HHS Public Access

Author manuscript

Exp Gerontol. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Exp Gerontol. 2017 August ; 94: 9–13. doi:10.1016/j.exger.2016.11.007.

Development and Aging of a Brain Neural Stem Cell Niche

Joanne C Conover[*] and **Krysti L. Todd**

Department of Physiology and Neurobiology Institute for Brain and Cognitive Sciences Center for Aging University of Connecticut Storrs, CT 06269

Abstract

In the anterior forebrain, along the lateral wall of the lateral ventricles, a neurogenic stem cell niche is found in a region referred to as the ventricular-subventricular zone (V-SVZ). In rodents, robust V-SVZ neurogenesis provides new neurons to the olfactory bulb throughout adulthood; however, with increasing age stem cell numbers are reduced and neurogenic capacity is significantly diminished, but new olfactory bulb neurons continue to be produced even in old age. Humans, in contrast, show little to no new neurogenesis after two years of age and whether V-SVZ neural stem cells persist in the adult human brain remains unclear. Here, we review functional and organizational differences in the V-SVZ stem cell niche of mice and humans, and examine how aging affects the V-SVZ niche and its associated functions.

DEVELOPMENT OF THE V-SVZ STEM CELL NICHE: MOUSE AND HUMAN

Mouse

During brain development highly proliferative neuroepithelial progenitor cells line the fluid-filled neural tube that defines the growing nervous system. This proliferative zone, or ventricular zone (VZ), expands through symmetric division to generate a rudimentary forebrain, midbrain and hindbrain and associated three-vesicle ventricular system. From the three-vesicle stage, brain development then progresses to a five-vesicle stage defined by the lateral ventricles and associated forebrain structures, the telencephalon and diencephalon; the third ventricle of the mesencephalon; the cerebral aqueduct and fourth ventricle adjacent to the metencephalon (cerebellum) and myelencephalon (medulla and pons); and the central canal of the spinal cord. Symmetric division by the neuroepithelial cells increases both the cell number and thereby the size of the VZ proliferative zone. Basal contact of the neuroepithelial cells to the meninges introduces retinoic acid signaling (Siegenthaler et al., 2009; Siegenthaler and Pleasure 2011), and this is thought to be responsible for neuroepithelial cells transitioning from symmetric to asymmetric division and the initiation of neurogenesis (Malatesta et al., 2000; Miyata et al., 2001; Noctor et al., 2001; Noctor et al., 2004). With the onset of robust neurogenesis in the VZ, the neuroepithelial cells become elongated, maintaining an apical process at the ventricle surface and contact with the

[*]Corresponding author. joanne.conover@uconn.edu.

circulating cerebrospinal fluid (CSF) and stretching a long basal, radial process to the pial surface for contact with superficial boundary blood vessels (Noctor et al., 2001; Noctor et al., 2004). Neuroepithelial cells with a long radial process are classified as radial glia and are responsible for the bulk of neurogenesis in the embryonic brain (Rakic 2006). If we focus specifically on the anterior forebrain and cortical development, the asymmetric division of radial glia provides the resulting daughter cells with a long radial process that functions as a scaffold for migration into the developing cortical plate. Migration of newly generated intermediate precursor cells and neuroblasts into the cortical plate initiates cortical layer development in an 'inside first – outside last' fashion, with the inside (or deep) layer being generated first and then the outside (or superficial) layer being generated last (Kriegstein and Alvarez-Buylla 2009; Kriegstein and Noctor 2004; Malatesta et al., 2003; Malatesta et al., 2000). Later in embryonic and early postnatal development, radial glia, now also referred to as neural stem/progenitor cells (NSPCs), generate astrocytes and oligodendrocytes that populate neighboring brain structures through both radial and tangential migration. Radial glia/NSPCs also generate ciliated epithelial cells, ependymal cells, that line the ventricle, displacing the soma of the NSPCs to the subependymal layer of the ventricle (SVZ) so that only a thin NSPC process is retained at the ventricle surface. Each NSPC process possesses a single primary cilium that projects into the ventricle and senses the ventricle environment via receptors along the cilium length and at its interface with the cell membrane (Mirzadeh et al., 2008). Ependymal cells do not fully differentiate until late in postnatal development in rodents or during the third trimester in humans, when they possess multiple motile cilia and significant adherens junctional proteins at their apical surface (Del Bigio 1995; Del Bigio 2010; Spassky et al., 2005). Fully differentiated ependymal cells function as both a barrier and transport system for exchange between the interstitial fluid of the CSF in the adult brain. Following early postnatal development only the lateral wall of the lateral ventricles retains an associated neurogenic stem cell niche (V-SVZ), neither the medial walls of the lateral ventricles, the third ventricle, nor the fourth ventricle support robust neurogenesis in the adult mouse. In summary, the mouse V-SVZ stem cell niche develops from the highly proliferative neuroepithelium that lines the ventricular system of the brain to a much restricted stem cell niche found only along the lateral wall of the lateral ventricles. This neurogenic capacity, primarily supporting the genesis of new neurons destined for the olfactory bulb, persists into adulthood, but is significantly diminished in old age (see **MOUSE V-SVZ NICHE IN AGING**).

