

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Typical and Atypical Stem Cell Niches of the Adult Nervous System in Health and Inflammatory Brain and Spinal Cord Diseases

Joshua Bernstock, Jeroen Verheyen, Bing Huang,
John Hallenbeck and Stefano Pluchino

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/58599>

1. Introduction

“Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated.” -Santiago Ramon y Cajal

The central nervous system (CNS) is inhabited by a heterogeneous population of cells (i.e. neurons and glia) and is marked by a highly complex anatomical structure [1]. In states of host homeostasis the putative majority of cells in the CNS are long-lived and typically do not require replacement. Nonetheless, neurogenesis in the adult mammalian brain has been shown to occur in a myriad of locations, under a diverse set of physiologic/pathophysiologic conditions [2-10]. Neurogenesis is driven by stem cells which can be defined by their ability to produce both identical daughter cells (self-renewal) and progeny with more restricted fates (commitment and differentiation) [11]. To be classified as a neural stem cell (NSC), cells should be able to self-renew and give rise to a variety of mature progeny that make up the CNS, including neurons, astrocytes and oligodendrocytes [12-16]. However, fate-restricted precursor cells capable of self-renewal, but which concurrently display restricted differentiation potential, also reside in the CNS. These cells are often unipotent and are referred to as neural progenitor cells (NPC) [17, 18], for example, oligodendrocyte precursor cells (OPC) are able to self-renew, but typically produce only oligodendrocytes [18, 19].

Identification of NSC *in vivo* is clearly complicated and relies on the analysis of cell morphology, mitotic activity, and gene and protein expression. Commonly used NSC markers include nestin, glial fibrillary acidic protein (GFAP), Musashi 1/2, and the Shy-related high mobility

group box transcription factor 2 (Sox2) [20-23]. Nestin is a class VI intermediate filament linked to mitotically active cells in the CNS [20, 24]. GFAP is expressed in multipotent ependymal cells, radial glia, and also in mature astrocytes [21]. Musashi 1 and 2 expression can be found in embryonic neuroepithelial cells [22] while Sox2 is found primarily in undifferentiated cells that possess self-renewal capabilities [23]. As noted above, NSC can exist in either a quiescent or mitotically active state. Quiescent cells have been shown to express Sox2 and FoxO3A, and are further demarcated by a prolonged retention of bromodeoxyuridine (BrdU) [24-28]. Dividing cells, on the other hand, show a rapid turnover of BrdU and simultaneously contain various markers of cell-cycle entry/progression: Mcm-2, Ki67, cyclin D1 and E (G1 phase), cyclin A (S phase), cytoplasmic cyclin B1 (G2 phase), and phosphohistone H3 (M phase) [10, 29]. Fate restricted precursor cells have traditionally been recognized via the expression of doublecortin (DCX) and the polysialylated-neural adhesion molecule (PSA-NCAM) [30, 31].

As stem cells (SC) continue to be identified, characterized and localized, the critical importance of specific signals from their microenvironment, or niche, have become apparent. Stem cell niches in the brain can be classified as either “typical” or “non-typical”. The three typical NSC niches found in the CNS are the subventricular zone (SVZ), the subgranular zone (SGZ) and the central canal (CC) of the spinal cord [32-34]. Non-typical (germinal) niches have been identified in the hypothalamus, circumventricular organs (CVO), the meninges and the subpial layer of the cerebellum [32, 35-37]. Further, non-typical (non-germinal) niches can be found throughout parenchyma of the cerebral cortex, cerebellum and spinal cord, and are mainly comprised of restricted neuroglia precursors [10, 32, 38, 39]. Much of the aforementioned has recently been confirmed *in vitro* via an assortment of neurosphere assays, which are considered to represent the “gold-standard” technique for identifying the presence of NSC in the adult brain [33, 40]. Neurospheres have been obtained from many regions in the brain, including the olfactory bulb, cerebellum, various white matter tracts, spinal cord, substantia nigra, retina, hypothalamus, and hypophysis [41-45]. Finally, the concept of atypical niches has recently emerged and references the unique microenvironment formed upon exogenous stem cell transplantation. These niches are reported to evolve in close proximity to perivascular regions [32, 46].

The capacities of stem cells to contribute to growth and diversification during development and in so doing sustain homeostasis/repair processes throughout adult life is now clear. Elucidation of the mechanisms that govern stem cell behavior is therefore of fundamental significance in cell, developmental, and organismal biology. The capabilities arising from such knowledge are anticipated to have major biomedical and clinical translational applications [11, 47]. The remainder of this chapter will therefore offer an overview that will touch upon the distribution and relevant components (e.g. stem cells, support cells, signaling molecules) of stem cell niches in the CNS, in states of both homeostasis and various pathobiologies (e.g. ischemic, inflammatory, traumatic) and in the process will attempt to highlight potential therapeutic targets that may be manipulated in an effort to promote effective and translational repair and regeneration of the CNS after insult/injury.

2. Neural stem cells niches within the central nervous system

2.1. Definition/critical components of the “niche”

As stem cells in adult organs continue to be identified, characterized and localized, it has become clear that the vast majority of these cells depend on specific signals from the microenvironment of their niche to regulate their quiescence, activation, self-renewal and ultimate survival. Such a phenomenon was hypothesized by Schofield nearly 35 years ago and has been shown to hold true today [48]. The evolution of this concept has led to the definition of the niche as a microenvironment capable of integrating intrinsic and extrinsic factors and in so doing, influence stem cell proliferation, migration and fate specification [49, 50]. Intrinsic determinants are governed mainly by the genetic/epigenetic status of stem cells and their subsequent ability to decipher signals within the niche. Extrinsic determinants may be thought of as the processing of extracellular signals and include such events as cell-to-cell and cell-to-extracellular matrix (ECM) signaling [50, 51]. Generally, the cellular makeup of these niches has been shown to consist of a variety of cells, which typically include the immature progeny of NSC accompanied by endothelial, astroglial, and ependymal cells [50, 52]. Along with the ECM, they provide not only structural/trophic support, but have been shown to provide critical temporal and spatial information, thereby enabling stem cells to respond to both physiological and pathological stimuli [49]. Acting through these pathways, stem cell niches in the CNS have been shown to play essential roles in supporting active neurogenesis via the mobilization of endogenous neural stem/precursor cells and further serve to regulate different stages of adult neurogenesis in health/disease [52]. Clearly, an understanding of the detailed molecular, structural and functional properties of the niche may help to influence intractable neurological disease processes and/or yield novel clinically relevant NSC-based therapeutic approaches via the enhancement of endogenous regeneration and repair.

2.2. Subventricular zone (SVZ)

In the adult brain, NSC have traditionally been assumed to be restricted to certain regions, such as the SVZ of the lateral ventricles and the SGZ of the dentate gyrus (DG) of the hippocampus. Both of these niches have been shown to be capable of sustaining neurogenesis in the adult CNS [53-55]. The vast majority of adult neurogenesis in mammalian species has been demonstrated to occur within the SVZ niche as it retains many of its early embryonic features/primitive germinal layers. The SVZ also represents the largest neurogenic region and has by most accounts been the best characterized of the endogenous CNS niches [50]. Interestingly, recent work suggests that SVZ neural stem cells are not homogenous; rather they may represent a heterogeneous population capable of differentiating into restricted subsets/cells of differential fates [42]. Within the niche, a subset of GFAP-expressing astrocytes (type B/B1 cells) are thought to represent the NSC population (Figure 1) [56, 57]. These primary progenitors either slowly self-renew or differentiate and give rise to transit-amplifying cells (type C cells), which are capable of generating a substantial number of neuroblasts (type A cells) [58, 59]. SVZ neuronal precursors have been shown to migrate extensive distances in chains via the rostral migratory stream (RMS) [60] toward the olfactory bulb [61]. Upon arrival, they

undergo the process of differentiation into mature neurons, and migrate into the granular and periglomerular layers [62, 63]. The type B cells mentioned above share morphologic features that are similar to astrocytes and strengthen the argument for a radial glial origin [64]. Uniquely, type B cells are in direct contact with blood vessels via their basal processes and concurrently interact with the ventricular lumen through apical processes [26, 65, 66].

Cells that eventually give rise to olfactory bulb neurons in the human brain have been identified via the expression of DCX in the SVZ [67]. Detailed studies have revealed a ribbon of SVZ astrocytes that line the lateral ventricles of adult human brain, and work has confirmed that these cells are in fact self-renewing and multipotent [68]. Interestingly humans do not display features characteristic of the RMS [68]. However, the migration of immature neurons away from the SVZ has been documented to occur [69, 70]. While some studies have indicated progressive decline in neuroblasts over the course of an adult life [70-72], recent work-utilizing carbon-14 has demonstrated that neurons continue to be generated and to integrate into host circuitry [73, 74]. Additionally, contemporary studies have begun to suggest a role for supraependymal 5-hydroxytryptamine (5-HT, serotonin) axons that directly contact NSC and therefore may serve in part to regulate neurogenesis via 5-HT_{2C} receptors [75]. Such complex cytoarchitecture coupled with the emerging diversity of SVZ precursor cells leads to a unique microenvironment capable of supporting sustained neurogenesis throughout the life of an organism [25].

2.3. Subgranular Zone (SGZ) of the hippocampus

The second major region that produces new neurons in the adult mammalian brain is the SGZ of the hippocampus, which is located at the interface of the granule cell layer (GCL) and the hilus of the dentate gyrus [76, 77]. This has been shown to be true in a variety of mammalian species (e.g. rodents, primates, humans) [78-85]. In stark contrast to the new neurons born in the subventricular zone, newly formed hippocampal neurons transmigrate only a short distance into the granule cell layer before functionally integrating into existing hippocampal circuitry [77, 86-88]. While it has been suggested that neurogenesis in the adult hippocampus contributes to the processes involved in learning and memory, the definitive function of neuronal replacement in DG has yet to be elucidated [88, 89]. Similar to the SVZ, neurogenesis in the dentate gyrus has been demonstrated to occur throughout life [89, 90] and has been shown to be influenced/regulated by a multiplicity of physiological and environmental cues. These cues have not been fully characterized, but they include adrenal steroids, glutamate receptor activation, seizures, enriched environmental conditions, exercise, inflammation/brain injury, and antidepressant medication [59, 81, 83, 91, 92].

Given the presence of multiple precursor subtypes found within the adult hippocampus, a reliable method to distinguish molecular identities is needed in order to adequately reveal the degree to which primary precursors self-renew and/or differentiate into multiple progeny [93]. Briefly, a core tenant of the prevailing model of adult hippocampal neurogenesis is that GFAP/nestin/Sox2 expressing radial glia-like cells (RGL) [77, 86, 89, 93], or type-1 cells [94], represent a quiescent population which may be induced to generate the proliferative precursors known as intermediate progenitors, IPC1 (type-2a) and IPC2 (type-2b) cells. Via the use of anti-mitotic

