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Regulation of neural stem cell in the human SVZ by trophic and morphogenic factors

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Abstract

The subventricular zone (SVZ), lining the lateral ventricular system, is the largest germinal region in mammals. In there, neural stem cells express markers related to astogial lineage that give rise to new neurons and oligodendrocytes *in vivo*. In the adult human brain, *in vitro* evidence has also shown that astrocytic cells isolated from the SVZ can generate new neurons and oligodendrocytes. These proliferative cells are strongly controlled by a number of signals and molecules that modulate, activate or repress the cell division, renewal, proliferation and fate of neural stem cells. In this review, we summarize the cellular composition of the adult human SVZ (hSVZ) and discuss the increasing evidence showing that some trophic modulators strongly control the function of neural stem cells in the SVZ.

Keywords

Subventricular zone; neural stem cell; human; neurodegenerative; astrocyte

Introduction

In the 20th century, new neurons generation was first suggested in the sixties when [3H]-thymidine-labeled neurons were described along of the ventricular walls [1]. Then, ongoing neurogenesis was demonstrated in many vertebrates including song-birds [2] lizards [3], rodents [4], rabbits [5], dogs [6], piglets [7] monkeys [8] and humans [9–11]. In the adult brain, there are two germinal regions: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone (SGZ) in the dentate gyrus of hippocampus [12]. In these regions, there exists a population of multipotent cells, known as neural stem cells (NSCs), that self renew and give rise to neurons and oligodendrocytes *in vivo* [13]

The SVZ is the largest germinal region and source of NSCs in the adult brain. In rodents and non-human primates, it has been demonstrated that NSCs in the SVZ generate new neurons

that migrate to the olfactory bulb where they become into functional interneurons [14, 15]. An equivalent migrating route in humans have been suggested [16], but this evidence is still controversial [17]. The organization of these germinal regions and the pattern of division and migration of neural stem cells are still not well-known, raising questions about the mechanism that controls adult neurogenesis.

Understanding molecular mechanisms that control self-renewal, growth, proliferation and migration of adult NSCs is the first step to eventually design cell-based therapies to the repair of brain damage. Here, we summarize the cellular composition of the human SVZ (hSVZ) and some of the molecular signals involved in the control of NSCs.

Neural stem cells

Adult NSCs are precursor cells within the central nervous system (CNS) that can self-renew and give rise to neurons and glia [18]. In addition, NSCs appear to be able to repair brain tissue [19, 20] and it has been suggested that these characteristics last long-life [21]. The presence of NSCs in the CNS was indirectly shown in non-adherent cell cultures, where they produced cell clusters called neurospheres [22, 23]. To date, it is well-accepted that NSCs remain in specific niches into the brain: the SVZ and the SGZ [24, 25]. In humans, isolated cells from the lateral wall of the ventricles can form neurospheres. However, the precise location of NSCs germinal niches along the lateral ventricles is not well-known [25–28].

NSCs in the SVZ are known as Type-B cells that origin to intermediate transit-amplifying progenitors (Type-C cells) [29]. Type-C cells in turn give rise migrating neuroblasts, named Type-A cells, which differentiate in mature interneurons in the olfactory bulb (Figure 1) [29, 30]. Type B-cells in the SVZ are also an important source of oligodendroglial cells that migrate to the white matter at the corpus callosum and fimbria fornix [31–33]. Type-B cells display ultrastructural and morphological characteristics of astrocytes and have a primary cilium that contacts the cerebrospinal fluid [34]. NSCs share some molecular markers with radial glia cells the NSCs in developing brain, but specific markers for characterizing NSCs remain elusive [35]. Thus, the combination of cell culture features and immunoreactivity is an acceptable approach to identify NSCs [36, 37].

NSCs express glial fibrillary acidic protein (GFAP), the glutamate transporter GLAST [38, 39], vimentin and nestin [40–42]. A transcriptomic analysis established that GFAP-positive NSCs express prominin1 (CD133 in humans) [43, 44]. Recently a GFAP isoform (GFAP-delta) has been proposed as a marker of NSCs, because it stains a subpopulation of SVZ astrocytes in rodents and humans [45–47]. GFAP- delta differs from the GFAP-alpha isoform in the carboxy-terminus tail, resulting in a unique 41-aminoacid sequence [47].