Human

Development of the human V-SVZ is less well characterized, but proceeds along a similar sequence to that found in rodents. However, the main distinction is the gyrencephalic cerebral cortex found in humans which suggests a need for increased proliferative capacity. This appears to be achieved by an expansion of the V-SVZ proliferative zone to include a unique, massively expanded outer SVZ (oSVZ) region superior to the SVZ. The oSVZ contains radial glia-like cells that may retain both an apical process that contacts the CSF of the ventricle and a basal process that extends into the developing cortical plate (Hansen et al., 2010). Research suggests that both proliferative and self-renewing asymmetric divisions occur within the oSVZ and contribute to the extensive cortical expansion that marks the gyrencephalic brain (Hansen et al., 2010). While neurogenic capacity is maintained in

adulthood in the mouse V-SVZ stem cell niche, production of new neurons by the human V-SVZ is greatly diminished by 2 years of age in humans and little to no neurogenesis is seen beyond childhood (Sanai et al., 2011; Wang et al., 2011a). Below, we will compare and contrast the mouse and human V-SVZ and the discuss the potential consequences of these differences.

THE V-SVZ STEM CELL NICHE CYTOARCHITECTURE PROMOTES CONTROLLED PROLIFERATION AND MIGRATION: MOUSE AND HUMAN

Mouse

The V-SVZ stem cell niche in adult mice is very well characterized (Alvarez-Buylla et al., 2001; Alvarez-Buylla et al., 2008; Alvarez-Buylla and Lim 2004; Doetsch et al., 1999a; Ihrie and Alvarez-Buylla 2011; Kokovay et al., 2010; Kriegstein and Alvarez-Buylla 2009; Lledo and Saghatelyan 2005; Luskin 1993). The apical aspect of the stem cell niche is defined by a monolayer of ependymal cells that line the lateral ventricle. NSPCs punctuate the ependymal lining with an apical process – a cluster of several NSPC processes are surrounded by ependymal cells. If viewed as an *en face* wholemount preparation of the lateral wall of the lateral ventricle, ependymal cells and NSPC projections are organized in ‘pinwheels’ with the NSPC projections forming the ‘pin’ of the pinwheel (Mirzadeh et al., 2008). The cell bodies of the NSPCs lie subjacent to the ependymal cell monolayer.

Adult NSPCs are typically quiescent with only approximately 2.5% actively dividing at any particular time in young adult mice (Capela and Temple 2002; Conover and Shook 2011; Shook et al., 2012) and data from clonal analysis studies suggests that activated NSPCs go through several rounds of division before becoming exhausted (Calzolari et al., 2015). Activated NSPCs are thought to divide asymmetrically, allowing self-renewal and the generation of a daughter transit amplifying cell. These transitory cells then go through several divisions before generating new immature neurons, neuroblasts, that are also capable of division (Alvarez-Buylla and Lim 2004; Doetsch et al., 1997; Doetsch et al., 1999b; Mirzadeh et al., 2008; Nam and Benezra 2009; Tavazoie et al., 2008; Temple 2001; Tramontin et al., 2003). Effectively, the transit amplifying cells, functioning as intermediate precursor cells, together with the neuroblasts are responsible for the bulk of the robust proliferation observed within the V-SVZ (Doetsch et al., 1999a; Doetsch et al., 1997; Doetsch et al., 1999b; Luo et al., 2006).

The cytoarchitecture of the adult V-SVZ is defined by NSPCs that span the entire width of the V-SVZ niche and have an apical process in contact with the ventricular CSF and a basal process that contacts blood vessels at the basal boundary. During development, blood vessels invade the newly generated brain tissue and basal processes of radial glia extend to nearby blood vessels. The NSPC contact with the vasculature is important as the extensive network of blood vessels at the basal boundary of the NSPC niche provides cellular scaffolding as well as diffusible cues, establishing an important neurovascular niche that is critical to the regulation of NSPC activation (Kokovay et al., 2010; Mirzadeh et al., 2010; Shen et al., 2008; Tavazoie et al., 2008). In addition, extracellular matrix from the blood vessel basal lamina creates intricate branching (fractones) around cells of the stem cell niche, binding

growth and other regulatory factors (Kerever et al., 2014; Kerever et al., 2007; Mercier et al., 2002; Shen et al., 2008) as a means to control local concentration of growth factors.

