1364–1369.
[61] E. Mezey, A. Nagy, I. Szalayova, S. Key, A. Bratincsak, J. Baffi, T. Shahar, Comment on "Failure of bone marrow cells to transdifferentiate into neural cells in vivo", Science 299 (2003) 1184, author reply 1184.
[62] A.V. Molofsky, R. Pardal, T. Iwashita, I.K. Park, M.F. Clarke, S.J. Morrison, Bmi-1 dependence distinguishes neural stem cell self-renewal from progenitor proliferation, Nature 425 (2003) 962–967.
[63] A. Morizane, J. Takahashi, Y. Takagi, Y. Sasai, N. Hashimoto, Optimal conditions for in vivo induction of dopaminergic neurons from embryonic stem cells through stromal cell-derived inducing activity, J. Neurosci. Res. 69 (2002) 934–939.
[64] C.M. Morshead, B.A. Reynolds, C.G. Craig, M.W. McBurney, W.A. Staines, D. Morassutti, S. Weiss, D. van der Kooy, Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells, Neuron 13 (1994) 1071–1082.
[65] J. Namiki, C.H. Tator, Cell proliferation and nestin expression in the ependyma of the adult rat spinal cord after injury, J. Neuropathol. Exp. Neurol. 58 (1999) 489–498.
[66] T.D. Palmer, J. Takahashi, F.H. Gage, The adult rat hippocampus contains primordial neural stem cells, Mol. Cell. Neurosci. 8 (1997) 389–404.
[67] K.I. Park, Y.D. Teng, E.Y. Snyder, The injured brain interacts reciprocally with neural stem cells supported by scaffolds to reconstitute lost tissue, Nat. Biotechnol. 20 (2002) 1111–1117.
[68] N. Picard-Riera, L. Decker, C. Delarasse, K. Goude, B. Nait-Oumesmar, R. Liblau, D. Pham-Dinh, A.B. Evercooren, Exper-

imental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 13211–13216.
[69] S. Pluchino, A. Quattrini, E. Brambilla, A. Gritti, G. Salani, G. Dina, R. Galli, U. Del Carro, S. Amadio, A. Bergami, R. Furlan, G. Comi, A.L. Vescovi, G. Martino, Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis, Nature 422 (2003) 688–694.
[70] L. Prestoz, J.B. Relvas, K. Hopkins, S. Patel, P. Sowinski, J. Price, C. ffrench-Constant, Association between integrin-dependent migration capacity of neural stem cells in vitro and anatomical repair following transplantation, Mol. Cell. Neurosci. 18 (2001) 473–484.
[71] X. Qian, Q. Shen, S.K. Goderie, W. He, A. Capela, A.A. Davis, S. Temple, Timing of CNS cell generation: a programmed sequence of neuron and glial cell production from isolated murine cortical stem cells, Neuron 28 (2000) 69–80.
[72] M. Ramalho-Santos, S. Yoon, Y. Matsuzaki, R.C. Mulligan, D.A. Melton, "Stemness": transcriptional profiling of embryonic and adult stem cells, Science 298 (2002) 597–600.
[73] R.M. Ransohoff, The chemokine system in neuroinflammation: an update, J. Infect. Dis. 186 (Suppl. 2) (2002) S152–S156.
[74] B.E. Reubinoff, M.F. Pera, C.Y. Fong, A. Trounson, A. Bongso, Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro, Nat. Biotechnol. 18 (2000) 399–404.
[75] B.E. Reubinoff, P. Itsykson, T. Turetsky, M.F. Pera, E. Reinhartz, A. Itzik, T. Ben-Hur, Neural progenitors from human embryonic stem cells, Nat. Biotechnol. 19 (2001) 1134–1140.
[76] B.A. Reynolds, W. Tetzlaff, S. Weiss, A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes, J. Neurosci. 12 (1992) 4565–4574.
[77] B.A. Reynolds, S. Weiss, Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system, Science 255 (1992) 1707–1710.
[78] N. Rosenthal, Prometheus's vulture and the stem-cell promise, N. Engl. J. Med. 349 (2003) 267–274.
[79] J. Rossant, Stem cells from the mammalian blastocyst, Stem Cells 19 (2001) 477–482.