Intracellular and membrane compounds are also useful NSCs biomarkers. The RNA-binding protein musashi 1 has been identified as a marker of asymmetric cell division that stops cell-cycle progression and maintains the “stemness” stage [41, 48]. Transcription factors *Oct4* and *Sox2* are found in NSCs and co-regulate each other [49, 50]. *Oct 4* is implicated in pluripotency and fate determination [50]. This transcription factor was first described in embryonic NSCs [51], but there is evidence in adult human NSCs that challenges these data [49]. *Sox2* expression in NSCs promotes self-renewal and proliferation [49]. Lacto- and globo-series glycolipids, such as SSEA-1 and SSEA-4 in SVZ cells, are helpful to identify a proliferative state, self-renewal and multipotentiality [52, 53]. In summary, identifying NSCs in vivo is a challenge because, to date, there are not specific markers to fully identify them.

Adult subventricular zone in the human brain

A persistent proliferation has been found in the young, adult and senescent hSVZ [54, 55]. Increasing evidence indicates that hSVZ harbors multipotent neural stem cells (Figure 2), as demonstrated in cell culture assays using intraoperative and postmortem brain samples [11, 28, 56, 57]. These NSCs were identified when cultured in enriched and non-enriched media with growth factors [26, 58]. The cell-of-origin of human neurospheres is GFAP-expressing cells, which also have the morphological and ultrastructural characteristics of astrocytes [59]. Thus, a subpopulation of GFAP-expressing astrocytes in the SVZ behaves as putative NSCs in the adult human brain [10].

The anatomical subdivision of lateral ventricular system in humans [60] is shown in Figure 3. The human SVZ, lining the lateral wall of the ventricles, has unique features as compared to other mammals [10, 11, 28]. It possesses four layers, starting from the inside layer of lateral ventricle towards basal structures (Figure 4). The first layer contacts the ventricular cavity and cerebrospinal fluid and comprises a monolayer of ependymal cells. The second layer, also known as hypocellular gap, contains an important amount of GFAP+ and doublecortin+ processes but scarce cell somas. The third layer is replenished by cells with GFAP-expressing astrocytes, organized in a ribbon. The last layer is a stratum of myelinated axons bordering deep subcortical white and gray matter [11]. No rostral migratory stream, as that found in rodents, has been fully demonstrated in the adult brain [10]. Yet, a later study described neuroblasts-like cells that appear to reach the adult olfactory bulb [16, 61]. Interestingly, in the human fetal brain, a rostral extension of the ventricle and chains of migratory neuroblasts have been recently described [62]. Therefore, it still unclear whether the rostral migratory stream persists in the adult brain or it is only a remnant of the fetal ventricle.

Cell signals that control adult NSCs

NSCs in the SVZ are responsive to a number of molecules of their microenvironment, such as: cytokines [63], growth factors [64, 65], neurotransmitters [35], hormones [66–68] drugs and other molecules [69, 70]. All these chemical signals can modify the proliferation, migration, survival and differentiation of NSCs. Polypeptide growth factors (GFs) regulate some of the properties of NSCs via tyrosine kinase (RTK) or cytokine receptors [35, 63, 71] (Table 1). These factors include: epidermal growth factor (EGF), basic fibroblast growth factor (bFGF or FGF-2), platelet-derived growth factor (PDGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and nerve growth factor (NGF). In general, GFs affect cell generation and differentiation processes in NSCs [64, 72–76]. IL-6 and TGF- β 1 cause a negative effect on NSCs from SVZ, producing a decrease on proliferation and differentiation of multipotential cells [76]. BDNF has been implicated in NSCs' survival and differentiation [77]. bFGF induces proliferation of SVZ cells when administered *in vivo* and the SVZ cells after bFGF stimulation have multipotent properties [78, 79].

Type-B SVZ cells highly express receptors for PDGF and bFGF, while Type-C cells predominantly express EGFR [65, 80]. Excessive stimulation with PDGF-AA induces NSCs expansion in the hallmarks of glioma [73]. Signaling through the EGF receptor promotes the expansion of Type-C cells [65], which behave as multipotent NSCs, evidencing they are not fully committed cells [81]. EGF reduces the pool of neuronal precursors and increases oligodendrogenesis *in vitro* and *in vivo* [64, 82]. VEGF is a mitogen that affects cell fate and migration of NSCs in the SVZ [83]. VEGF inhibits caspase-3 activity in SVZ [84] and promotes the growth and migratory capacity of NSCs [85]. NGF not only controls growth, differentiation and survival of NSCs in the SVZ, but also downregulates pro-inflammatory signals that, in turn, induce NSCs survival, clonal expansion and proliferation [29, 86]

Ciliary neurotrophic factor (CNTF) [87], leukemia inhibitory factor (LIF), interleukin-4 (IL-4), IL-6 and B cell stimulating factor 3 (BSF3) belong to a family of structurally related cytokines that signal through gp130. This transmembrane glycoprotein interacts with the JAK-STAT pathway to convey survival signals into the nucleus and promote multipotentiality of NSCs [12, 63, 88]. These cytokines have shown synergistic effects on differentiation of NSCs [89]. CNTF induces proliferation of SVZ cells by prolonging the S-phase [87]. CNTF also promotes differentiation of Type-C cells into astrocyte lineage [88]. LIF promotes asymmetrical divisions of NSCs by phosphorylating Stat-3; in consequence, it increases the number of undifferentiated neural progenitors [90, 91]