Neuroblasts, which are highly migratory, transit the anterior forebrain via the rostral migratory stream to their final destination, the olfactory bulb. Neuroblast migration occurs via contact attraction and contact repulsion mechanisms with the neuroblasts forming dynamic chains of migratory cells. Neuroblast migration is aided by V-SVZ astrocytes that are arranged as a meshwork around the neuroblast chains (Ahlenius et al., 2009; Conover and Shook 2011; Doetsch et al., 1999a; Enwere et al., 2004; Jin et al., 2003; Luo et al., 2006; Luo et al., 2008; Maslov et al., 2004; Shook et al., 2012; Tropepe et al., 1997). Migration through the astrocyte meshwork is aided by the chemorepulsive factor, SLIT, which acts on its ROBO receptors located on V-SVZ astrocytes (Kaneko et al., 2010). Other factors are likely involved to keep the highly migratory neuroblasts to their specific migration pathway.

Human

Organization of the fetal and neonatal human V-SVZ is presently less documented and thereby less understood than the mouse V-SVZ. In general, the human V-SVZ organization is similar to the mouse, but unique differences exist and account for disparities in brain development and the absence of V-SVZ neurogenesis in adulthood. As pointed out above, an additional layer of NSPCs are located in what is known as the outer-SVZ (oSVZ) (Hansen et al., 2010) and these NSPCs are important for the extensive neurogenesis that gives rise to the gyri of the human cortex. Following corticogenesis, the neurogenic stem cell niche along the lateral ventricles remains proliferative in neonates, producing new neurons that populate the prefrontal cortex via the medial migratory stream and to a lesser extent the olfactory bulb (Sanai et al., 2011; Sanai et al., 2004). However, by 2 years of age, human brains show minimal V-SVZ neurogenesis and an acellular zone consisting primarily of astrocyte processes is found directly beneath the ependymal cell lining of the lateral ventricles with the astrocyte cell bodies forming a ‘ribbon’ subjacent to the acellular zone (Sanai et al., 2004). While the organization of the human V-SVZ astrocytes is reminiscent of the astrocyte meshwork observed in rodents, the meshwork in adult humans is devoid of neuroblasts.

V-SVZ NICHE IN AGING: MOUSE AND HUMAN

Mouse

The aging rodent V-SVZ undergoes a number of cytoarchitectural and proliferative changes that are well defined (Figure 1). Stenosis of part of the ventral portion of the lateral ventricles leads to loss of intact ependymal cell coverage and underlying V-SVZ in areas of adhesion, thereby restricting the majority of neurogenesis to the dorsolateral region of the lateral ventricles (Figure 1B) (Luo et al., 2008). While lateral ventricle volume does not change in the aged mouse, areas of stenosis lead to conformational changes in which portions of the dorsal lateral ventricle expand. Areas of the ventricle that show expansion also harbor proliferative cells that have astrocyte-like qualities integrated within the existing ventricle lining. These cells also display multiple characteristics of ependymal cells, including cuboidal shape, adherens junctions and multiple basal bodies indicative of motile

cilia (Luo et al., 2008). Incorporation of these cells into the ventricle lining suggests reparation of the ventricle cell lining at sites of conformational change. This likely helps maintain critical functions such as boundary maintenance and CSF and interstitial fluid transport and exchange.

With increased age, the V-SVZ shows a spatially uniform 50–75% loss of proliferative capacity compared to that of young adult mice (3 months) (Ahlenius et al., 2009; Doetsch et al., 1999a; Enwere et al., 2004; Jin et al., 2003; Luo et al., 2006; Maslov et al., 2004; Tropepe et al., 1997). This decrease likely leads to the 75% loss of neuroblasts that reach the olfactory bulb (Enwere et al., 2004; Tropepe et al., 1997). Specifically, NSPCs along the lateral ventricle show an >80% decline in total numbers per mm^2 of intact ependyma in 2-year-old versus 3-month-old mice. With fewer NSPC processes projecting to the ventricle surface there is an associated loss of pinwheel organizational units (Figure 1B). Loss of NSPCs and associated pinwheels is spatially uniform, with no region of the lateral ventricle wall showing particular resilience or exceptional decline. This is borne out in the reduced numbers of new olfactory bulb neurons, but there is conservation of olfactory bulb interneuron subtype ratios generated in old mice (Shook et al., 2012). This decline is thought to be mediated in part by age-associated microenvironmental changes including decreased expression of growth factors that support proliferation and neurogenesis, such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and insulin-like growth factor-1 (IGF-1) (Jin et al., 2003; Schanzer et al., 2004; Sonntag et al., 2005). DNA damage accumulation with age and related changes to the cell cycle, including increased cell cycle length and senescence, as well as decreased expression of telomerase have also been reported as factors negatively impacting V-SVZ proliferation (Ahlenius et al., 2009; Ferron et al., 2009; Tropepe et al., 1997). Surprisingly, although there is a decrease in the total number of V-SVZ stem cells with aging, the percent of actively dividing stem cells increases with age (Shook et al., 2012), representing a compensatory mechanism to maintain the same number of actively dividing NSCs as found in young mice. Additionally, it has been shown that infusion of FGF or EGF in aged mice restores proliferation to the level seen in young mice (Jin et al., 2003) and isolated aged NSPCs retain the same capacity for neurosphere formation as their young counterparts (Ahlenius et al., 2009). Taken together this suggests that aged NSPCs maintain the same proliferative potential as young NSPCs, and that decreased neurogenesis seen in aging arises from defects downstream of NSPCs in transit-amplifying progenitors and/or neuroblasts. Studies suggest a potential feedback loop in which a decrease in transit-amplifying cells in the aged brain results in decreased epidermal growth factor receptor (EGFR) and Notch signaling, leading in turn to an increase in stem cell activation [see (Luo et al., 2006)]. In the mouse brain the functional consequence of these deficits includes a 75% decline in the total number of dividing cells that reach the olfactory bulb (Bouab et al., 2011; Enwere et al., 2004; Shook et al., 2012). This was previously suggested to result in deficits in fine odor discrimination (Enwere et al., 2004; Tropepe et al., 1997); however, recent work by Moreno et al. (Moreno et al., 2014) showed that olfactory deficits in aged mice could be attributed to impaired olfactory perceptual learning and granule cell responsiveness to learned odorants, while odor discrimination remains intact. This is in agreement with findings that the number of cells and synapses