[80] N.S. Roy, S. Wang, L. Jiang, J. Kang, A. Benraiss, C. Harrison-Restelli, R.A. Fraser, W.T. Couldwell, A. Kawaguchi, H. Okano, M. Nedergaard, S.A. Goldman, In vitro neurogenesis by progenitor cells isolated from the adult human hippocampus, Nat. Med. 6 (2000) 271–277.
[81] F.J. Rubio, C. Bueno, A. Villa, B. Navarro, A. Martinez-Serrano, Genetically perpetuated human neural stem cells engraft and differentiate into the adult mammalian brain, Mol. Cell. Neurosci. 16 (2000) 1–13.
[82] N. Sanai, A.D. Tramontin, A. Quinones-Hinojosa, N.M. Barbaro, N. Gupta, S. Kunwar, M.T. Lawton, M.W. McDermott, A.T. Parsa, J. Manuel-Garcia Verdugo, M.S. Berger, A. Alvarez-Buylla, Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration, Nature 427 (2004) 740–744.
[83] S. Saporta, J.J. Kim, A.E. Willing, E.S. Fu, C.D. Davis, P.R. Sanberg, Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior, J. Hematother. Stem Cell Res. 12 (2003) 271–278.
[84] R.S. Schmid, E.S. Anton, Role of integrins in the development of the cerebral cortex, Cereb. Cortex 13 (2003) 219–224.
[85] M. Sims, N.L. First, Production of calves by transfer of nuclei from cultured inner cell mass cells, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 6143–6147.
[86] A.G. Smith, J.K. Heath, D.D. Donaldson, G.G. Wong, J. Moreau, M. Stahl, D. Rogers, Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides, Nature 336 (1988) 688–690.
[87] D.L. Stemple, D.J. Anderson, Isolation of a stem cell for neurons and glia from the mammalian neural crest, Cell 71 (1992) 973–985.
[88] L. Studer, Stem cells with brainpower, Nat. Biotechnol. 19 (2001) 1117–1118.
[89] C.N. Svendsen, M.A. Caldwell, J. Shen, M.G. ter Borg, A.E. Rosser, P. Tyers, S. Karmiol, S.B. Dunnett, Long-term survival of human central nervous system progenitor cells transplanted into a rat model of Parkinson's disease, Exp. Neurol. 148 (1997) 135–146.
[90] C.N. Svendsen, M.A. Caldwell, T. Ostenfeld, Human neural stem cells: isolation, expansion and transplantation, Brain Pathol. 9 (1999) 499–513.
[91] Y. Takagi, K. Nozaki, J. Takahashi, J. Yodoi, M. Ishikawa, N. Hashimoto, Proliferation of neuronal precursor cells in the dentate gyrus is accelerated after transient forebrain ischemia in mice, Brain Res. 831 (1999) 283–287.
[92] P. Taupin, F.H. Gage, Adult neurogenesis and neural stem cells of the central nervous system in mammals, J. Neurosci. Res. 69 (2002) 745–749.
[93] S. Temple, Division and differentiation of isolated CNS blast cells in microculture, Nature 340 (1989) 471–473.
[94] S. Temple, The development of neural stem cells, Nature 414 (2001) 112–117.
[95] Y.D. Teng, E.B. Lavik, X. Qu, K.I. Park, J. Ourednik, D. Zurakowski, R. Langer, E.Y. Snyder, Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 3024–3029.
[96] P.B. Tran, R.J. Miller, Chemokine receptors: signposts to brain development and disease, Nat. Rev., Neurosci. 4 (2003) 444–455.
[97] C. Trebst, S.M. Staugaitis, B. Tucky, T. Wei, K. Suzuki, K.D. Aldape, C.A. Pardo, J. Troncoso, H. Lassmann, R.M. Ransohoff, Chemokine receptors on infiltrating leucocytes in inflammatory pathologies of the central nervous system (CNS), Neuropathol. Appl. Neurobiol. 29 (2003) 584–595.
[98] A.L. Vescovi, E.Y. Snyder, Establishment and properties of neural stem cell clones: plasticity in vitro and in vivo, Brain Pathol. 9 (1999) 569–598.