Several morphogens found in developing brain and related to self-renewal capacity of NSCs have also an effect on adult NSCs. bone morphogenetic proteins (BMP) 2 and 4 [88, 92], Noggin, ephrins, Wnt, Sonic hedgehog (Shh), Notch and others [24, 93] play an important role in the control of NSCs [25]. BMPs induce astrocyte differentiation *in vitro* [88] and, when antagonized by Noggin, promote neurogenesis [94]. A high and sustained stimulation with ephrins increases cell proliferation and diminishes migratory capacity of SVZ-derived neuroblasts [95]. In embryonic brain, Wnt promotes in NSCs a neuronal fate, whereas in the adult brain expands the population of Type-B and Type-C cells and induces differentiation into a glial lineage [96, 97]. Shh increases the number and self-renewal of SVZ NSCs. [98, 99] Shh also promotes differentiation towards neuronal lineage and functions as chemoattractant of migrating neuroblasts along RMS [98, 100]. Interestingly, an increase in Shh signaling induces oligodendrogenesis [99]

Notch has effect on NSCs' identity and self-renewal [101]. Notch strongly promotes gliogenesis and, in close collaboration with interleukin-6 mediators [101], reduces the pool of precursors committed into the neuronal fate [102]. Transcriptional regulators also play a role after a signal is given. Emx2 increases the population of the transit-amplifying cells (Type-C) [103]. Antisense suppression of Pten expression induces apoptosis in SVZ precursor cells [104]. FoxO3 linked closely to oxygen metabolism preserves NSC pool by impeding premature differentiation [105].

In conclusion, the regulation of NSCs in the adult SVZ depends on a strong balance in the levels of several morphogenic molecules [76]. Dysregulation on these signaling factors affects the tissue homeostasis into the brain, which may lead to neurological disorders. Therefore, further research is necessary to fully establish the interactions of these compounds and their effects on the regulation of NSCs.

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References

1. Altman J, Das GD. Autoradiographic and histological studies of postnatal neurogenesis. I. A longitudinal investigation of the kinetics, migration and transformation of cells incorporating tritiated thymidine in neonate rats, with special reference to postnatal neurogenesis in some brain regions. *J Comp Neurol*. 1966; 126:337–389.
2. Goldman SA, Nedergaard M. Newly generated neurons of the adult songbird brain become functionally active in long-term culture. *Brain Res Dev Brain Res*. 1992; 68:217–223.
3. Perez-Canellas MM, Garcia-Verdugo JM. Adult neurogenesis in the telencephalon of a lizard: a [3H]thymidine autoradiographic and bromodeoxyuridine immunocytochemical study. *Brain Res Dev Brain Res*. 1996; 93:49–61.