within the olfactory network remain stable with increasing age despite decreased neurogenesis (Richard et al., 2010).

Human

The human neonatal V-SVZ is characterized by robust neurogenesis and a stream of newborn neurons that populates the layer of the V-SVZ directly beneath the ependyma and adjacent to the astrocyte ribbon. By 6 months of age, there is a progressive decline in V-SVZ proliferation and the total number of immature, migratory neurons. By 18 months of age, an acellular gap region containing just astrocyte processes is found in the place of migratory neuroblasts (Figure 1C). In addition, the number of proliferating cells and immature neurons has reached the trace levels seen in adulthood (Sanai et al., 2011). The medial migratory stream of neuroblasts leading to the prefrontal cortex is not observed after 6 months of age (Sanai et al., 2011). The few existing neuroblasts in the adult human V-SVZ and RMS do not form chains and migration from the V-SVZ to the olfactory bulbs is either extremely rare or nonexistent (Sanai et al., 2004; Wang et al., 2011b).

Several studies show activation and directed migration of NSPCs in the adult human brain following injury (Curtis et al., 2007; Jin et al., 2006; Macas et al., 2006) and in cases of neurodegeneration (Galan et al., 2011; Nait-Oumesmar et al., 2008; Shan et al., 2006); however, the precise identity, site of origin, and regenerative role of these NSPCs are unclear. There have also been reports of successful isolation of multipotent stem cells from the adult V-SVZ, specifically the astrocyte ribbon layer (Sanai et al., 2004) and the olfactory bulb (Pagano et al., 2000), but their organization, function, and capacity for regeneration remains controversial.

The human ventricular system is necessary for critical CSF-interstitial fluid exchange of nutrients as well as clearance of harmful metabolites from the brain interstitial fluid. In contrast to what is seen in mice, aging humans display a progressive enlargement of the lateral ventricles. This is accompanied by the replacement of portions of the ependymal cell lining with dense patches of astrocytes along the ventricle wall (Figure 1D) (Shook et al., 2012). Regional glial ‘scars’ in the place of a functional epithelial cell monolayer would compromise trans-ependymal bulk flow and lead to edema and toxin accumulation in periventricular regions of the aging brain (Figure 1D). The apparent absence of any form of NSPC-mediated regenerative repair along the ventricle surface in humans highlights the need for further studies examining the existence and characterization of putative NSPCs within the human brain, as well as the difference in the microenvironment that would allow continuous regeneration and neurogenesis in rodents, but not humans.

DISCUSSION AND REMAINING QUESTIONS

Although there have been many great advances in the understanding of neural stem cell niche development and adult neurogenesis in mouse and human, there are still many questions that remain unanswered. While the rodent and human V-SVZ retain many cytoarchitectural similarities throughout development, neurogenesis in humans does not persist past 2 years of age. Reasons for the loss of adult V-SVZ neurogenesis in humans versus its persistence in rodents and other mammals remain unclear. The demand for and

evolutionary reliance on a high-functioning olfactory system in nocturnally-functioning rodents most likely necessitates continuous, lifelong production of new neurons destined to support the sense of smell. Humans do not have the same vital requirement for olfaction, which may in part explain the early decline in the supply of new neurons to the olfactory bulb via V-SVZ neurogenesis. It is important to note that humans do retain neurogenic capacity in the subgranular zone (SGZ) of the hippocampus throughout life (Aimone et al., 2014; Aimone et al., 2006; Gage 2000; Jessberger and Gage 2014); however, proliferative and neurogenic capacity in this region declines with age. Adult neurogenesis in the SGZ, in contrast to the lack of neurogenesis in the V-SVZ, could be based on the importance of new memory formation throughout life in humans (Aimone et al., 2014; Aimone et al., 2006). Comparative studies of mammalian neurogenic stem cell niches are necessary to understand the regulation and control mechanisms that govern stem cell activation, self-renewal and ultimately fate decisions. With the findings of injury-induced neurogenesis near the V-SVZ in adult humans, more studies are needed to determine the source of these neurogenic cells, activation cues that regulate their proliferation and their differentiation and regenerative potential.