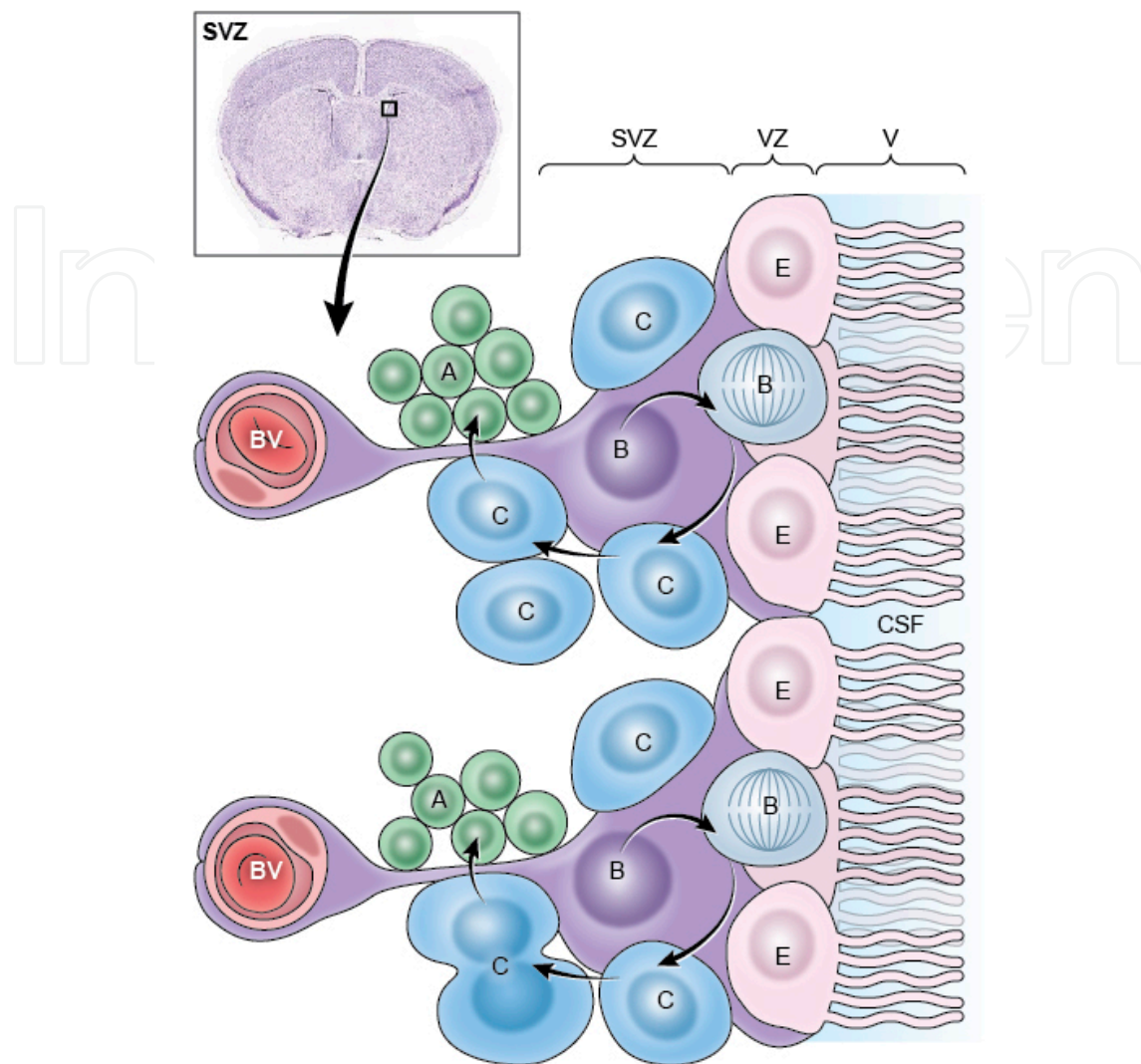


Figure 1. Subventricular Zone Niche. Coronal brain section (Allen Developing Mouse Brain Atlas) shows the location of the neurogenic subventricular zone (SVZ) niche. The SVZ can be found contacting the overlying ventricular zone (VZ), a pseudo-stratified epithelium layer that lines the cerebrospinal fluid (CSF) filled ventricles (V). NSC (type B cells, B) are found in a subependymal position, contacting both ependymal cells (E) and blood vessels (BV). Type B cells proliferate through asymmetric division, giving rise to transit-amplifying type C cells (C) that further differentiate to form neuroblasts (type A cells, A). Supported by type B cells, these neuroblasts proliferate, expand and migrate, allowing for adult neurogenesis. Adapted from Fuentealba et al. [100].

agents, genetic ablation, and transgenic fate mapping, a vast body of experimental evidence now exists in support of RGL as functional NSC [86, 95-98]. Of note, RGL seem to maintain both ultrastructural features and surface markers characteristic of astrocytes [59] and have been shown to be capable of undergoing several rounds of both self-renewal and differentiation over a prolonged period of time [99]. Importantly, RGL in the niche are polarized, a characteristic that provides a spatiotemporal nature to signals received within the niche. RGL zones within the niche can be subdivided into proximal, intermediate and distal domains along which RGL maintain their polarized structure (i.e. from apical-basal). They span from the hilar/

SGZ interface (proximal domain I) to the inner molecular layer (IML) (distal domain III) [100] (Figure 2). The proximal domain harbors a distinctive primary cilium which has been shown to be important for Sonic hedgehog (Shh) signaling, sensing/sampling of the hilus microenvironment, and contacting other RGL and blood vessels [100]. Here, endothelial cells provide access to critical factors, namely, vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF) and brain-derived neurotrophic factor (BDNF), which together serve to coordinate the complex regulation between proliferation and differentiation [100]. RGL cell bodies/main shafts are located within the SGZ and GCL (domain II) and facilitate cell-cell based interactions of the RGL with progeny (feedback from which may serve to regulate RGL quiescence or transition via Notch signaling) and simultaneous sampling of local neural activity via resident granular cells [101, 102]. In the IML (domain III), RGL terminate and display an elaborate/branched structure. While the governing dynamics in this area have yet to be fully elucidated, it seems reasonable to deduce that inputs via interneurons and mossy cells have a role to play in the regulation of RGL/NSC [103].

Returning to the abovementioned progeny of the RGL, the IPC, it should be noted that they produce novel neuroblasts and eventually immature granule neurons (type-3 cells), which migrate into the inner granule cell layer, thereby differentiating into immature granule cells of the DG [88, 89, 100]. Retroviral mediated gene transduction has allowed such newborn neurons to be labeled and subsequently tracked. Using this technique, Zhao et al. demonstrated that these novel neurons extend dendrites toward the molecular layer and project axons through the hilus toward the CA3 region in a matter of days in an effort to become functionally integrated into host circuitry [104, 105]. Despite the complexity of events outlined above, and the relatively high rate of neurogenesis occurring in the SGZ, it is important to note that only a minority of newly born cells ultimately survive to mature and integrate within the granule cell layer of the hippocampus, highlighting the need for further exploration/characterization of the niche/neurogenic processes in the SGZ [106].

2.4. Central canal of the spinal cord

The spinal cord comprises the caudal part of CNS, extending from the medulla to the cauda equina. It contains 33 nerve segments, rostro-caudally grouped as the cervical, thoracic, lumbar, sacral, and coccygeal segments. At the center of the spinal cord lays the central canal, an ependymal region forming a round-shaped lumen, lined by epithelium, which contains cerebrospinal fluid (CSF). The spinal cord transmits signals between the brain and the rest of the body and contains complex circuitry thereby enabling reflexive and rhythmic motor patterns [107]. The inner region of the spinal cord surrounding the central canal is comprised of gray matter and contains neurons that are commonly arranged by function: motor neurons are clustered anteriorly, sensory projection neurons posteriorly, with a more mixed population in the intermediate areas, including the afferent and efferent neurons of autonomic nuclei. All regions are supported by and connected through a complex network of interneurons, which serve to modulate transmission and activity. The outer region is comprised of white matter and contains afferent and efferent axons arranged in tracts. Like the gray matter, white matter

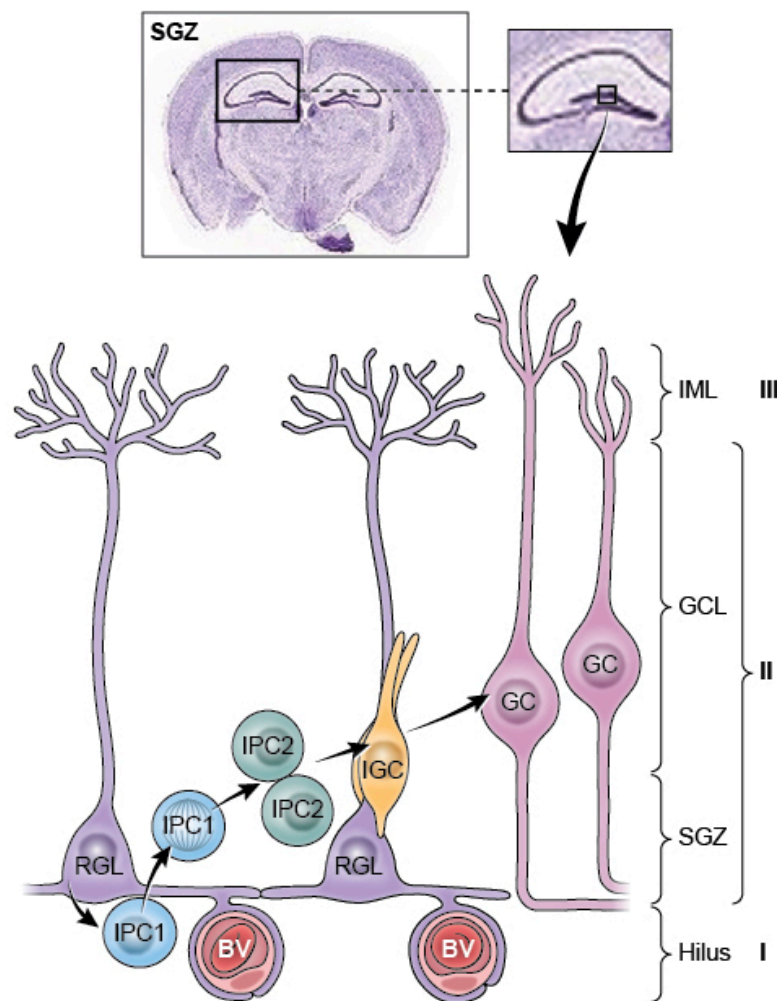


Figure 2. Subgranular Zone Niche. Coronal brain section (Allen Developing Mouse Brain Atlas) shows the location of the subgranular zone (SGZ) niche in the dentate gyrus of the hippocampus. Radial glial-like cells (RGL) are the type of NSC that make up the SGZ. In the proximal domain (I) or hilus, they contact blood vessels (BV) and their radial processes span the granule cell layer (GCL), in domain II, to reach the inner molecular layer (IML) in the distal domain (III). RGL divide asymmetrically to generate intermediate progenitor cells 1 (type-2a cells, IPC1) and 2 (type-2b cells, IPC2). These progenitors give rise to neuroblasts that differentiate to immature granule neurons (type-3 cells) that in turn migrate to the GCL and differentiate to immature granule cells (IGC). These cells further differentiate to form mature granule cells (GC), allowing for adult neurogenesis. Adapted from Fuentealba et al. [100].

exhibits functional organization, with afferent tracts clustered dorsally and at the lateral periphery, and efferent tracts clustered anteriorly and medially [107, 108].

The ependymal layer of the spinal cord is well known for its role in embryonic development and its function as neuroprogenitor niche. Ependymal cells divide symmetrically and migrate away from the central canal, giving rise to the different neural lineages [19, 109]. Postnatally, the spinal cord elongates and increases in size [110]. The proliferation required for such growth gradually declines, leaving adult rodents and humans with little to no ependymal proliferation [111, 112].

The presence of multipotent cells in the adult mammalian spinal cord was first discovered in the late 1990s. Rat and mouse NSC were isolated and characterized *in vitro*. Cultured cells were able to produce neurospheres capable of self-renewal, extended proliferation, passaging, and differentiation into the three major CNS cell types, i.e. neurons, oligodendrocytes, and astrocytes [12, 15, 113]. It was shown later that NSC reside at the central canal and in the parenchyma of the spinal cord [13, 14]. Although able to self-renew and generate mature oligodendrocytes, these parenchymal cells do not produce neurospheres, indicating that they are progenitors (i.e. restricted in fate) rather than NSC [114]. When spinal cord derived neurospheres are transplanted into the hippocampus they can give rise to neurons, a property that is not observed when transplanted back to the cord, and is suggestive of a non-conductive progenitor microenvironment [18].

The adult central canal is comprised of a pseudo-stratified epithelium with a myriad of cell types that contact the lumen or are present in a subependymal position (all Sox2⁺) (Figure 3) [34, 112, 115]. The main constituents are ependymal cells, some of which are positive for GFAP [112, 116-118]. Although under physiological conditions most of these ependymal cells are quiescent, some proliferation has been observed at the dorsal tip of the central canal and ependymal cells from this region have enriched neurosphere-forming capabilities [112, 114, 119]. Dorsal ependymal cells show a radial morphology, much like radial glia, and their processes can reach up to the white matter or even the pial surface [112, 117, 119, 120]. They divide symmetrically, as they did during postnatal development [114]. Dorsal ependymal cells show enriched expression of GFAP, nestin, CD15 and/or brain lipid-binding protein (BLBP) [34, 112, 117, 119, 120]. A similar population and morphology has also been observed at the ventral part of the central canal, although to a lesser extent [112, 117, 119]. It has now been shown that ependymal cells are able to generate progeny of multiple fates under physiological and pathological conditions [114, 119, 121]. Other cells that make up the central canal are tanycytes and CSF-contacting neuron-like cells. Tanycytes, a specific subset of ependymal cells, contact blood vessels through their long basal processes and thus bridge the CSF and capillaries [119, 122]. Neuron-like cells that contact the CSF through dendrite-like processes are thought to be involved in CSF homeostasis (e.g. pressure sensing) and/or spinal cord extension/flexion sensing [112, 123, 124]. Surrounding the central canal, nerve fibers, neurons (NeuN⁺), oligodendrocytes (Olig2⁺) and blood vessels can also be found [34, 112]. Pericytes that are an active part of the blood brain barrier surrounding blood vessels have also been shown to be an important source of astrocytes, implicating stem cell-like properties for these cells. These astrocytes mainly contribute to astrogliosis during injury [125].