4. Alvarez-Buylla A, Garcia-Verdugo JM, Tramontin AD. A unified hypothesis on the lineage of neural stem cells. *Nat Rev Neurosci.* 2001; 2:287–293.
5. Ponti G, Aimar P, Bonfanti L. Cellular composition and cytoarchitecture of the rabbit subventricular zone and its extensions in the forebrain. *J Comp Neurol.* 2006; 498:491–507. [PubMed: 16874818]
6. Siwak-Tapp CT, Head E, Muggenburg BA, et al. Neurogenesis decreases with age in the canine hippocampus and correlates with cognitive function. *Neurobiol Learn Mem.* 2007; 88:249–259.
7. Ara J, Fekete S, Zhu A, et al. Characterization of neural stem/progenitor cells expressing VEGF and its receptors in the subventricular zone of newborn piglet brain. *Neurochem Res.* 2010; 35:1455–1470.
8. Gould E, Reeves AJ, Graziano MS, et al. Neurogenesis in the neocortex of adult primates. *Science.* 1999; 286:548–552.
9. Curtis MA, Waldvogel HJ, Synek B, et al. A histochemical and immunohistochemical analysis of the subependymal layer in the normal and Huntington's disease brain. *J Chem Neuroanat.* 2005; 30:55–66.
10. Sanai N, Tramontin AD, Quinones-Hinojosa A, et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature.* 2004; 427:740–744.
11. Quinones-Hinojosa A, Sanai N, Soriano-Navarro M, et al. Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. *J Comp Neurol.* 2006; 494:415–434.
12. Emsley JG, Mitchell BD, Kempermann G, et al. Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. *Prog Neurobiol.* 2005; 75:321–341.
13. Gritti A, Bonfanti L, Doetsch F, et al. Multipotent neural stem cells reside into the rostral extension and olfactory bulb of adult rodents. *J Neurosci.* 2002; 22:437–445.
14. Kelsch W, Lin CW, Mosley CP, et al. A critical period for activity-dependent synaptic development during olfactory bulb adult neurogenesis. *J Neurosci.* 2009; 29:11852–11858.
15. Luskin MB, Boone MS. Rate and pattern of migration of lineally-related olfactory bulb interneurons generated postnatally in the subventricular zone of the rat. *Chem Senses.* 1994; 19:695–714.
16. Curtis MA, Kam M, Nannmark U, et al. Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. *Science.* 2007; 315:1243–1249.
17. Sanai N, Berger MS, Garcia-Verdugo JM, et al. Comment on "Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension". *Science.* 2007; 318:393. author reply 393.
18. Ihrie RA, Alvarez-Buylla A. Cells in the astroglial lineage are neural stem cells. *Cell Tissue Res.* 2008; 331:179–191.
19. Marti-Fabregas J, Romaguera-Ros M, Gomez-Pinedo U, et al. Proliferation in the human ipsilateral subventricular zone after ischemic stroke. *Neurology.* 2010; 74:357–365.
20. Picard-Riera N, Nait-Oumesmar B, Baron-Van Evercooren A. Endogenous adult neural stem cells: limits and potential to repair the injured central nervous system. *J Neurosci Res.* 2004; 76:223–231.
21. Alvarez-Buylla A, Herrera DG, Wichterle H. The subventricular zone: source of neuronal precursors for brain repair. *Prog Brain Res.* 2000; 127:1–11.
22. Reynolds BA, Rietze RL. Neural stem cells and neurospheres--re-evaluating the relationship. *Nat Methods.* 2005; 2:333–336.
23. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science.* 1992; 255:1707–1710.
24. Miller FD, Gauthier-Fisher A. Home at last: neural stem cell niches defined. *Cell Stem Cell.* 2009; 4:507–510.
25. Taupin P. Adult neural stem cells, neurogenic niches, and cellular therapy. *Stem Cell Rev.* 2006; 2:213–219.
26. Ferrari D, Binda E, De Filippis L, et al. Isolation of neural stem cells from neural tissues using the neurosphere technique. *Curr Protoc Stem Cell Biol Chapter.* 2010; 2(Unit2D):6.