Advances in our understanding of adult neurogenesis will increase our ability to enhance and possibly harness the potential of NSPCs for therapeutic reparative and regenerative purposes.

REFERENCES

Ahlenius H, Visan V, Kokaia M, Lindvall O, Kokaia Z. Neural stem and progenitor cells retain their potential for proliferation and differentiation into functional neurons despite lower number in aged brain. J Neurosci. 2009; 29:4408–4419. [PubMed: 19357268]

Aimone JB, Li Y, Lee SW, Clemenson GD, Deng W, Gage FH. Regulation and function of adult neurogenesis: from genes to cognition. Physiol Rev. 2014; 94:991–1026. [PubMed: 25287858]

Aimone JB, Wiles J, Gage FH. Potential role for adult neurogenesis in the encoding of time in new memories. Nature neuroscience. 2006; 9:723–727. [PubMed: 16732202]

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. [PubMed: 11283751]

Alvarez-Buylla A, Kohwi M, Nguyen TM, Merkle FT. The heterogeneity of adult neural stem cells and the emerging complexity of their niche. Cold Spring Harb Symp Quant Biol. 2008; 73:357–365. [PubMed: 19022766]

Alvarez-Buylla A, Lim DA. For the long run: maintaining germinal niches in the adult brain. Neuron. 2004; 41:683–686. [PubMed: 15003168]

Bouab M, Paliouras GN, Aumont A, Forest-Berard K, Fernandes KJ. Aging of the subventricular zone neural stem cell niche: evidence for quiescence-associated changes between early and mid-adulthood. Neuroscience. 2011; 173:135–149. [PubMed: 21094223]

Calzolari F, Michel J, Baumgart EV, Theis F, Gotz M, Ninkovic J. Fast clonal expansion and limited neural stem cell self-renewal in the adult subependymal zone. Nature neuroscience. 2015; 18:490–492. [PubMed: 25730673]

Capela A, Temple S. LeX/ssea-1 is expressed by adult mouse CNS stem cells, identifying them as nonependymal. Neuron. 2002; 35:865–875. [PubMed: 12372282]

Conover JC, Shook BA. Aging of the subventricular zone neural stem cell niche. Aging and Disease. 2011; 2:49–63. [PubMed: 22396866]

Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelso C, Holtas S, van Roon-Mom WM, Bjork-Eriksson T, Nordborg C, Frisen J, Dragunow M, Faull RL, Eriksson PS. Human

neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science. 2007; 315:1243–1249. [PubMed: 17303719]

Del Bigio MR. The ependyma: a protective barrier between brain and cerebrospinal fluid. Glia. 1995; 14:1–13. [PubMed: 7615341]

Del Bigio MR. Ependymal cells: biology and pathology. Acta Neuropathol. 2010; 119:55–73. [PubMed: 20024659]

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell. 1999a; 97:703–716. [PubMed: 10380923]

Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 1997; 17:5046–5061. [PubMed: 9185542]

Doetsch F, Garcia-Verdugo JM, Alvarez-Buylla A. Regeneration of a germinal layer in the adult mammalian brain. Proc Natl Acad Sci U S A. 1999b; 96:11619–11624. [PubMed: 10500226]

Enwere E, Shingo T, Gregg C, Fujikawa H, Ohta S, Weiss S. Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. J Neurosci. 2004; 24:8354–8365. [PubMed: 15385618]

Ferron SR, Marques-Torrejon MA, Mira H, Flores I, Taylor K, Blasco MA, Farinas I. Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2009; 29:14394–14407. [PubMed: 19923274]

Gage FH. Mammalian neural stem cells. Science. 2000; 287:1433–1438. [PubMed: 10688783]

Galan L, Gomez-Pinedo U, Vela-Souto A, Guerrero-Sola A, Barcia JA, Gutierrez AR, Martinez-Martinez A, Jimenez MS, Garcia-Verdugo JM, Matias-Guiu J. Subventricular zone in motor neuron disease with frontotemporal dementia. Neurosci Lett. 2011; 499:9–13. [PubMed: 21616125]

Hansen DV, Lui JH, Parker PR, Kriegstein AR. Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature. 2010; 464:554–561. [PubMed: 20154730]