Central canal derived neurospheres tend to house a heterogeneous population of cells, much like neurospheres derived from other neurogenic regions [34]. Neurosphere cells all express nestin but show variable expression levels of prominin-1 (CD133) (stem cell marker), GFAP, and aldehyde dehydrogenase 1 family member, L1 (ALDH1L1) (astrocytic markers), CD15, BLBP, glutamate aspartate transporter (GLAST), and radial glial cell marker-2 (RC2) (radial glial markers), and neuron-glial antigen 2 (NG2), A2B5 antigen (A2B5), and platelet-derived growth factor receptor α (PDGFR α) (oligodendrocytic markers) [34]. Only a small number of cells express neuronal markers such as microtubule-associated protein 2 (MAP2) and DCX,

which correlates with the overall preference of the cord toward oligodendrocytic and astrocytic differentiation [34]. Expression of motor neuron development transcription factors (Islet1, lim1, HB9) has not been observed, reflecting the *in vivo* tendency towards production of GABAergic neurons [16, 112, 126]. Motor neuron differentiation can however be induced by certain morphogens, such as retinoic acid (RA) and Shh [126]. Notably, neurospheres preserve information related to their rostro-caudal location, namely the expression of certain combinations of developmental genes of the Hox family [112, 127].

In conclusion, the central canal of the spinal cord is mainly comprised of a heterogeneous population of ependymal cells. Stem cell properties have mainly been attributed to ependymal cells at the dorsal tip of the central canal and to pericytes. Further research is needed to fully unravel the neurogenic properties/potential of the central canal in states of both health and disease.

2.5. Non-typical neural stem cell niches

Beyond the typical NSC niches referenced above it should be noted that non-typical niches have now been identified and have begun to be characterized. These non-typical niches can be further divided into those areas that are germinal (neurogenic) and those that are not. Non-typical germinal regions include the hypothalamus, CVO, the meninges and the subpial layer of the cerebellum. Non-typical, non-germinal regions can be found throughout parenchyma of the cerebral cortex and spinal cord, and are mainly comprised of restricted neuroglia precursors [10, 32, 35-39, 128-131]. Accordingly, the following paragraphs will briefly discuss selected non-typical niches in neurogenic and non-neurogenic areas.

2.5.1. Non-typical germinal regions

As was the case with the typical niches, non-typical germinal regions are characterized by their inherent neurogenic capabilities, i.e. composed of a heterogeneous population of NSC able to self-renew and give rise to most of the neuronal and glial precursors [32, 132, 133]. To be characterized as neurogenic, isolated cells should be able to give rise to secondary neurospheres *in vitro* whilst being able to produce all three neuronal lineages [36, 37].

Constitutive adult neurogenesis has been identified in regions lining the third ventricle, including the hypothalamus and the CVO [131, 134-137]. Cells from these areas are not only positive for nestin, GFAP, Sox2 and Ki-67, but have also been shown to incorporate BrdU. Their ability to produce both proliferating and differentiating neurospheres *in vitro* strongly suggests that these areas represent germinal neurogenic NSC niches [137]. Furthermore, it should be noted that the ECM structure and composition of the aforesaid areas strongly resemble that of the SVZ [138].

Cells positive for nestin and DCX have also been found in the meninges of the brain and spinal cord [139-143]. These nestin⁺ cells are able to give rise to neurospheres *in vitro* and show highly efficient generation of excitable cells with neuronal phenotype and morphology [139], congruent with the meninges' important role during development, harboring neuroepithelial cells [144]. Further, within the adult meninges, neurogenic factors such as basic fibroblast

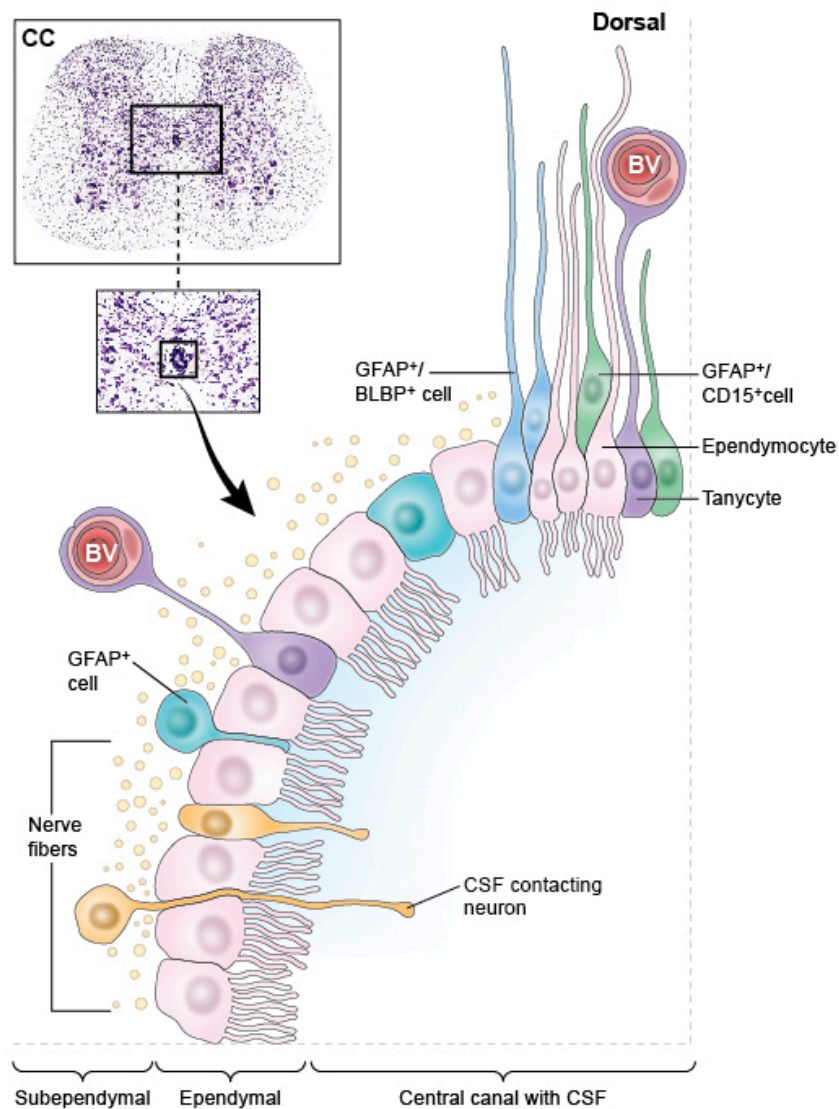


Figure 3. Central Canal Niche. Cross-section through the spinal cord at lumbar level 1 (Allen Developing Mouse Brain Atlas) shows the location of the central canal. Lining the lumen of the cerebrospinal fluid (CSF)-filled central canal is a pseudo-stratified epithelium with interspersed ependymal cells (ependymocytes). Ependymal cells GFAP can be found throughout the canal and are enriched in the dorsal and ventral part (latter not shown) where they have a radial morphology, much like that of radial glia. These radial GFAP⁺ cells are believed to be NSC since they proliferate and differentiate, allowing for (glial-restricted) neurogenesis. This is further supported by co-expression of stem cell markers, BLBP or CD15. Although mainly quiescent under physiological conditions, these cells become mitotically active under pathological conditions. After symmetrical division their progeny differentiate to astrocytes and oligodendrocytes. Other cells that make up the central canal are tanycytes that bridge the CSF and blood vessels (BV), and CSF-contacting neurons. Pericytes surrounding BV (not shown) have been found to also contribute to the generation of astrocytes under pathological conditions, and are thus considered another form of NSC around the central canal.

growth factor (bFGF), Chemokine (C-X-C motif) ligand 2 (CXCL2)/macrophage inflammatory protein 2- α (MIP2- α) and RA can still be observed [145-147].

Neurosphere-forming NSC have also been obtained from the cerebellum and are isolated based on their expression of the NSC marker prominin-1 (CD133) and their lack of markers of

neuronal and glial lineage markers. Purified CD133⁺ cells form self-renewing neurospheres and can differentiate into astrocytes, oligodendrocytes and neurons *in vitro* [148]. Although the exact location and composition of this niche remains unclear, proliferative elements have been putatively allocated to the subpial layer [149-151], with newly generated cells divided in two populations: DCX⁺/PSA-NCAM⁺/Pax⁺ neuroblast neural precursors and microtubule-associated protein 5 (MAP5⁺)/Olig2⁺/Sox2⁺ glial precursors [149, 150].

2.5.2. Non-typical non-germinal regions

Non-typical non-germinal regions are those that demonstrate proliferative properties, but are unable to induce comprehensive neurogenesis. Often these are areas within the parenchyma and consist of committed precursor cells that can self-renew and give rise only to a specific type of neuronal cell. The potential of cells in these areas to produce multipotent neurospheres is lost soon after birth [32, 38, 152, 153]. While there are non-typical regions that may be germinal in nature rather than non-germinal, proof is still lacking. These putative areas include the striatum, amygdala, substantia nigra, and vagal nucleus [35, 153].

In the cerebral cortex, A2B5⁺ glial restricted precursors give rise to oligodendrocytes and astrocytes [154]. Oligodendrocyte precursor cells that express integral chondroitin sulfate proteoglycan 4 (CSPG4), also known as NG2⁺ cells, can also be found through the cerebral cortex [155, 156]. These cells are restricted to producing oligodendrocytes and astrocytes. In the spinal cord, these NG2⁺ cells can also be observed [152, 156]. Olig2⁺ OPC are also widely found in the spinal cord. These cells are typically deemed to be more committed than NG2⁺ cells, only able to give rise to oligodendrocytes [114, 152]. Furthermore, progenitors that produce immature DCX⁺/GAD-65⁺/GAD-67⁺/GABA⁺ neurons have been found enriched in the dorsal part of the spinal cord [19, 157].

The abovementioned progenitors are some of the more predominant cellular populations, yet it should be noted that parenchymal progenitors consist of an incredibly heterogeneous population, as evidenced by expression of stem cell markers. While crosstalk between cells populating non-typical niches under varied pathological conditions have also been begun to be highlighted [153], much work still needs to be done to fully elucidate the function and therapeutic potential of such regions [10, 35, 152, 153].

3. Neural stem cell niches in CNS disease

"I say all the most acute, most powerful, and most deadly diseases, and those which are most difficult to be understood by the inexperienced, fall upon the brain."-Hippocrates

Diseases of the central nervous system pose a massive societal burden and continue to be a leading cause of morbidity and mortality throughout the world; however, the medical community possesses few effective therapies that are able to modulate the pathogenesis of brain injury/illness. The paucity of viable therapeutic options stands in stark contrast to the intensity of research efforts and number of clinical trials that have been performed to date. As

of yet, there are few, if any, treatments capable of markedly improving functional recovery to levels concordant with a pre-disease state (i.e. regenerative therapies). The restricted success of such a massive research investment demands a reevaluation of the pathobiology of the injured and/or dysfunctional brain.

Beyond homeostasis, it has been clearly established that the basic biological descriptors of neural stem cells—which include self-renewal, proliferation/differentiation, and migration—are affected by certain pathogenic stimuli e.g. excitotoxicity, mechanical trauma, ischemic and/or inflammatory) [158-167]. It follows that a greater knowledge of the factors involved in the dynamic regulation of adult neurogenesis may pave the way for the development of suitable treatments and preventative strategies that would delay the onset and/or mitigate the symptoms of a number of devastating brain disorders. Therefore, the remainder of this section will seek to highlight core components of the response of adult neurogenic regions in the face of the distinctly relevant clinical entities: ischemic stroke, multiple sclerosis (MS) and spinal cord injury (SCI).