27. Chaichana KL, Capilla-Gonzalez V, Gonzalez-Perez O, et al. Preservation of glial cytoarchitecture from ex vivo human tumor and non-tumor cerebral cortical explants: A human model to study neurological diseases. *J Neurosci Methods*. 2007; 164:261–270.
28. Quinones-Hinojosa A, Sanai N, Gonzalez-Perez O, et al. The human brain subventricular zone: stem cells in this niche and its organization. *Neurosurg Clin N Am*. 2007; 18:15–20. vii. [PubMed: 17244550]
29. Imitola J, Snyder EY, Khoury SJ. Genetic programs and responses of neural stem/progenitor cells during demyelination: potential insights into repair mechanisms in multiple sclerosis. *Physiol Genomics*. 2003; 14:171–197.
30. Ahmed S. The culture of neural stem cells. *J Cell Biochem*. 2009; 106:1–6.
31. Levison SW, Druckman SK, Young GM, et al. Neural stem cells in the subventricular zone are a source of astrocytes and oligodendrocytes, but not microglia. *Dev Neurosci*. 2003; 25:184–196.
32. Menn B, Garcia-Verdugo JM, Yaschine C, et al. Origin of oligodendrocytes in the subventricular zone of the adult brain. *J Neurosci*. 2006; 26:7907–7918.
33. Nait-Oumesmar B, Decker L, Lachapelle F, et al. Progenitor cells of the adult mouse subventricular zone proliferate, migrate and differentiate into oligodendrocytes after demyelination. *Eur J Neurosci*. 1990; 11:4357–4366.
34. Mirzadeh Z, Merkle FT, Soriano-Navarro M, et al. Neural stem cells confer unique pinwheel architecture to the ventricular surface in neurogenic regions of the adult brain. *Cell Stem Cell*. 2008; 3:265–278.
35. Abrous DN, Koehl M, Le Moal M. Adult neurogenesis: from precursors to network and physiology. *Physiol Rev*. 2005; 85:523–569.
36. Landgren H, Curtis MA. Locating and labeling neural stem cells in the brain. *J Cell Physiol*. 2011; 226:1–7.
37. Beckervordersandforth R, Tripathi P, Ninkovic J, et al. In vivo fate mapping and expression analysis reveals molecular hallmarks of prospectively isolated adult neural stem cells. *Cell Stem Cell*. 2010; 7:744–758.
38. Ninkovic J, Mori T, Gotz M. Distinct modes of neuron addition in adult mouse neurogenesis. *J Neurosci*. 2007; 27:10906–10911.
39. Garcia AD, Doan NB, Imura T, et al. GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. *Nat Neurosci*. 2004; 7:1233–1241.
40. Bentivoglio M, Mazzarello P. The history of radial glia. *Brain Res Bull*. 1999; 49:305–315.
41. Stojnik T, Rosland GV, Sakariassen PO, et al. Neural stem cell markers, nestin and musashi proteins, in the progression of human glioma: correlation of nestin with prognosis of patient survival. *Surg Neurol*. 2007; 68:133–143. discussion 143–134.
42. Ayuso-Sacido A, Roy NS, Schwartz TH, et al. Long-term expansion of adult human brain subventricular zone precursors. *Neurosurgery*. 2008; 62:223–229. discussion 229–231.
43. Coskun V, Wu H, Blanchi B, et al. CD133+ neural stem cells in the ependyma of mammalian postnatal forebrain. *Proc Natl Acad Sci U S A*. 2008; 105:1026–1031.
44. Huang Q, Dong J, Zhu YD, et al. Isolation and culture of tumor stem cells from human brain glioma tissues. *Zhonghua Zhong Liu Za Zhi*. 2006; 28:331–333.
45. van den Berge SA, Middeldorp J, Zhang CE, et al. Longterm quiescent cells in the aged human subventricular neurogenic system specifically express GFAP-delta. *Aging Cell*. 2010; 9:313–326.
46. Boer K, Middeldorp J, Spliet WG, et al. Immunohistochemical characterization of the out-of frame splice variants GFAP Delta164/Deltaexon 6 in focal lesions associated with chronic epilepsy. *Epilepsy Res*. 2010; 90:99–109.
47. Roelofs RF, Fischer DF, Houtman SH, et al. Adult human subventricular, subgranular, and subpial zones contain astrocytes with a specialized intermediate filament cytoskeleton. *Glia*. 2005; 52:289–300.
48. Macnicol MC, Cragle CE, Macnicol A. Context-dependent regulation of Musashi-mediated mRNA translation and cell cycle regulation. *Cell Cycle*. 2011; 10 In press.
49. Kim JB, Zaehres H, Wu G, et al. Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors. *Nature*. 2008; 454:646–650.