Ihrie RA, Alvarez-Buylla A. Lake-front property: a unique germinal niche by the lateral ventricles of the adult brain. Neuron. 2011; 70:674–686. [PubMed: 21609824]

Jessberger S, Gage FH. Adult neurogenesis: bridging the gap between mice and humans. Trends Cell Biol. 2014; 24:558–563. [PubMed: 25124338]

Jin K, Sun Y, Xie L, Batteur S, Mao XO, Smelick C, Logvinova A, Greenberg DA. Neurogenesis and aging: FGF-2 and HB-EGF restore neurogenesis in hippocampus and subventricular zone of aged mice. Aging Cell. 2003; 2:175–183. [PubMed: 12882410]

Jin K, Wang X, Xie L, Mao XO, Zhu W, Wang Y, Shen J, Mao Y, Banwait S, Greenberg DA. Evidence for stroke-induced neurogenesis in the human brain. Proc Natl Acad Sci U S A. 2006; 103:13198–13202. [PubMed: 16924107]

Kaneko N, Marin O, Koike M, Hirota Y, Uchiyama Y, Wu JY, Lu Q, Tessier-Lavigne M, Alvarez-Buylla A, Okano H, Rubenstein JL, Sawamoto K. New neurons clear the path of astrocytic processes for their rapid migration in the adult brain. Neuron. 2010; 67:213–223. [PubMed: 20670830]

Kerever A, Mercier F, Nonaka R, de Vega S, Oda Y, Zalc B, Okada Y, Hattori N, Yamada Y, Arikawa-Hirasawa E. Perlecan is required for FGF-2 signaling in the neural stem cell niche. Stem Cell Res. 2014; 12:492–505. [PubMed: 24434631]

Kerever A, Schnack J, Vellinga D, Ichikawa N, Moon C, Arikawa-Hirasawa E, Efird JT, Mercier F. Novel extracellular matrix structures in the neural stem cell niche capture the neurogenic factor fibroblast growth factor 2 from the extracellular milieu. Stem Cells. 2007; 25:2146–2157. [PubMed: 17569787]

Kokovay E, Goderie S, Wang Y, Lotz S, Lin G, Sun Y, Roysam B, Shen Q, Temple S. Adult SVZ lineage cells home to and leave the vascular niche via differential responses to SDF1/CXCR4 signaling. Cell Stem Cell. 2010; 7:163–173. [PubMed: 20682445]

Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci. 2009; 32:149–184. [PubMed: 19555289]

Kriegstein AR, Noctor SC. Patterns of neuronal migration in the embryonic cortex. Trends Neurosci. 2004; 27:392–399. [PubMed: 15219738]

Lledo PM, Saghatelyan A. Integrating new neurons into the adult olfactory bulb: joining the network, life-death decisions, and the effects of sensory experience. Trends Neurosci. 2005; 28:248–254. [PubMed: 15866199]

Luo J, Daniels SB, Lennington JB, Notti RQ, Conover JC. The aging neurogenic subventricular zone. Aging Cell. 2006; 5:139–152. [PubMed: 16626393]

Luo J, Shook BA, Daniels SB, Conover JC. Subventricular zone-mediated ependyma repair in the adult mammalian brain. J Neurosci. 2008; 28:3804–3813. [PubMed: 18385338]

Luskin MB. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. Neuron. 1993; 11:173–189. [PubMed: 8338665]

Macas J, Nern C, Plate KH, Momma S. Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2006; 26:13114–13119. [PubMed: 17167100]

Malatesta P, Hack MA, Hartfuss E, Kettenmann H, Klinkert W, Kirchhoff F, Gotz M. Neuronal or glial progeny: regional differences in radial glia fate. Neuron. 2003; 37:751–764. [PubMed: 12628166]

Malatesta P, Hartfuss E, Gotz M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. Development. 2000; 127:5253–5263. [PubMed: 11076748]

Maslov AY, Barone TA, Plunkett RJ, Pruitt SC. Neural stem cell detection, characterization, and age-related changes in the subventricular zone of mice. J Neurosci. 2004; 24:1726–1733. [PubMed: 14973255]

Mercier F, Kitasako JT, Hatton GI. Anatomy of the brain neurogenic zones revisited: fractones and the fibroblast/macrophage network. J Comp Neurol. 2002; 451:170–188. [PubMed: 12209835]

Mirzadeh Z, Doetsch F, Sawamoto K, Wichterle H, Alvarez-Buylla A. The subventricular zone enface: wholemount staining and ependymal flow. J Vis Exp. 2010

Mirzadeh Z, Merkle FT, Soriano-Navarro M, Garcia-Verdugo JM, Alvarez-Buylla A. 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. [PubMed: 18786414]

Miyata T, Kawaguchi A, Okano H, Ogawa M. Asymmetric inheritance of radial glial fibers by cortical neurons. Neuron. 2001; 31:727–741. [PubMed: 11567613]