3.1. Effects of ischemic stroke on the neurogenic process/niche

Stroke is the one of the most common causes of death and disability worldwide. Due to an aging population, the burden will markedly increase in the coming decades and will be particularly pronounced in developing countries [168, 169]. Of strokes that occur in the United States, 87% are ischemic and 10% are intracerebral hemorrhagic strokes, whereas 3% are subarachnoid hemorrhage strokes [169]. Based on this distribution, the remainder of this discussion will focus on ischemic stroke. Cerebral ischemia triggers the pathological pathways of the “ischemic cascade” that if untreated causes irreversible neuronal injury in the ischemic core within mere minutes of the onset [170-172]. Cerebral ischemia and, if applicable, reperfusion cause extreme changes in the parenchymal microenvironment to include variations in oxygen (O_2) concentrations, depletion of cellular energy stores e.g. adenosine triphosphate (ATP), perturbation of ion homeostasis, inflammation and aberrant neurotransmitter release [173]. The primary drivers of this pathogenic process stem from a crisis in energy availability and result from a reduction in O_2 and glucose [173]. Clearly such a vast array of pathology would suggest that the incidence/activity of endogenous neurogenic niches would be affected and this has proven correct.

Numerous studies have now demonstrated that ischemic stroke is in fact capable of increasing neural stem cell proliferation [158, 159, 174-184]. In the SGZ, ischemia seems to act preferentially on proliferation of type 1 and 2 progenitor cells, and to a lesser extent neuroblasts [167, 185]. Within the SVZ, stroke selectively increases the number of type A and C cells [186], yet there is also data to suggest that type B cells undergo a period of transient symmetric division after stroke [187]. Ependymal cells bordering the SVZ have also been noted to proliferate transiently after ischemic stroke [188]. Mitotic activity appears to peak during between 7-10 days post ischemia then returns to baseline levels between the 3-5th week [160, 175, 187, 189-191]. While maximal cell proliferation occurs on the order of days-weeks it should be noted that neuroblasts have been documented to exist for at least one year after an ischemic insult [176]. Signals that stimulate the stroke-induced neurogenesis have yet to be fully elucidated

but likely involve the interplay of many non-dominant effectors, namely cytokines and growth factors/neurotrophins that have been shown to be upregulated during brain ischemia, the putative majority of which have established links to the neurogenic process [189, 192]. bFGF, BDNF, epidermal growth factor (EGF), glial cell-derived neurotrophic factor (GDNF), bone morphogenic protein (BMP) and erythropoietin (EPO), ciliary neurotrophic factor (CNTF), transforming growth factor (TGF)- α , VEGF and erythropoietin (EPO) have all been proposed to play prominent roles in neurogenesis [191, 193-210]. Insulin-like factor-1 (IGF-1) and granulocyte-colony stimulating factor (G-CSF) have also been shown to be inextricably involved in the abovementioned stroke-induced neurogenic process [211, 212]. It is also important to note that the physiologic stressors of ischemia directly affect other components of the neurogenic niche and in so doing may influence neurogenesis as highlighted by studies of cerebral endothelial cells [27, 213, 214].

Of particular note, inflammation also accompanies ischemic insults/injuries and is predominantly driven in the CNS by the activation of resident microglia, astrocytes and infiltrating immune cells, which go on to release a plethora of inflammatory cytokines/chemokines and reactive oxygen species [189, 215]. Inflammatory mediators have been shown to have varying effects on neural progenitor cell proliferation, migration, differentiation, survival and incorporation of newly born neurons into the CNS circuitry [216-222]. These studies suggest that additional work is warranted and will be needed to clarify the precise effects/outcomes as influenced by inflammation post-stroke. Further complicating the picture, evidence has emerged to suggest that neurotransmitters and associated excitotoxicity also mediate stroke-induced neurogenesis [223, 224].

In the post-ischemic brain newly generated cells from DG and SVZ have been shown to be capable of replacing dying neurons via directed migration toward areas of damage [225]. Studies have indicated that newly arrived neuroblasts in the ischemic boundary zones display phenotypes that are indeed characteristic of mature/functional neurons [160, 176, 181, 190, 191, 226-228]. The neural precursors that develop, transmigrate and integrate display an innate form of pathotropism [229, 230]. Work has come to suggest that EPO may promote neuroblast migration via the secretion of matrix metalloproteinases, MMP2 and MMP9, by EPO-activated endothelial cells [231]. Additional factors presumed to be involved in the progenitor cell migration to sites of injury are C-X-C motif chemokine 12/stromal cell-derived factor 1 (SDF-1)/its receptor CXCR4: stroke has been shown to upregulate penumbral SDF-1 and NSC/neuroblast CXCR4 expression [232-236]. Lastly, chemokine (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein-1 (MCP-1) has also been shown to regulate migration of neuroblasts to the areas of damage as the expression of MCP-1 has been localized to the activated microglia/astrocytes present in ischemic areas post reperfusion [237]; correspondingly, ischemia-induced migrating neuroblasts express the MCP-1 receptor CCR2 [237, 238].

The experimental evidence that has been put forth hitherto clearly suggests that ischemia stimulates neurogenesis in the adult brain. Recently reports have emerged which demonstrate that the endogenous neurogenic response following experimental stroke influences the course of recovery in both short and long-term settings [239, 240]. Although this evidence indicates that cerebral ischemia-induced neurogenesis may affect neurological recovery after stroke, it

is clear that such an endogenous repair response is far from ideal as patients continue to experience various levels of physical/cognitive morbidities post-injury [241-243]. In order to become a clinically valuable tool, the stroke induced neurogenic response will need to be markedly enhanced which requires consideration of ways to support/supplement the process. Understanding that the process of generating new neurons essentially consists of four phases: proliferation, migration, differentiation, and survival [89, 244] one might begin to design interventions that rationally target one or more of the aforementioned (e.g. therapeutics to prevent the death of the vast majority of neuroblasts) [176, 245]. Specifically, Kokaia et al. note “of particular importance for the promotion of neurogenesis and its functional benefit [will] be to increase the survival of stroke-induced neuroblasts and mature neurons [as the] the majority of new neuroblasts die soon after formation” [176, 245, 246].

3.2. Effects of multiple sclerosis on CNS neurogenic processes/niches

Multiple sclerosis is one of the most common causes of chronic neurologic disability beginning in early to middle adult life (median age of onset being 29 years of age) and is characterized by a triad of inflammation, demyelination and gliosis [247-249]. MS is idiopathic in nature yet is presumed to be driven by the complex interaction of autoimmunity, genetic predisposition, and environmental associations [248, 250]. MS affects approximately 400,000 people in the United States and 2.5 million worldwide [251]. Symptoms of MS have primarily been shown to result from a disruption in the integrity of myelinated tracts in the CNS [247, 252]. More recently research has also highlighted the underappreciated involvement of gray matter in MS pathogenesis, which may be especially relevant when one considers the development of irreversible disability [253, 254]. As such, the need to understand mechanisms governing endogenous stem cell/stem cell niches in MS is clearly justified.

Contrasting reports have emerged with regard to the activation of the SVZ and its cellular components in MS, in both the human disease state and in animal models. SVZ activation has been shown to be especially dependent on the temporal nature of the disease (i.e. acute vs. chronic inflammation) [163, 255, 256]. Such findings suggest that inflammation may be either advantageous or deleterious depending on the pathophysiologic context (see Table 2). In experimental autoimmune encephalomyelitis (EAE), the most widely used/accepted animal model of MS [257], alterations in SVZ NSC proliferation and mobilization have been demonstrated throughout the disease process [87, 163, 255, 258]. Such changes are concordant with other models of CNS injury (e.g. stroke) in which surviving cells that activate locally or infiltrate post-damage, secrete mediators that alter the neurogenic process [256, 259, 260]. Beyond the preclinical animal models, increases in SVZ activity have also been noted in humans with MS [261]. Further, enhanced proliferation has been found at the level of the hippocampal neurogenic niche in animal models of MS. However, the downstream network dynamics of these progenitors appears to be altered, leading to aberrant differentiation i.e. these EAE animals exhibited a significantly higher percentage of newborn radial-glia-like NSC yet the mean percentage of newborn/mature neurons was decreased [262, 263]. Such findings align with the clinical phenotypes/histopathology [264, 265] displayed by many human patients and correlate with findings on magnetic resonance imaging (MRI), which highlight

the existence of focal hippocampal hyperintensities [266] and hippocampal atrophy [267]. Of note, neurogenesis/gliogenesis in the spinal cord in various murine models of MS [46, 166, 268] and in human patients with MS [269] have also been demonstrated to occur. Although accumulating evidence indicates that endogenous neurogenesis/gliogenesis do occur as part of an intrinsic attempt at self-repair (i.e. oligodendrocyte precursors in the MS lesions of human patients) [270-272], it has become clear that the endogenous stem cell compartment's capacity for mobilization is unable to achieve meaningful restoration of impaired CNS function in the face of a chronic inflammatory disorder [46]. Data now suggest that inflammatory components, such as infiltrating blood-born mononuclear cells, reactive CNS-resident cells (i.e. astrocytes, endothelial cells and microglia), and humoral mediators such as cytokines/chemokines may be partially responsible for such an inadequate response as they can and do affect proliferation/differentiation of NSC [32, 46, 87, 163, 222, 256, 259, 273]. It is clear then, that the molecular mechanisms capable of inducing and/or inhibiting neurogenesis in the CNS of MS patients under defined spatiotemporal conditions warrant further investigation.

3.3. Effects of spinal cord injury on CNS neurogenic processes/niches

SCI is often induced by trauma and subsequently leads to both motor and sensory deficiencies [274]. Typically, such injuries manifest clinically in presentations of pain, anesthesia/paresis, fasciculations, and/or weakness [275]. In severe cases, SCI can lead to complete paralysis and/or result immediately in life threatening impairments to respiration, heart rate, and blood pressure [107, 108]. SCI pathophysiology is marked by a pathophysiology with a complex temporospatial profile, and is characterized by three phases: acute (seconds to minutes after injury), subacute (hours to weeks post-injury), and chronic (weeks to years post-injury) [276, 277]. During these phases the injured environment undergoes distinct biochemical and anatomical alterations, involving a diverse group of molecules and cells (i.e. nervous, immune, vascular) [276]. The acute phase is initiated by mechanical disruption which results in such insults as ischemia, edema, vasospasm, ionic/neurotransmitter imbalance and ultimately cell death [276]. Factors released during the acute phase result in secondary inflammatory degeneration, the hallmark of the subacute phase. During the subacute period, progressive neurodegeneration occurs as a result of the pro-inflammatory neurotoxic environment (driven by neutrophils, monocytes, microglia, T-cells) and results in the continued demyelination/Wallerian degeneration of damaged axons [276, 278-281]. Over the course of the same period, astrocytes become reactive in a process called astrogliosis which ultimately facilitates the formation of glial scar. This scar tissue poses a physical and chemical barrier to axonal regrowth, thus inhibiting regeneration [282-284]. On the other hand, this scar tissue aids in regeneration and repair by regulating the immune response, preventing the spread of neurotoxic factors, enabling partial reestablishment of homeostasis, and by providing neurotrophic support through enrichment of IGF, nerve growth factor (NGF), BDNF and neurotrophins (NT-3) [282-295]. The provision of these neuroprotective, neurogenic and regenerative cues (and others) is continued during the chronic phase in an effort to repair damaged axons. This effect is however limited, due to an inhibitory microenvironment created by the glial scar and the persistence of other secondary degeneration mechanisms referenced earlier [281, 296].

Interestingly, ependymal stem cells which are quiescent under physiological conditions become activated following SCI [39]. Evidence suggests a proliferative and pathotrophic NSC response. Such mitotic activation has also been observed *in vitro* through enhancement of neurosphere-formation capabilities post-injury [13, 114, 119, 152]. These proliferating ependymal cells show a transient increase in GFAP, S100b, nestin, and Pax6 expression [16, 297, 298]. The lineage potential of these transiently activated progenitors *in vivo* seems to be predominantly restricted to glial cells, namely astrocytes and oligodendrocytes [114, 119, 121]. As mentioned before, pericytes are another source of astrocytes during spinal cord injury [125]. Newly produced astrocytes function mainly in aiding the establishment of the glial scar [114, 119, 121]. Parenchymal NG2⁺ OPC are also activated and lead to oligodendrocyte differentiation. Newly produced oligodendrocytes participate in attempts to remyelinate injured axons [114]. Unfortunately, neuronal production has not yet been reported, and may be explained by the host of powerful pro-glial cues that emanate from the spinal cord [114, 119, 121, 299]; as a result functional recovery post-injury is modest at best.