50. Avilion AA, Nicolis SK, Pevny LH, et al. Multipotent cell lineages in early mouse development depend on SOX2 function. *Genes Dev.* 2003; 17:126–140.
51. Nichols J, Zevnik B, Anastassiadis K, et al. Formation of pluripotent stem cells in the mammalian embryo depends on the POU transcription factor Oct4. *Cell.* 1998; 95:379–391.
52. Capela A, Temple S. LeX/ssea-1 is expressed by adult mouse CNS stem cells, identifying them as nonependymal. *Neuron.* 2002; 35:865–875.
53. Yanagisawa M, Yu RK. The expression and functions of glycoconjugates in neural stem cells. *Glycobiology.* 2007; 17:57R–74R.
54. Leonard BW, Mastroeni D, Grover A, et al. Subventricular zone neural progenitors from rapid brain autopsies of elderly subjects with and without neurodegenerative disease. *J Comp Neurol.* 2009; 515:269–294.
55. Weickert CS, Webster MJ, Colvin SM, et al. Localization of epidermal growth factor receptors and putative neuroblasts in human subependymal zone. *J Comp Neurol.* 2000; 423:359–372.
56. Feldmann RE Jr, Mattern R. The human brain and its neural stem cells postmortem: from dead brains to live therapy. *Int J Legal Med.* 2006; 120:201–211.
57. Chaichana KL, Guerrero-Cazares H, Capilla-Gonzalez V, et al. Intra-operatively obtained human tissue: protocols and techniques for the study of neural stem cells. *J Neurosci Methods.* 2009; 180:116–125.
58. Pastrana E, Cheng LC, Doetsch F. Simultaneous prospective purification of adult subventricular zone neural stem cells and their progeny. *Proc Natl Acad Sci U S A.* 2009; 106:6387–6392.
59. Danilov AI, Gomes-Leal W, Ahlenius H, et al. Ultrastructural and antigenic properties of neural stem cells and their progeny in adult rat subventricular zone. *Glia.* 2009; 57:136–152.
60. Rhoton AL Jr. The lateral and third ventricles. *Neurosurgery.* 2002; 51:S207–271.
61. Kam M, Curtis MA, McGlashan SR, et al. The cellular composition and morphological organization of the rostral migratory stream in the adult human brain. *J Chem Neuroanat.* 2009; 37:196–205.
62. Guerrero-Cazares H, Soriano-Navarro M, Zamora-Berridi G, et al. Cytoarchitecture of the lateral ganglionic eminence and rostral extension of the lateral ventricle in the human fetal brain. *J Comp Neurol.* 2011; 519 In press.
63. Gonzalez-Perez O, Jauregui-Huerta F, Galvez-Contreras AY. Immune system modulates the function of adult neural stem cells. *Curr Immunol Rev.* 2010; 6:167–173.
64. Gonzalez-Perez O, Romero-Rodriguez R, Soriano-Navarro M, et al. Epidermal growth factor induces the progeny of subventricular zone type B cells to migrate and differentiate into oligodendrocytes. *Stem Cells.* 2009; 27:2032–2043.
65. Jackson EL, Garcia-Verdugo JM, Gil-Perotin S, et al. PDGFR alpha-positive B cells are neural stem cells in the adult SVZ that form glioma-like growths in response to increased PDGF signaling. *Neuron.* 2006; 51:187–199.
66. Brannvall K, Bogdanovic N, Korhonen L, et al. 19-Nortestosterone influences neural stem cell proliferation and neurogenesis in the rat brain. *Eur J Neurosci.* 2005; 21:871–878.
67. Brannvall K, Korhonen L, Lindholm D. Estrogen-receptor-dependent regulation of neural stem cell proliferation and differentiation. *Mol Cell Neurosci.* 2002; 21:512–520.
68. Yu S, Patchev AV, Wu Y, Lu J, et al. Depletion of the neural precursor cell pool by glucocorticoids. *Ann Neurol.* 2010; 67:21–30.
69. Tomycz ND, Friedlander RM. Novel neurogenesis drugs uncovered from in vivo chemical library screen. *Neurosurgery.* 2010; 67:N16–18.
70. Taupin P. Neurogenic drugs and compounds. *Recent Pat CNS Drug Discov.* 2010; 5:253–257.
71. Li E, Hristova K. Role of receptor tyrosine kinase transmembrane domains in cell signaling and human pathologies. *Biochemistry.* 2006; 45:6241–6251.
72. Bath KG, Lee FS. Neurotrophic factor control of adult SVZ neurogenesis. *Dev Neurobiol.* 2010; 70:339–349.
73. Jackson EL, Alvarez-Buylla A. Characterization of adult neural stem cells and their relation to brain tumors. *Cells Tissues Organs.* 2008; 188:212–224.