Moreno M, Richard M, Landrein B, Sacquet J, Didier A, Mandairon N. Alteration of olfactory perceptual learning and its cellular basis in aged mice. Neurobiol Aging. 2014; 35:680–691. [PubMed: 24112795]

Nait-Oumesmar B, Picard-Riera N, Kerninon C, Baron-Van Evercooren A. The role of SVZ-derived neural precursors in demyelinating diseases: from animal models to multiple sclerosis. Journal of the neurological sciences. 2008; 265:26–31. [PubMed: 17961598]

Nam HS, Benezra R. High levels of Id1 expression define B1 type adult neural stem cells. Cell Stem Cell. 2009; 5:515–526. [PubMed: 19896442]

Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR. Neurons derived from radial glial cells establish radial units in neocortex. Nature. 2001; 409:714–720. [PubMed: 11217860]

Noctor SC, Martinez-Cerdeno V, Ivic L, Kriegstein AR. Cortical neurons arise in symmetric and asymmetric division zones and migrate through specific phases. Nature neuroscience. 2004; 7:136–144. [PubMed: 14703572]

Pagano SF, Impagnatiello F, Girelli M, Cova L, Grioni E, Onofri M, Cavallaro M, Etteri S, Vitello F, Giombini S, Solero CL, Parati EA. Isolation and characterization of neural stem cells from the adult human olfactory bulb. Stem Cells. 2000; 18:295–300. [PubMed: 10924096]

Rakic P. A century of progress in corticoneurogenesis: from silver impregnation to genetic engineering. Cereb Cortex. 2006; 16(Suppl 1):i3–i17. [PubMed: 16766705]

Richard MB, Taylor SR, Greer CA. Age-induced disruption of selective olfactory bulb synaptic circuits. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:15613–15618. [PubMed: 20679234]

Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, Gupta N, Berger MS, Huang E, Garcia-Verdugo JM, Rowitch DH, Alvarez-Buylla A. Corridors of migrating neurons in the human brain and their decline during infancy. Nature. 2011; 478:382–386. [PubMed: 21964341]

Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, Lawton MT, McDermott MW, Parsa AT, Manuel-Garcia Verdugo J, Berger MS, Alvarez-Buylla A. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. Nature. 2004; 427:740–744. [PubMed: 14973487]

Schanzer A, Wachs FP, Wilhelm D, Acker T, Cooper-Kuhn C, Beck H, Winkler J, Aigner L, Plate KH, Kuhn HG. Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor. Brain Pathol. 2004; 14:237–248. [PubMed: 15446578]

Shan X, Chi L, Bishop M, Luo C, Lien L, Zhang Z, Liu R. Enhanced de novo neurogenesis and dopaminergic neurogenesis in the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease-like mice. Stem Cells. 2006; 24:1280–1287. [PubMed: 16424396]

Shen Q, Wang Y, Kokovay E, Lin G, Chuang SM, Goderie SK, Roysam B, Temple S. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. Cell Stem Cell. 2008; 3:289–300. [PubMed: 18786416]

Shook BA, Manz DH, Peters JJ, Kang S, Conover JC. Spatiotemporal Changes to the Subventricular Zone Stem Cell Pool through Aging. J Neurosci. 2012; 32:6947–6956. [PubMed: 22593063]

Siegenthaler JA, Ashique AM, Zarbalis K, Patterson KP, Hecht JH, Kane MA, Folias AE, Choe Y, May SR, Kume T, Napoli JL, Peterson AS, Pleasure SJ. Retinoic acid from the meninges regulates cortical neuron generation. Cell. 2009; 139:597–609. [PubMed: 19879845]

Siegenthaler JA, Pleasure SJ. We have got you 'covered': how the meninges control brain development. Current opinion in genetics & development. 2011; 21:249–255. [PubMed: 21251809]

Sonntag WE, Ramsey M, Carter CS. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Ageing Res Rev. 2005; 4:195–212. [PubMed: 16024298]

Spassky N, Merkle FT, Flames N, Tramontin AD, Garcia-Verdugo JM, Alvarez-Buylla A. Adult ependymal cells are postmitotic and are derived from radial glial cells during embryogenesis. J Neurosci. 2005; 25:10–18. [PubMed: 15634762]

Tavazoie M, Van der Veken L, Silva-Vargas V, Louissaint M, Colonna L, Zaidi B, Garcia-Verdugo JM, Doetsch F. A specialized vascular niche for adult neural stem cells. Cell Stem Cell. 2008; 3:279–288. [PubMed: 18786415]

Temple S. The development of neural stem cells. Nature. 2001; 414:112–117. [PubMed: 11689956]

Tramontin AD, Garcia-Verdugo JM, Lim DA, Alvarez-Buylla A. Postnatal development of radial glia and the ventricular zone (VZ): a continuum of the neural stem cell compartment. Cereb Cortex. 2003; 13:580–587. [PubMed: 12764031]