4. Molecular characteristics of neural stem cell niches

“Look deep into nature, and then you will understand everything better.” – Albert Einstein

A wealth of molecular signals have been shown to influence NSC maintenance and neurogenesis via control of survival, self-renewal, activation of quiescent NSC and regulation of their proliferative expansion/differentiation. Cues that influence the behavior of NSC within the niche include autocrine, paracrine and endocrine factors, as well as direct cell-cell and cell-ECM contact [10, 300, 301]. A summarized overview of molecular signaling influencing NSC maintenance and neurogenesis is given in Table 1.

4.1. Growth factors

4.1.1. Fibroblast Growth Factors (bFGF) and Epidermal Growth Factors (EGF)

EGF and bFGF are factors necessary for *in vitro* growth and expansion of NSC [40]. They are produced by cells in the SVZ and induce proliferation in cells that reside in the subependymal layer lining the lateral ventricles of the forebrain [302, 303].

4.1.2. Hepatocyte Growth Factor (HGF)

HGF is also expressed in SVZ cells and has been shown to function as a survival factor for neuroblasts and cortical neurons while also increasing proliferation of SVZ cells [304, 305]. Furthermore, it has been shown that HGF has neuroprotective properties as it can reduce apoptosis in stress conditions, probably mediated by PI3K/Akt signaling [306, 307].

4.1.3. Vascular Endothelial Growth Factor (VEGF)

VEGF is important for angiogenesis and hematopoiesis [308-310]. However, VEGF receptors have also been found in the subependymal zone of the SVZ, the SGZ, and on NSC [311, 312]. It is secreted by endothelial cells, NSC, and astrocytes [313]. VEGF exerts indirect effects on NSC and neurogenesis by inducing angiogenesis thereby providing structural and trophic support [313]. It also operates directly via the promotion of proliferation and maintenance of NSC and neurogenesis [314, 315]. Furthermore, VEGF has been shown to be neuroprotective during disease and injury [316, 317].

4.1.4. Insulin-like Growth Factors (IGF)

IGF activate the PI3K/Akt signaling pathway, activating the target of rapamycin (TOR) kinase and FoxO transcription factors [318]. IGF-1 is expressed in various areas of the CNS, including hippocampus, olfactory bulbs, and cerebellum [319, 320]. Multiple knockout studies have indicated that IGF-1 is needed for maintaining proliferation and stem cell characteristics [321, 322].

4.1.5. Pigment-Epithelium Derived Growth Factor (PEGF)

PEGF was first identified as a factor that induces differentiation of retinoblastoma cells into a neuronal phenotype [323, 324]. It has been found to be expressed by retinal cells, adipocytes and hepatocytes, and also endothelial and ependymal cells in the adult brain [325]. Although NSC do not express these factors themselves, they are responsive to them. It has no effect on survival, but increases NSC self-renewal and activates quiescent subependymal cells [325]. It is believed that PEGF function is dependent on Notch signaling and keeps cells undifferentiated through upregulation of Hes1, Hes5, and Sox2 [325, 326].

4.1.6. Platelet-Derived Growth Factors (PDGF)

PDGF is produced by endothelial cells and binds PDGF receptor α (PDGFR α) on NSC whereby it regulates neurogenesis [327]. PDGF receptor β (PDGFR β) is expressed in brain pericytes, neurons and astrocytes and is implicated in neuroprotection after ischemic stroke [328].

4.2. Developmental factors and morphogens

4.2.1. Wingless-related integration site (Wnt) signaling

Wnt signaling pathways are major regulators of stem cell activity in the developing and adult brain, where it functions in both NSC maintenance and neurogenesis [300, 329-333]. These diverse and opposing functions are enabled by heterogeneous group of Wnt proteins that modulate canonical (involving β -catenin) and non-canonical signaling pathways with further regulation by a wide range of interaction partners and regulators [300, 334, 335]. Wnt3, for instance, is secreted by astrocytes and induces NSC proliferation and neurogenesis [333]. Wnt7b is regulated by retinoic acid and can expand the number of proliferating cells [336, 337]. The canonical pathway normally allows for an increase in cytoplasmic β -catenin, which

induces proliferation and inhibits differentiation. However, when factors such as homeodomain interacting protein kinase 1 (HipK1) are upregulated in the SVZ, the same pathway can induce differentiation [338]. Furthermore, in pathological conditions such as stroke and hypoxia, Wnt signaling has been shown to drive neurogenesis through NSC proliferation and differentiation. Interestingly, these activated cells divide symmetrically leading to NSC expansion, as opposed to the asymmetrical division that normally takes place in the subdymal zone [303, 339].

4.2.2. Bone Morphogenic Proteins (BMP)

BMP and their receptors are expressed by cells adjacent to the SVZ. They inhibit proliferation of neuroblasts while blocking neurogenesis and favoring gliogenesis [340]. Noggin is secreted by ependymal cells of the SVZ and SGZ and opposes the effect of BMP by binding and inactivating them thereby maintaining cell proliferation [340-342].

4.2.3. Sonic Hedgehog (Shh)

Activation of the Shh can increase proliferation of NSC. Shh receptors (Patched (Ptc)) can for instance be found in hippocampal regions such as the hilus and pyramidal cells in CA1-CA3 [343]. Shh also plays a role in maintenance of NSC pools in telencephalic niches [344].

4.3. Hormones

4.3.1. Erythropoietin (EPO)

Although mainly produced by the kidney, EPO and its receptor were found to be expressed in adult neurogenic regions, such as the SVZ and SGZ [210, 345]. Under hypoxic stress EPO expression is upregulated in the adult brain [346]. EPO affects NSC by increasing proliferation, increasing neurogenesis, and enhancing survival [202, 347-352]. Conditional knockouts of EPO have shown that it is a critical factor for proliferation [202]. Its promotion of survival operates by reducing apoptosis of NSC and their progeny [350, 352].

4.3.2. Insulin

Insulin is produced by beta cells of the pancreas. Controversial evidence now suggests that it is also produced by cultured neuronal and glial cells and in the hippocampus [353]. In general, it allows for survival, self-renewal and proliferation of NSC [353-357]. Insulin is able to replace EGF and bFGF *in vitro*, allowing for self-renewal and long-term passaging [354].

4.3.3. Adipocyte-derived leptin and adiponectin

Leptin and adiponectin enhance the survival of NSC *in vivo* and *in vitro* [358-362]. They activate the glycogen synthase kinase β (GSK β) signaling pathway in hippocampal NSC, allowing for accumulation of β -catenin and consequent promotion of proliferation of NSC [358, 359].

4.4. Cytokines

4.4.1. Leukemia Inhibitory Factor (LIF)

LIF is highly expressed in the adult injured brain, mediating inflammation and inducing NSC proliferation [363, 364]. LIF leads to an expansion of astrocytes while depleting neurons. Furthermore, it promotes NSC self-renewal rather than the generation of committed progenitors [364, 365]. Treatment of neurospheres with LIF *in vitro* increases the generation of secondary neurospheres [364].

4.4.2. Ciliary Neurotrophic Factor (CNTF)

CNTF receptor (CNTFR) expression is restricted to periventricular regions [365]. CNTF binding activates the LIF receptor/gp130 complex, enhancing maintenance, survival and self-renewal of NSC, while restricting differentiation of the glial lineage [366, 367]. Endogenous CNTF expression is upregulated after stroke and leads to increased proliferation of SVZ cells [204].

4.4.3. Stem Cell-Derived Neural Stem/Progenitor Cell Supporting Factor (SDNSF)

SDNSF is expressed in the DG of the hippocampus and is upregulated after ischemia. It has been shown to allow NSC to survive *in vitro* when bFGF is removed. Although cells maintain their self-renewal and differentiation potential, SDNSF alone does not promote proliferation [368].

4.4.4. C-X-C Motif Chemokine 12 (CXCL12)/Stromal Cell-Derived Factor 1 (SDF-1)

SDF-1 also known as CXCL12 is a chemokine produced by endothelial cells. It binds C-X-C motif receptor 4 (CXCR4) on NSC. It favors neurogenesis by driving survival and migration of neuronal and oligodendrocytic progenitors [369, 370]. After stroke, SDF-1 promotes migration and integration of new neurons, participating in functional recovery [371].

4.4.5. Macrophage Migration Inhibitory Factor (MIF)

Dendritic cells secrete MIF which mediates NSC expansion through the MIF receptor CD74, both *in vivo* and *in vitro* [372, 373].

4.4.6. Interleukin 1 (IL-1)

IL-1 α and IL-1 β have both been found to positively regulate neurogenesis [374, 375]. Interestingly, the effect of IL-1 β depends on its concentration. Under physiological conditions, it increases differentiation of neural progenitors, whereas it inhibits neurogenesis under high inflammatory concentrations [376-378].

4.4.7. Interleukin 6 (IL-6)

At low concentrations, IL-6 promotes differentiation of NSC to neurons, astrocytes and oligodendrocytes [379-381]. However, at high concentrations IL-6 has been shown to reduce neurogenesis [161].

4.4.8. Cytokines during inflammation

Inflammatory cytokines (pro/anti) are produced by activated immune cells (including leukocytes, lymphocytes, astrocytes, microglia, and endothelial cells) after disturbance of homeostasis or during pathology. These cytokines influences NSC maintenance and neurogenesis in a very heterogeneous and context dependent manner, summarized in Table 2 [382, 383].

4.5. Neurotransmitters

4.5.1. Glutamate

Glutamate acts on NSC through metabotropic glutamate receptors (mGluR). Although excitotoxic for neurons, high levels of glutamate have been shown to promote survival and proliferation of NSC in the SVZ and DG [384-389].

4.5.2. Gamma-aminobutyric acid (GABA)

GABA is non-synaptically released by neuroblasts after spontaneous depolarization. It has been shown to reduce proliferation of GFAP+ NSC, suggestive of a feedback system regulating the NSC population [390, 391].

4.5.3. Serotonin

Serotonin has been shown to positively influence survival, proliferation, and neurogenesis [392-396]. Serotonin receptors have been found in the SVZ and the DG [392]. Their activation increases neurogenesis and affects symmetric division of a specific population of NSC [395].

4.5.4. Dopamine

Adult NSC in the SVZ and the DG have receptors for dopamine. Activation of certain dopamine receptors can indirectly promote NSC survival and differentiation due to the activation of A-disintegrin and metalloproteinases (ADAM) and consequent release of membrane bound EGF [397, 398]. By contrast, activation of the dopamine D2 receptor on NSC inhibits their proliferation and neurogenesis in a CNTF-dependent manner [399, 400].

4.5.5. D-Serine

Although mainly produced by astrocytes, D-Serine has recently found to be expressed by neurons and NSC [401-408]. Although it does not enhance NSC expansion and neurogenesis, D-Serine is associated with NSC self-renewal and maintenance [409, 410].

4.5.6. Nitric oxide (NO)

NO is produced by neurons and inflammatory cells, but not NSC. Conflicting evidence exists on whether they stimulate or reduce SVZ and hippocampal NSC proliferation. It has been postulated that high NO concentrations promote proliferation, whereas low NO concentrations inhibit proliferation [411-413].

4.6. Extracellular matrix (ECM) components

Chondroitin sulfate proteoglycans (CSPG) are major constituents of the NSC niche ECM and play pivotal roles in the development, regeneration and plasticity of neuronal networks [414-416]. Enzymatic degradation of CSPG reduces self-renewal of NSC in the SVZ, as well as of neurospheres *in vitro* [417]. In other studies, however, degradation of CSPG resulted in increased NSC proliferation, differentiation and migration via an integrin-dependent mechanism [418]. These different outcomes may be the result of differences in the cell types being analyzed and further studies are needed to unravel the exact role of CSPG on adult NSC [418]. Heparan sulfate proteoglycans (HSPG) have also been implicated in the survival and proliferation of NSC, probably by interaction with bFGF [419, 420]. Sulfotransferases are expressed in adult neurogenic regions and in neurospheres and have been shown to be important for preserving the functional activity of CSPG and HSPG in NSC survival [421].