74. Lu H, Li M, Song T, et al. Retrovirus delivered neurotrophin-3 promotes survival, proliferation and neuronal differentiation of human fetal neural stem cells in vitro. *Brain Res Bull.* 2008; 77:158–164.
75. Mudo G, Bonomo A, Di Liberto V, et al. The FGF-2/FGFRs neurotrophic system promotes neurogenesis in the adult brain. *J Neural Transm.* 2009; 116:995–1005.
76. Werry EL, Enjeti S, Halliday GM, et al. Effect of age on proliferation-regulating factors in human adult neurogenic regions. *J Neurochem.* 2010; 115:956–964.
77. Galvao RP, Garcia-Verdugo JM, Alvarez-Buylla A. Brain-derived neurotrophic factor signaling does not stimulate subventricular zone neurogenesis in adult mice and rats. *J Neurosci.* 2008; 28:13368–13383.
78. Liard O, Segura S, Pascual A, et al. In vitro isolation of neural precursor cells from the adult pig subventricular zone. *J Neurosci Methods.* 2009; 182:172–179.
79. Sun D, Bullock MR, McGinn MJ, et al. Basic fibroblast growth factor-enhanced neurogenesis contributes to cognitive recovery in rats following traumatic brain injury. *Exp Neurol.* 2009; 216:56–65.
80. Ishii Y, Matsumoto Y, Watanabe R, et al. Characterization of neuroprogenitor cells expressing the PDGF beta-receptor within the subventricular zone of postnatal mice. *Mol Cell Neurosci.* 2008; 37:507–518.
81. Nait-Oumesmar B, Picard-Riera N, Kerninon C, et al. The role of SVZ-derived neural precursors in demyelinating diseases: from animal models to multiple sclerosis. *J Neurol Sci.* 2008; 265:26–31.
82. Gonzalez-Perez O, Quinones-Hinojosa A. Dose-dependent effect of EGF on migration and differentiation of adult subventricular zone astrocytes. *Glia.* 2010; 58:975–983.
83. Namiecinska M, Marciniak K, Nowak JZ. VEGF as an angiogenic, neurotrophic, and neuroprotective factor. *Postepy Hig Med Dosw (Online).* 2005; 59:573–583.
84. Jin K, Zhu Y, Sun Y, et al. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proc Natl Acad Sci U S A.* 2002; 99:11946–11950.
85. Mani N, Khaibullina A, Krum JM, et al. Vascular endothelial growth factor enhances migration of astroglial cells in subventricular zone neurosphere cultures. *J Neurosci Res.* 2010; 88:248–257.
86. Triaca V, Tirassa P, Aloe L. Presence of nerve growth factor and TrkA expression in the SVZ of EAE rats: evidence for a possible functional significance. *Exp Neurol.* 2005; 191:53–64.
87. Emsley JG, Hagg T. Endogenous and exogenous ciliary neurotrophic factor enhances forebrain neurogenesis in adult mice. *Exp Neurol.* 2003; 183:298–310.
88. Bauer S, Kerr BJ, Patterson PH. The neuropoietic cytokine family in development, plasticity, disease and injury. *Nat Rev Neurosci.* 2007; 8:221–232.
89. Nakashima K. Mechanism of neural stem cell fate specification. *Tanpakushitsu Kakusan Koso.* 2004; 49:718–726.
90. Bauer S. Cytokine control of adult neural stem cells. *Ann N Y Acad Sci.* 2009; 1153:48–56.
91. Bonaguidi MA, McGuire T, Hu M, et al. LIF and BMP signaling generate separate and discrete types of GFAP-expressing cells. *Development.* 2005; 132:5503–5514.
92. Cate HS, Sabo JK, Merlo D, et al. Modulation of bone morphogenic protein signalling alters numbers of astrocytes and oligodendroglia in the subventricular zone during cuprizone-induced demyelination. *J Neurochem.* 2010; 115:11–22.
93. Lim DA, Huang YC, Alvarez-Buylla A. The adult neural stem cell niche: lessons for future neural cell replacement strategies. *Neurosurg Clin N Am.* 2007; 18:81–92. ix.
94. Ueki T, Tanaka M, Yamashita K, et al. A novel secretory factor, Neurogenesisin-1, provides neurogenic environmental cues for neural stem cells in the adult hippocampus. *J Neurosci.* 2003; 23:11732–11740.
95. Conover JC, Doetsch F, Garcia-Verdugo JM, et al. Disruption of Eph/ephrin signaling affects migration and proliferation in the adult subventricular zone. *Nat Neurosci.* 2000; 3:1091–1097. [PubMed: 11036265]
96. Adachi K, Mirzadeh Z, Sakaguchi M, et al. Beta-catenin signaling promotes proliferation of progenitor cells in the adult mouse subventricular zone. *Stem Cells.* 2007; 25:2827–2836.

97. Piccin D, Morshead CM. Wnt Signaling Regulates Symmetry of Division of Neural Stem Cells in the Adult Brain and in Response to Injury. *Stem Cells*. 2010 In press.
98. Lai K, Kaspar BK, Gage FH, et al. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nat Neurosci*. 2003; 6:21–27.
99. Ahn S, Joyner AL. In vivo analysis of quiescent adult neural stem cells responding to Sonic hedgehog. *Nature*. 2005; 437:894–897.
100. Hor CH, Tang BL. Sonic hedgehog as a chemoattractant for adult NPCs. *Cell Adh Migr*. 2010; 4:1–3.
101. Aguirre A, Rubio ME, Gallo V. Notch and EGFR pathway interaction regulates neural stem cell number and self-renewal. *Nature*. 2010; 467:323–327.
102. Watts C, McConkey H, Anderson L, et al. Anatomical perspectives on adult neural stem cells. *J Anat*. 2005; 207:197–208.
103. Gangemi RM, Daga A, Muzio L, et al. Effects of Emx2 inactivation on the gene expression profile of neural precursors. *Eur J Neurosci*. 2006; 23:325–334.
104. Li L, Liu F, Ross AH. PTEN regulation of neural development and CNS stem cells. *J Cell Biochem*. 2003; 88:24–28.
105. Renault VM, Rafalski VA, Morgan AA, et al. FoxO3 regulates neural stem cell homeostasis. *Cell Stem Cell*. 2009; 5:527–539.
106. Craig CG, Tropepe V, Morshead CM, et al. In vivo growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain. *J Neurosci*. 1996; 16:2649–2658.
107. Baron W, Metz B, Bansal R, et al. PDGF and FGF-2 signaling in oligodendrocyte progenitor cells: regulation of proliferation and differentiation by multiple intracellular signaling pathways. *Mol Cell Neurosci*. 2000; 15:314–329.
108. Lachapelle F, Avellana-Adalid V, Nait-Oumesmar B, et al. Fibroblast growth factor-2 (FGF-2) and platelet-derived growth factor AB (PDGF AB) promote adult SVZ-derived oligodendrogenesis in vivo. *Mol Cell Neurosci*. 2002; 20:390–403.
109. Ben-Hur T. Immunomodulation by neural stem cells. *J Neurol Sci*. 2008; 265:102–104.
110. Liu SY, Zhang ZY, Song YC, et al. SVZa neural stem cells differentiate into distinct lineages in response to BMP4. *Exp Neurol*. 2004; 190:109–121.
111. Hirabayashi Y, Gotoh Y. Epigenetic control of neural precursor cell fate during development. *Nat Rev Neurosci*. 2010; 11:377–388.
112. Russo I, Barlati S, Bosetti F. Effects of Neuroinflammation on the Regenerative Capacity of Brain Stem Cells. *J Neurochem*. 2010 In press.
113. Skold MK, Kanje M. Vascular endothelial growth factor in central nervous system injuries - a vascular growth factor getting nervous? *Curr Neurovasc Res*. 2008; 5:246–259.
114. Rossi F, Cattaneo E. Opinion: neural stem cell therapy for neurological diseases: dreams and reality. *Nat Rev Neurosci*. 2002; 3:401–409.