Tropepe V, Craig CG, Morshead CM, van der Kooy D. Transforming growth factor-alpha null and senescent mice show decreased neural progenitor cell proliferation in the forebrain subependyma. J Neurosci. 1997; 17:7850–7859. [PubMed: 9315905]

Wang C, Liu F, Liu YY, Zhao CH, You Y, Wang L, Zhang J, Wei B, Ma T, Zhang Q, Zhang Y, Chen R, Song H, Yang Z. Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. Cell Res. 2011a; 21:1534–1550. [PubMed: 21577236]

Wang L, Klein R, Zheng B, Marquardt T. Anatomical coupling of sensory and motor nerve trajectory via axon tracking. Neuron. 2011b; 71:263–277. [PubMed: 21791286]

Highlights

- SVZ stem cell niche development in mouse and human displays some unique differences.
- SVZ neurogenesis in humans stops by 2-years of age.
- Mouse SVZ neurogenesis continuously provides olfactory bulb neurons even in aging.
- However, stem cell numbers do decline in the aging mouse SVZ.

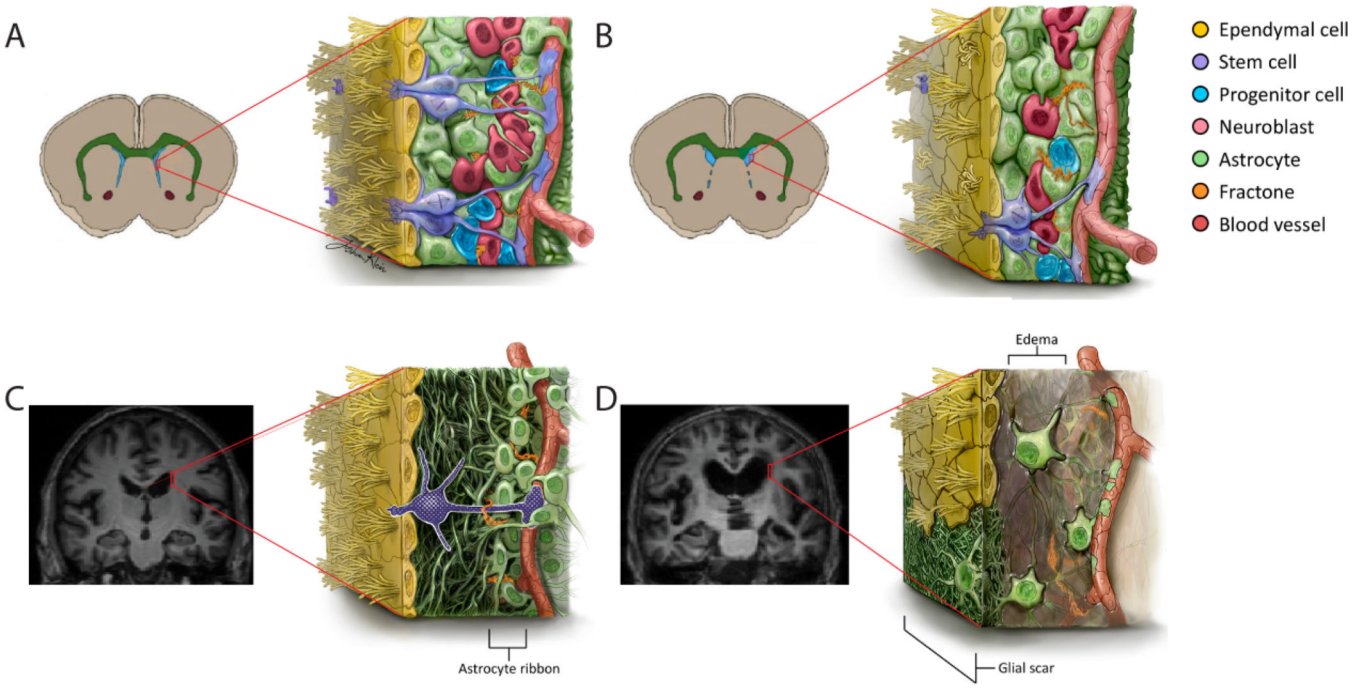

Figure 1. V-SVZ Aging in Mouse and Human

(A) Adult mouse brain shown in a coronal section representation with a red box denoting region of V-SVZ depicted graphically, based on electron micrograph imaged cellular organization. (B) An analogous representation in the aging mouse brain is similarly shown. (C) Adult human brain shown in a representative coronal MRI scan with a red box denoting region of V-SVZ depicted graphically based on immunohistochemical staining of human brain tissue. A corresponding representation of the aging human brain is shown in (D) and indicates a region of glial ‘scar’ and its associated tissue edema. Legend to the right of all schematics shows color coding of each cell type shown.