Laminins are other ECM components that can be found in NSC niches such as those in the SVZ [422]. Laminin receptors such as integrins, syndecans and dystroglycans can all be found expressed on NSC [423]. Notably, $\alpha 6 \beta 1$ integrins are expressed in high levels on proliferating NSC and progenitors [65, 424, 425]. Quiescent NSC do not express $\beta 1$ integrins; activation of NSC through daughter cell depletion or administration of CXCL12/SDF-1, however, leads to upregulation of $\beta 1$ integrins, showing the pivotal role of $\beta 1$ integrins in neurogenesis and NSC proliferation [425].

4.7. Direct cell-to-cell signals

4.7.1. Notch signaling

Notch is a membrane bound developmental factor and its signaling is of major importance in maintaining and expanding embryonic and adult NSC [426, 427]. Notch ligands such as Jagged and delta like ligand 4 (Dll4) are also membrane bound and regulate neurogenesis by stimulating NSC proliferation [428, 429]. Interestingly, NSC but not fate-restricted progenitors express Notch, a characteristic which has been used to distinguish between both populations [430, 431]. Progenitors communicate with NSC through Notch-epidermal growth factor receptor (EGFR) interactions, whereby regulating the balance between both cell populations in the SVZ. Enhanced EGFR signaling results in the expansion of the progenitor pool and reduces NSC numbers and their self-renewal [431]. Recent work also suggests that there is a strong interplay between Notch and Shh in regulating neurogenesis [432].

4.7.2. Ephrin signaling

Ephrin ligands and receptors are also membrane bound developmental factors. Ephrin A and B ligands and their receptors are expressed by NSC in the SVZ [433]. Ephrin signaling has been implicated in both proliferative and anti-proliferative effects on NSC [433-437]. They have been linked to NSC maintenance, survival, and inhibition of differentiation [438-441].

4.8. Neurotrophic Factors (NTF)

The NTF family includes BDNF, NGF, GDNF and NT-3, NT-4. They are important for differentiation, survival, and functioning of neurons in both the developing and adult brain [300]. NTF and their tropomyosin-related kinase (Trk) receptors are expressed in NSC. They have been shown to protect NSC against excitotoxicity and apoptosis during injury and to promote NSC differentiation [442-445].

4.9. Other factors

4.9.1. Apolipoprotein E (ApoE)

ApoE is a constituent of plasma lipoprotein particles. It has been found to be secreted by astrocytes *in vivo* and by neurospheres *in vitro*, contributing to neuritogenesis and maintenance of NSC in the DG [446-450].

Signaling factors	Source	Effect on NSC	References
Growth factors			
FGF	EC, A, CSF	Renewal, proliferation, differentiation, migration	[40, 302, 303]
EGF	EC, A, CSF	Renewal, proliferation, differentiation, migration	[40, 302, 303]
HGF	NSC	Survival, proliferation	[304-307]
VEGF	EC, NSC, A	Survival, renewal, migration	[308-317]
IGF	CSF	Renewal	[318-322]
PEGF	EC, NSC	Renewal	[323-326]
PDGF	EC	Survival, renewal	[327, 328]
Developmental factors			
Wnt signaling	A	Renewal, proliferation, differentiation*	[329-331, 333, 338, 339]
BMP	EC, A, CSF	Differentiation	[340-342]
Noggin	NSC	Renewal, proliferation	[340-342]
Shh	A, CSF	Renewal, proliferation, migration	[343, 344]
Hormones			
EPO	B, A, N	Survival, proliferation	[347-349, 351, 352,
Insulin	B	Survival, renewal, proliferation	451, 452]
Leptin/adiponectin	B	Proliferation	[353-357]

Signaling factors	Source	Effect on NSC	References
[358-362]			
Cytokines			
LIF	IC	Renewal, differentiation	[363, 364]
CNTF	IC	Survival, renewal, differentiation	[204, 366, 367]
SDNSF	IC	Survival, renewal	[368]
SDF-1	IC, EC, NSC	Survival, migration	[369-371]
MIF	IC	Proliferation	[372, 373]
IL-1	IC	Differentiation	[374-378]
IL-6	IC	Differentiation	[161, 379, 380]
Neurotransmitters			
Glutamate	N	Survival, proliferation, differentiation	[384, 385, 387-389]
GABA	N, NB	Proliferation**, differentiation, migration	[391, 453]
Serotonin	N	Survival, proliferation	[392-396]
Dopamine	N	Survival, proliferation, differentiation	[397, 399, 400]
D-Serine	A, N, NSC	Renewal	[401-405, 407, 410]
NO	N, IC	Proliferation*	[411-413]
Extracellular matrix			
CSPG		Survival, renewal	[415-418, 454, 455]
HSPG		Survival, renewal	[419, 420]
Laminins		Survival, proliferation*	[65, 424, 425]
Direct cell-to-cell signals			
Notch	NSC	Renewal*, proliferation*	[426, 429-432]
Ephrin	NSC	Renewal*, proliferation*	[433-439, 441]
Neurotrophic factors			
BDNF, NGF, GDNF, NT-3, NT-4	NSC, A, EC	Survival, renewal, proliferation differentiation	[442-444]
Others			
ApoE	A	Renewal, differentiation	[446, 447, 449, 450]

Abbreviations: bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; IGF, insulin-like growth factor; PEGF, pigment-epithelium derived growth factor; PDGF, platelet-derived growth factors; Wnt, wingless-related integration site; BMP, bone morphogenic proteins; Shh, sonic hedgehog; EPO, erythropoietin; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; SDNSF, stem cell-derived neural stem/progenitor cell supporting factor; SDF-1, stromal cell-derived factor 1; MIF, macrophage migration inhibitory factor; IL-1, interleukin 1; IL-6, interleukin 6; TNF- α , tumor necrosis factor α ; GABA, gamma-Aminobutyric acid; NO, nitric oxide; CSPG, chondroitin sulfate proteoglycans; HSPG, heparan sulfate proteoglycans; NTF, neurotrophic factors; BDNF, bone-derived neurotrophic factor; NGF, nerve growth factor; GDNF, glial cell-line derived neurotrophic factor; NT, neurotrophin; A, astrocytes; B, blood; CSF, cerebrospinal fluid; EC, endothelial cells; IC, immune cells; N, neurons; NB, neuroblasts; NSC: neuronal stem cells. * context dependent; ** of progenitors, not stem cells.

Table 1. Molecular Components of the Niche Environment

Soluble factors	Role in NSC biology	Cell sources	Pathological models	Ref
CCL5	NSC proliferation↑	Reactive astrocytes, activated lymphocytes, microglia/macrophages	Entorhinodentate lesions; axonal degeneration (<i>in vivo</i>).	[456-458]
CXCL12/SDF1α	NSC migration↑	Reactivated astrocytes, activated endothelial cells, meningeal cells	Hypoxic–Ischemic (HI) Cerebral Injury; multiple sclerosis; stroke	[459-462]
CX3CL1	NSC proliferation↑	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	Neurospheres, hippocampal slice cultures (<i>in vitro</i>)	[458]
CCL11	NSC proliferation↓ differentiation ↓	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	Aging model	[463]
IFN-α	NSC proliferation↓	Plasmacytoid dendritic cells, activated macrophages, endothelial cells, neurons	Young and old Cr2(-/-) mice	[464]
IL-1β	Neuronal fate (dopaminergic neurons)	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	Tyrosine hydroxylase (TH)-induced immunoreactivity (<i>in vitro</i>)	[465-467]
IFN-γ	NSC proliferation↓	T cells (Th1), natural killer cells	Experimental allergic encephalomyelitis (EAE)	[468, 469]
IL-6 family of neurotrophic cytokines (LIF, CNTF, CT-1)	(Astro)glial differentiation	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	Cortical precursor culture (<i>in vitro</i>)	[465, 470]
IL-4	NSC migration↑ differentiation↑	T cells (Th2), through effect on microglia/macrophages	EAE related chemokines treatment (<i>in vitro</i>)	[471, 472]
IL-10	NSC migration↑	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	EAE related chemokines treatment (<i>in vitro</i>)	[472]
IL-15	NSC proliferation↑	Activated microglia	IL-15–/– mice	[473]
TNF-α	NSC proliferation↓	Activated microglia/ macrophages	EAE; TNF-R1(-/-),TNF-R2(-/-) and TNF-R1/R2(-/-) mice. Lipopolysaccharide (LPS)-stimulation (<i>in vitro</i>).	[468, 474, 475]

Abbreviations: CC/CXC, chemokines; SDF1α, stromal cell-derived factor 1α; IFN, interferon; IL, interleukin; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin-1; LIF, leukaemia inhibitory factor; TNF-α, tumor necrosis factor α.

Table 2. The Influence of Inflammatory Mediators on NSC [382, 383]

5. Therapeutic modulation of the neural stem cell niche

Due to the indispensable role of the niche microenvironment in regulating NSC (e.g. control of the maintenance, expansion and differentiation), different molecular strategies have been investigated in an effort to modulate the NSC response and in so doing enhance neurogenesis. Such work has the potential to benefit a myriad of degenerative neurological disorders by facilitating repair and aiding in functional recovery. Most prominent are approaches using novel pharmacological targets within NSC niches [50]. Rational engineering of the niche must also be considered as an approach for CNS homeostasis and repair [476]. This section will therefore focus both on selected drugs that have been shown capable of modulating the niche and on current efforts geared toward the engineering of microenvironments to support enhanced/sustained niche homeostasis.

5.1. Molecular therapies

Various endogenous regulators of NSC have been investigated for their therapeutic value with regard to neurogenesis. Intraventricular administration of exogenous EGF, PEDF, HGF and CNTF in mice has been shown to enhance NSC proliferation [305, 325, 366, 477]. Additionally, the peripheral administration of human recombinant EPO (hrEPO) has been shown to enhance neurogenesis and improve functional outcome in models of both ischemic stroke and traumatic injury. It is unlikely, however, that such effects can be solely attributed to the enhancement of neurogenesis, being that hrEPO has also been demonstrated to suppress inflammation and induce angiogenesis [478]. Administration of other factors such as RA, bFGF, EGF, BDNF and VEGF have also been shown to enhance neurogenesis in similar disease models ultimately leading to enhanced recovery [177, 213, 311, 479-483]. Despite the plethora of positive effects demonstrated in animal models, many of these endogenous factors have been difficult to translate into clinical use due to invasive routes of administration, off target physiologic effects, cost of recombinant factors, etc.

5.2. FDA approved small molecules

Certain small molecules have been shown to exert similar effects via the direct or indirect modification of endogenous cues. Briefly, certain antidepressants have been shown capable of increasing the neurogenic response [484, 485]. As an example, *Fluoxetine* (a selective serotonin reuptake inhibitor) has been shown to give rise to maturation of immature neurons and enhanced neurogenesis [486]. Whether this function is mediated through an increase in 5-HT receptor activation on NSC remains unclear [395]. However, it is prudent to note that the clinical benefits of such typical antidepressant drugs are only partly dependent on neurogenesis [487]. Antipsychotic drugs have also been associated with neurogenesis, yet the precise mechanisms of action remain unclear. The antipsychotic drug *Haloperidol* (D2 receptor antagonist) has been shown to reverse dopamine-induced inhibition of NSC proliferation [399]. Similar effects have also been observed for other antipsychotics including *Clonazepam* and *Risperidone* [409, 488-490]. GABA has been observed to have a negative influence on NSC proliferation and migration [491-493] and so it should not be surprising that GABA-based

treatments, such as *Phenobarbital* and *Clonazepam* have been shown to inhibit cell proliferation in the DG of the hippocampus [494, 495]. In contrast, pharmacological inhibition of GABA receptors via such agents as *Bicuculline* (i.e. GABA antagonists) can enhance NSC proliferation and differentiation, thereby positively influencing neurogenesis [489, 490].

As discussed above, behavior of NSC is largely regulated by signals from the niche under physiological and pathological conditions. Small molecules capable of altering NSC niche function may provide a tool for modulation of NSC and neurogenesis in disease states and concurrently open up novel experimental routes for the investigation of mechanisms of niche activation.