Figure 1.

Schematic drawing of aNSCs. Multipotent NSCs (Type-B cells) originate Type-C cells, also called transit-amplifying precursors. *In vitro* and *in vivo* evidence indicates that SVZ NSCs give rise to oligodendrocytes, astrocytes, neurons. Red short arrows represent the self-renewal capacity of the cell.

Figure 2.

NSCs reside in the SVZ along the walls of lateral ventricles. The SVZ contains multipotent Type-B cells that originate Type-C cells, which give rise to migrating neuroblasts (Type-A cells). In several species, new neurons derived from the SVZ migrate to the olfactory bulb via the rostral migratory stream. Nevertheless, in the adult human brain such migratory route has not been confirmed, yet.

Figure 3.

Schematic representation of the lateral ventricular system in adult human brain. Coronal sections represent the division of regions suggested by Rotho [60]: the anterior horn (red), the body of the ventricle (yellow), the occipital horn (green) and the temporal horn (blue). Each region has been subdivided in dorsal, intermediate and ventral parts.

Figure 4.

Schematic drawing of the cytoarchitecture of the human SVZ. The human SVZ displays unique characteristics in the layer II and layer III. In the hypocellular gap (Layer II), there are some doublecortin-positive filaments and several clusters of 3 or 4 displaced ependymal cells. Layer III shows an organization in ribbon formed by stellate GFAP+ cells.

Table 1

Chemical mediators of neural stem cells in the SVZ

Modulator	Predominant effect	Cell fate	Reference
Growth factors			
bFGF	Represses differentiation, increases number of proliferative divisions	oligodendr ocyte	[78, 79, 107, 114]
BDNF	Induces proliferation of NSCs and migration of new born neurons	neurons	
EGF	Increases NSCs proliferation, decreases cell migration to OB	astrocytes , oligodendr ocytes	[64, 101, 106]
NGF	NSCs survival, clonal expansion and proliferation	oligodendr octe	[29, 86]
PDGF	Stimulates NSCs division and proliferation	astrocytes , oligodendr ocyte	[107, 108]
VEGF	NSCs survival, proliferation and differentiation	neuron	[7, 113]
Trophic factors/cytokines			
CTNF	Clonal expansion of Type-C cells, self-renewal and differentiation of NSCs	astrocytes	[63, 87]
IL-4	NSCs differentiation	neurons and oligodendr ocytes	[112]
IL-6	Promotes NSCs proliferation and commitment	astroglial	[63, 109]
LIF	Self renewal and proliferation of NSCs		[88, 90]
Morphogens			
BMPs	Exit of cell cycle and cell differentiation. Inhibition of neuronal genesis	astrocyte	[110]
Ephrin	Induces NSCs differentiation	neuron	[95]
Noggin	Antagonist of BMPs, inhibits differentiation to glial lineage	neuron	
Notch	Induces NSCs self-renewal and differentiation, reduces NSC proliferation	astroglia	[101, 102, 111]
Shh	Promotes NSC self-renewal, and expands B and C cell population. Chemoattractant of migrating neuroblasts	neuron, oligodendr ocytes	[98–100]
Wnt	Self renewal and proliferation of B cells	neuron	[96]
Other signals			
Emx2	Clonal expansion of Type-C cells		[103]
Pten	Maintains B and C cell population, promotes migration of neuroblasts to OB		[104]
FOXO3	NSCs survival and self-renewal, preventing differentiation		[105]