[99] A.L. Vescovi, A. Gritti, R. Galli, E.A. Parati, Isolation and intracerebral grafting of nontransformed multipotential embryonic human CNS stem cells, J. Neurotrauma 16 (1999) 689–693.
[100] A.L. Vescovi, E.A. Parati, A. Gritti, P. Poulin, M. Ferrario, E. Wanke, P. Frolichsthal-Schoeller, L. Cova, M. Arcellana-Panlilio, A. Colombo, R. Galli, Isolation and cloning of multipotential stem cells from the embryonic human CNS and establishment of transplantable human neural stem cell lines by epigenetic stimulation, Exp. Neurol. 156 (1999) 71–83.
[101] K.E. Vrana, J.D. Hipp, A.M. Goss, B.A. McCool, D.R. Riddle, S.J. Walker, P.J. Wettstein, L.P. Studer, V. Tabar, K. Cunniff, K. Chapman, L. Vilner, M.D. West, K.A. Grant, J.B. Cibelli, Nonhuman primate parthenogenetic stem cells, Proc. Natl. Acad. Sci. U. S. A. 100 (Suppl. 1) (2003) 11911–11916.
[102] A.J. Wagers, R.I. Sherwood, J.L. Christensen, I.L. Weissman, Little evidence for developmental plasticity of adult hematopoietic stem cells, Science 297 (2002) 2256–2259.
[103] T. Wakayama, I. Rodriguez, A.C. Perry, R. Yanagimachi, P. Mombaerts, Mice cloned from embryonic stem cells, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 14984–14989.
[104] S. Wakitani, K. Takaoka, T. Hattori, N. Miyazawa, T. Iwanaga, S. Takeda, T.K. Watanabe, A. Tanigami, Embryonic stem cells injected into the mouse knee joint form teratomas and subsequently destroy the joint, Rheumatology (Oxford) 42 (2003) 162–165.
[105] G. Wei, G. Schubiger, F. Harder, A.M. Muller, Stem cell plasticity in mammals and transdetermination in Drosophila: common themes? Stem Cells 18 (2000) 409–414.
[106] J.M. Weimann, C.A. Charlton, T.R. Brazelton, R.C. Hackman, H.M. Blau, Contribution of transplanted bone marrow cells to Purkinje neurons in human adult brains, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 2088–2093.
[107] S. Weiss, C. Dunne, J. Hewson, C. Wohl, M. Wheatley, A.C.

Peterson, B.A. Reynolds, Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis, J. Neurosci. 16 (1996) 7599–7609.
[108] S. Wu, Y. Suzuki, T. Noda, H. Bai, M. Kitada, K. Kataoka, Y. Nishimura, C. Ide, Immunohistochemical and electron microscopic study of invasion and differentiation in spinal cord lesion of neural stem cells grafted through cerebrospinal fluid in rat, J. Neurosci. Res. 69 (2002) 940–945.
[109] J. Yanai, T. Doetchman, N. Laufer, J. Maslaton, S. Mor-Yosef, A. Safran, M. Shani, D. Sofer, Embryonic cultures but not embryos transplanted to the mouse's brain grow rapidly without immunosuppression, Int. J. Neurosci. 81 (1995) 21–26.
[110] M. Yang, N.D. Stull, M.A. Berk, E.Y. Snyder, L. Iacovitti, Neural stem cells spontaneously express dopaminergic traits after transplantation into the intact or 6-hydroxydopamine-lesioned rat, Exp. Neurol. 177 (2002) 50–60.
[111] R.H. Zetterstrom, L. Solomin, L. Jansson, B.J. Hoffer, L. Olson, T. Perlmann, Dopamine neuron agenesis in Nurr1-deficient mice, Science 276 (1997) 248–250.
[112] S.C. Zhang, M. Wernig, I.D. Duncan, O. Brustle, J.A. Thomson, In vitro differentiation of transplantable neural precursors from human embryonic stem cells, Nat. Biotechnol. 19 (2001) 1129–1133.
[113] Z.G. Zhang, L. Zhang, Q. Jiang, M. Chopp, Bone marrow-derived endothelial progenitor cells participate in cerebral neovascularization after focal cerebral ischemia in the adult mouse, Circ. Res. 90 (2002) 284–288.