5.3. Therapeutic stem cell transplantation in CNS diseases and the development of atypical neural stem cell niches

The therapeutic benefits of stem cell transplantation in modulating CNS disease processes have been supported by a multitude of reports. Yet, the therapeutic efficacy appears to be most pronounced in disorders that display key components of inflammation (i.e. multiple sclerosis, stroke and spinal cord injury) [87, 301, 496]. It is relevant to note that this effect is not limited to direct delivery (i.e. focal), but has also been reported after systemic or subcutaneous injection of stem cells [87, 496, 497]. While NSC have the potential to integrate into the host system and may contribute to replacement of damaged cells, other somatic stem cells such as hematopoietic stem cells (HSC), mesenchymal stem cells (MSC), and umbilical cord cells also allow for functional recovery in mouse models of inflammatory degeneration [87, 496, 498-502]. This suggests that the therapeutic effect of stem cells goes beyond mere cell integration, differentiation, and replacement and involves a “shared stemness-related” functional signature.

Transplanted NSC migrate toward well-defined areas in the inflamed perivascular microenvironment [503, 504]. This leads to the establishment of ectopic stem cell niches, also called atypical niches, which are molecularly reminiscent of prototypical germinal niches and regulate the long-term survival and the behavior of NSC [503, 505, 506]. The term “therapeutic plasticity” has been suggested to describe the remarkable inherent flexibility of NSC to migrate to inflamed CNS areas and establish atypical ectopic stem cell niches through which they modulate their environment in support of a therapeutically beneficial outcome [496, 507]. This modulatory capacity is exerted through regulated cross-talk of NSC with other components of the atypical niche, including endothelial cells, blood-born inflammatory cells, activated macrophages and microglia, and reactive astrocytes [301, 496]. A myriad of cell-to-cell signaling pathways allows for this NSC-driven pathophysiologic modulation and enhanced clinical recovery [301, 496, 499, 508, 509].

The preferential migration of NSC toward CNS lesions is referred to as pathotropism. During an insult (e.g. hypoxia or injury) cytokines cause a subsequent activation of microglia, astrocytes and endothelial cells [46, 510]. As a result, reactive astrocytes and activated endothelial cells produce chemokines such as SDF-1, MCP-1, and VEGF that function collectively as a homing beacon, not only for inflammatory cells, but also for NSC [301, 510-514]. Much like leukocytes, NSC express adhesion molecules (CD44), integrins ($\alpha 4 \beta 1$) and chemokine receptors (CCR1, CCR2, CCR5, CXCR3, CXCR4). This enables NSC to follow the concentration

gradient of these chemokines toward the inflamed parenchyma and extravasate in a process of tethering, rolling and adhering to endothelial cells followed by transendothelial migration [183, 503, 515-517]. Factors such as bFGF and IGF-1 are also produced by activated astrocytes and support NSC proliferation, survival and differentiation [510, 511, 518]. Conversely, hypertrophic GFAP-enriched astrocytes of the glial scar produce factors such as slit homologue 2 (SLIT2), TNF- α and hyaluronan that repel NSC and limit the regenerative potential of their progeny [510, 511, 519, 520].

Once an atypical niche is established, undifferentiated NSC survive in the perilesional region in close proximity to activated microglia (expressing ionized calcium-binding adapter molecule 1 (IBA)) and to blood vessels [502, 521, 522]. The mechanisms by which transplanted NSC remodel the injured nervous system is irrespective of the experimental disease characteristics (e.g. focal vs. multifocal) and only a small number of cells undergo final differentiation [522-524]. When migrating to the lesional parenchyma, NSC contribute to cell replacement, mainly by differentiating into astrocytes, but also into neurons [522, 525, 526]. More striking, however, are the “bystander” capacities of undifferentiated NSC, which include the provision of trophic support and the modulation of the immune response. These beneficial effects lead to the establishment of a homeostatic environment [382, 496, 497, 524, 527]. In models for MS and stroke this has been shown to mediate efficient myelin repair and axon rescue [515, 525, 526, 528-531].

Trophic and neuroprotective effects are exerted by providing neurotrophins, growth factors, developmental stem cell regulators, and immune modulators through modulation of the microenvironment [301, 382, 496]. In models for MS, systemically administered NSC have shown to stimulate OPC proliferation and differentiation, and consequent remyelination through secretion of PDGF-A and bFGF [515, 528]. In models for stroke, focally injected NSC have been shown to enhance expression of BDNF, GDNF, CNTF, bFGF, VEGF, HGF, and IGF in the perilesional region [525, 526]. Finally, focal grafting of NSC in SCI models has been shown to support growth of motor and sensory axons due to upregulation of NGF, BDNF, and GDNF [532].

Transplantation of stem cells enables the switch to a more conservative and anti-inflammatory lesional environment [87, 301, 498]. In models for MS, NSC drive the reduction of perivascular infiltrates and CD3⁺ T-cells and the increase of regulatory CD25⁺ or CD25⁺/CD62L⁺ T-cells, accompanied by a downregulation of inflammatory markers, intercellular adhesion molecule 1 (ICAM-1), and lymphocyte function-associated antigen 1 (LFA-1) [503, 533]. *In vitro* studies have shown that NSC can 1) induce apoptosis of Th1 and Th17, but not Th2 lymphocytes through Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL) and Apo-3 ligand (APO3L), 2) reduce T-cell proliferation through nitric oxide and prostaglandin E2 (PGE2), 3) reduce T-cell receptor (TCR) dependent T-cell activation, 4) inhibit interleukin 2 (IL-2) (T-cell) and IL-6 (B-cell) signaling, and 5) reduce local populations of monocytes and macrophages through cytotoxic TNF- α secretion [503, 505, 506, 533-539]. Immune-modulating capabilities have also been shown in models for stroke, and include an increase of VEGF, SDF-1 and TGF- β , as well as a reduced expression of pro-inflammatory genes *lfn*, *TNF- α* , *il1b* and *Lepr* [502, 529]. Furthermore, NSC-induced increases in activated microglia (CD11b⁺) have been shown

to lead to IGF-1, VEGF, TGF- β , and BDNF production, yielding better motor function and axonal sprouting, highlighting the beneficial role of microglia [529-531]. However, other studies have shown that NSC transplantation reduced microglia/macrophage presence with improvement of both neuronal survival and locomotor functions [502, 540]. Models for SCI also show a skewing of microglia/macrophage infiltrates. Here, focally transplanted NSC have been shown to make cellular junctions (Connexin 43) with phagocytic cells and astrocytes, and to reduce the presence of classically-activated pro-inflammatory M1 macrophages [522].

Grafted stem cells do not only home to the the inflamed CNS, but also to the secondary lymphoid organs where they modulate inflammation [505, 506, 540, 541]. NSC hinder the activation of myeloid dendritic cells (DC), limiting the expansion of antigen-specific encephalogenic T-cells. DC maturation is hindered, partially due to secretion of BMP-4. Furthermore, induced secretion of BMP-4/7, Shh and Noggin by transplanted NSC and immune cells, promoted survival of endogenous NSC [505, 506, 541]. An increase in the presence of LIF leads to a reduction of Th17 differentiation, further ameliorating the functional outcome of MS. In stroke models, a reduction of both neutrophil infiltration and activation of macrophages in lymphoid organs can be observed after NSC transplantation [540].

In an effort to translate these therapeutic approaches to clinic, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSC) created from human fibroblasts have been studied for their neurogenic and neuroprotective properties after MS, stroke and SCI. Although some differences can be observed, e.g. higher cytotoxic potential against monocytes and lower cytotoxic potential against T-cells, human-derived cell functions are largely similar to those of animal-derived cells and they also increase clinical recovery. The therapeutic use of these cells is however limited by ethical constraints, genetic instability, and tumorigenicity [505, 538, 539, 542-545].

The therapeutic value of stem cell grafts, especially NSC, in inflammatory neurodegenerative disorders has become increasingly evident. Transplanted stem cells are able to home to the lesion areas where they take part in the establishment of an atypical perivascular niche, allowing stem cells to survive undifferentiated and to provide neurotropic support, modulate the inflammation, and allow for further migration into the lesional parenchyma to take part in neuronal differentiation and cell replacement. This has been shown to modulate the pathophysiology of disease, enhancing axonal conservation and regeneration, leading to increased functional recovery in animal models of MS, stroke and SCI.

5.4. Engineering the NSC niche

Approaches for niche engineering are centered around efforts to mimic multiple aspects of the niche microenvironment, which include architectural, mechanical, bioactive and growth factor cues [476]. ECM mimicking scaffolds support the survival and differentiation of transplanted NSC [546, 547]. Clearly, an understanding of ECM architecture is important in the designing of these scaffolds and to this extent studies have shown a correlation between scaffold fiber diameter and NSC behavior. For example, fibers with a 283nm diameter promote proliferation and differentiation to oligodendrocytes while fibers within 749-1452nm diameter range promote neuronal differentiation [548]. Apart from the 3D structure, the mechanical properties

of scaffolds have been shown to modulate morphology, proliferation, and differentiation of stem cells [549]. Polyethylene glycol (PEG) – poly-L-lysine (PLL) hydrogels allow for good NSC migration when their elastic modulus mimics that of brain tissue. Gels with a higher elastic modulus, on the other hand, limit migration [550]. Other studies have demonstrated that softer substrates promote neuronal differentiation whereas more rigid substrates induce glial differentiation [551]. Bioactive polymers such as those made from the laminin-1-derived IKVAV peptide further promote neuronal differentiation [552]. When seeded with NSC and transplanted into animal models of spinal cord injury, these structures have stimulated a marked enhancement in functional recovery [553]. Bioactive polymers which include tripeptide Arg-Gly-Asp (RGD) motifs showed promotion of cell attachment, self-renewal and differentiation [554]. Additionally, incorporation of signaling molecules relevant to NSC regulation can also positively influence the behavior of cells within these scaffolds [555]. Wnt and Notch ligands keep cells in a proliferative, undifferentiated state while the addition of BMP-4 enhances glial and neuronal differentiation [551]. Altogether, niche engineering represents a promising approach for regenerative medicine, as it enables control over the behavior of transplanted NSC, and may soon come to have vast therapeutic value.

6. Concluding remarks and future directions

“As long as our brain is a mystery, the universe, the reflection of the structure of the brain will also be a mystery.”—Santiago Ramón y Cajal

The presence of neural stem cells/neurogenic niches in the adult mammalian central nervous system has been clearly established by a body of rigorous scientific work. The functional significance of adult neurogenesis continues to grow as new studies describe its critical roles in states of both health and disease. Despite this growing body of information and improvements in our understanding of NSC and niche functions in both the physiologic/pathologic conditions, several critical questions remain. Chief among them is the relevance of the basic biology that has so far been described in animal models to the ultimate goal of translating adult neurogenesis into clinical trials. Further work with regard to the definitive nature/location of NSC needs also to be carried out. Finally the definitive molecular mechanisms that influence endogenous stem cell migration/pathotropism will also be key in helping to develop suitable treatments and strategies to prevent, mitigate, and treat varied CNS injuries and disease.

Abbreviations

SVZ-subventricular zone

SGZ-subgranular zone

NSC – neural stem/precursor cells

CNS – central nervous system

NPC – neural progenitor cells

OPC-Oligodendrocyte precursor cells

GFAP – glial fibrillary acidic protein

Sox2 – SRY (sex determining regionY) – box2

Oct4 – octamer-binding transcription factor 4

FoxO – Forkhead box

BrdU – bromodeoxyuridine

DCX – doublecortin

PSA-NCAM-polysialylated-neural adhesion molecule

SCs – stem cells

CC – central canal

CVO-circumventricular organs

ECM-extracellular matrix

DG-dentate gyrus

RMS-rostral migratory stream

5-HT – 5-hydroxytryptamine

GCL-granule cell layer

RGL-glial-like cells

IML-inner molecular layer

Shh-Sonic hedgehog signaling

VEGF-vascular endothelial growth factor

IGF-insulin-like growth factor

BDNF-brain-derived neurotrophic factor

CA – cornu ammonis region

CSF – cerebrospinal fluid

BLBP-brain lipid-binding protein

NeuN – neuronal nuclear antigen

Olig2⁺-oligodendrocytes

CD133 – prominin 1

ALDH1L1-aldehyde dehydrogenase 1 family member, L1

GLAST-glutamate aspartate transporter

RC2-radial glial cell marker-2

NG2-neuron-glial antigen 2

A2B5 – A2B5 antigen

PDGFR-platelet-derived growth factor receptor

GABA-gamma-aminobutyric acid

RA-retinoic acid

bFGF – basic fibroblast growth factor

CXCL12 –chemokine (C-X-C motif) ligand 2

MIP2-alpha – macrophage inflammatory protein 2-alpha

MAP-microtubule-associated protein

CSPG4-chondroitin sulfate proteoglycan

MS – multiple sclerosis

SCI – spinal cord injury

O₂ - oxygen

ATP-adenosine triphosphate

EGF – epidermal growth factor

GDNF – glia cell-derived neurotrophic factor

BMP – bone morphogenic protein

CNTF-ciliary neurotrophic factor

TGF – transforming growth factor

EPO – erythropoietin

G-CSF-granulocyte-colony stimulating factor

MMP – matrix metalloproteinase

SDF-1 – stromal cell derived factor-1

CXCR4 – chemokine receptor type 4

CCL2 – chemokine (C-C motif) ligand 2

MCP-1-monocyte chemoattractant protein-1

EAE-experimental autoimmune encephalomyelitis

MRI-magnetic resonance imaging

NGF-nerve growth factor

NT – neurotrophin

HGF – hepatocyte growth factor

TOR – target of rapamycin

PEGF – pigment-epithelium derived growth factor

PDGF – platelet-derived growth factors

PDGFR – platelet-derived growth factor receptor

Wnt – wingless-related integration site

HipK1-homeodomain interacting protein kinase 1

Ptc – Patched

GSK β -glycogen synthase kinase β

LIF – leukemia inhibitory factor

CNTFR-ciliary neurotrophic factor receptor

SDNSF – stem cell-derived neural stem/progenitor cell supporting factor

MIF – macrophage migration inhibitory factor

IL – interleukin

TNF- α – tumor necrosis factor α

TNFR-tumor necrosis factor receptor

mGluRs-metabotropic glutamate receptors

ADAM – A-disintegrin and metalloproteinase

NO-nitric oxid

CSPGs – chondroitin sulfate proteoglycans

HSPGs – heparan sulfate proteoglycans

Dll4 – delta like ligand 4

EGFR – epidermal growth factor receptor

NTF – neurotrophic factor

NT – neurotrophin

Trk-tropomyosin-related kinase

ApoE – apolipoprotein E

PEDF – pigment epithelium-derived factor

hrEPO – human recombinant erythropoietin
HSC-hematopoietic stem cells
MSC – mesenchymal stem cells
CCR, CXCR – chemokine receptor
SLIT2-slit homologue 2
IBA-ionized calcium-binding adapter molecule 1
PDGF-A – platelet derived growth factor-A
ICAM-1 – intercellular adhesion molecule 1
LFA-1 – lymphocyte function-associated antigen 1
FasL – fas ligand
TRAIL – tumor necrosis factor related apoptosis inducing ligand
APO3L-Apo-3 ligand
PGE2 – prostaglandin E2
TCR – reduced T-cell receptor
hESCs-human embryonic stem cells
iPSC-induced pluripotent stem cells
PEG – polyethylene glycol
PLL – poly-L-lysine
IKVAV-isoleucine-leucine-valine-alanine-valine
RGD – tripeptide-Arg-Gly-Asp

Acknowledgements

No conflicts of interest to disclose. The authors wish to thank Dr. Lee-Wickner and Mr. Connor Caples for their critical reading of the chapter. The authors would also like to thank Ms. Alicia Livinski for assistance with the literature review.

This work was supported by grants from the National Multiple Sclerosis Society (NMSS; RG-4001-A1 to SP), the Italian Multiple Sclerosis Foundation (FISM; RG 2010/R/31 to SP), the Italian Ministry of Health (GR08/7 to SP) the European Research Council (ERC) 2010-StG (RG 260511-SEM_SEM to SP), the European Community (EC) 7th Framework Program (FP7/2007-2013; RG 280772-iONE to SP), The Evelyn Trust (RG 69865 to SP). Additionally, JH was supported by the Intramural Research Program of NINDS/NIH. JB was supported by a NIH-OxCam fellowship. BH was supported by the China Scholarship Council (No.201306320024).

Author details

Joshua Bernstock^{1,2}, Jeroen Verheyen¹, Bing Huang¹, John Hallenbeck² and Stefano Pluchino¹

*Address all correspondence to: spp24@cam.ac.uk

1 John van Geest Centre for Brain Repair and Wellcome Trust-Medical Research Council Stem Cell Institute, Dept. of Clinical Neurosciences, University of Cambridge, Cambridge, UK

2 Stroke Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health (NINDS/NIH), USA

All authors contributed equally to this work.

References

- [1] Chklovskii DB, Mel BW, Svoboda K. Cortical rewiring and information storage. *Nature*. 2004;431(7010):782-8.
- [2] Brus M, Keller M, Levy F. Temporal features of adult neurogenesis: differences and similarities across mammalian species. *Frontiers in neuroscience*. 2013;7:135.
- [3] A A-B, DG H, H W. The subventricular zone: source of neuronal precursors for brain repair. *Prog Brain Res*. (0079-6123):1-11.
- [4] Gage FH. Isolation, Characterization, and use of Stem Cells from the CNS. *Annu Rev Neurosci*. 1995:159-92.
- [5] Kirschenbaum B, Doetsch F, Lois C, Alvarez-Buylla A. Adult subventricular zone neuronal precursors continue to proliferate and migrate in the absence of the olfactory bulb. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1999;19(6):2171-80.
- [6] Luskin MB, Zigova T, Soteres BJ, Stewart RR. Neuronal progenitor cells derived from the anterior subventricular zone of the neonatal rat forebrain continue to proliferate in vitro and express a neuronal phenotype. *Molecular and cellular neurosciences*. 1997;8(5):351-66.
- [7] Altman J, Das GD. Autoradiographic and Histological Evidence of Postnatal Hippocampal Neurogenesis in Rats. *The Journal of comparative neurology*. 1965;124:319-36.
- [8] 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. *The Journal of comparative neurology*. 1966;126:337-90

- [9] Bellenchi GC, Volpicelli F, Piscopo V, Perrone-Capano C, di Porzio U. Adult neural stem cells: an endogenous tool to repair brain injury? *Journal of neurochemistry*. 2013;124(2):159-67.
- [10] Decimo I, Bifari F, Krampera M, Fumagalli G. Neural stem cell niches in health and diseases. *Current Pharmaceutical Design*. 2012;18(13):1755-83.
- [11] Morrison SJ, Shah NM, Anderson DJ. Regulatory mechanisms in stem cell biology. *Cell*. 1997;88(3):287-98.
- [12] Weiss S, Dunne C, Hewson J, Wohl C, Wheatley M, Peterson AC, et al. Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1996;16(23):7599-609.
- [13] Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J. Identification of a neural stem cell in the adult mammalian central nervous system. *Cell*. 1999;96(1):25-34.
- [14] Yamamoto S, Yamamoto N, Kitamura T, Nakamura K, Nakafuku M. Proliferation of parenchymal neural progenitors in response to injury in the adult rat spinal cord. *Experimental neurology*. 2001;172(1):115-27.
- [15] Shihabuddin LS, Ray J, Gage FH. FGF-2 is sufficient to isolate progenitors found in the adult mammalian spinal cord. *Experimental neurology*. 1997;148(2):577-86.
- [16] Yamamoto S, Nagao M, Sugimori M, Kosako H, Nakatomi H, Yamamoto N, et al. Transcription factor expression and Notch-dependent regulation of neural progenitors in the adult rat spinal cord. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(24):9814-23.
- [17] Gross CG. Neurogenesis in the adult brain: death of a dogma. *Nat Rev Neurosci*. 2000;1(1):67-73.
- [18] Shihabuddin LS, Horner PJ, Ray J, Gage FH. Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(23):8727-35.
- [19] Horner PJ, Power AE, Kempermann G, Kuhn HG, Palmer TD, Winkler J, et al. Proliferation and differentiation of progenitor cells throughout the intact adult rat spinal cord. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(6):2218-28.
- [20] Lendahl U, Zimmerman LB, McKay RD. CNS stem cells express a new class of intermediate filament protein. *Cell*. 1990;60(4):585-95.

- [21] Doetsch F. The glial identity of neural stem cells. *Nature neuroscience*. 2003;6(11):1127-34.
- [22] Sakakibara S, Imai T, Hamaguchi K, Okabe M, Aruga J, Nakajima K, et al. Mouse-Musashi-1, a neural RNA-binding protein highly enriched in the mammalian CNS stem cell. *Developmental biology*. 1996;176(2):230-42.
- [23] Ellis P, Fagan BM, Magness ST, Hutton S, Taranova O, Hayashi S, et al. SOX2, a persistent marker for multipotential neural stem cells derived from embryonic stem cells, the embryo or the adult. *Dev Neurosci*. 2004;26(2-4):148-65.
- [24] Lothian C, Prakash N, Lendahl U, Wahlstrom GM. Identification of both general and region-specific embryonic CNS enhancer elements in the nestin promoter. *Experimental cell research*. 1999;248(2):509-19.
- [25] Garcia-Verdugo JM, Ferron S, Flames N, Collado L, Desfilis E, Font E. The proliferative ventricular zone in adult vertebrates: a comparative study using reptiles, birds, and mammals. *Brain research bulletin*. 2002;57(6):765-75.
- [26] Tavazoie M, Van der Veken L, Silva-Vargas V, Louissaint M, Colonna L, Zaidi B, et al. A specialized vascular niche for adult neural stem cells. *Cell stem cell*. 2008;3(3):279-88.
- [27] Shen Q, Goderie SK, Jin L, Karanth N, Sun Y, Abramova N, et al. Endothelial cells stimulate self-renewal and expand neurogenesis of neural stem cells. *Science*. 2004;304(5675):1338-40.
- [28] Chojnacki A, Weiss S. Pigment epithelium-derived growth factor: modulating adult neural stem cell self-renewal. *Nature neuroscience*. 2009;12(12):1481-3.
- [29] Scott IS, Morris LS, Bird K, Davies RJ, Vowler SL, Rushbrook SM, et al. A novel immunohistochemical method to estimate cell-cycle phase distribution in archival tissue: implications for the prediction of outcome in colorectal cancer. *The Journal of pathology*. 2003;201(2):187-97.
- [30] Cai Y, Xiong K, Chu Y, Luo DW, Luo XG, Yuan XY, et al. Doublecortin expression in adult cat and primate cerebral cortex relates to immature neurons that develop into GABAergic subgroups. *Experimental neurology*. 2009;216(2):342-56.
- [31] Nacher J, Lanuza E, McEwen BS. Distribution of PSA-NCAM expression in the amygdala of the adult rat. *Neuroscience*. 2002;113(3):479-84.
- [32] Pluchino S. Typical and Atypical Neural Stem Cell Niches. *Electronic Journal of Biology*. 2008;4(2):68-78.
- [33] Kempermann G. Adult neurogenesis : stem cells and neuronal development in the adult brain. New York: Oxford University Press; 2006. x, 426 p. p.
- [34] Hugnot JP. The Spinal Cord Neural Stem Cell Niche. In: Sun T, editor. *Neural Stem Cells and Therapy*: InTech; 2012.

- [35] Gould E. How widespread is adult neurogenesis in mammals? *Nat Rev Neurosci.* 2007;8(6):481-8.
- [36] Kondo T, Raff M. Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science.* 2000;289(5485):1754-7.
- [37] Palmer TD, Markakis EA, Willhoite AR, Safar F, Gage FH. Fibroblast growth factor-2 activates a latent neurogenic program in neural stem cells from diverse regions of the adult CNS. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 1999;19(19):8487-97.
- [38] Laywell ED, Rakic P, Kukekov VG, Holland EC, Steindler DA. Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. *Proceedings of the National Academy of Sciences of the United States of America.* 2000;97(25):13883-8.
- [39] Panayiotou E, Malas S. Adult spinal cord ependymal layer: a promising pool of quiescent stem cells to treat spinal cord injury. *Frontiers in physiology.* 2013;4:340.
- [40] Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science.* 1992;255(5052):1707-10.
- [41] Miyata T, Kawaguchi A, Okano H, Ogawa M. Asymmetric inheritance of radial glial fibers by cortical neurons. *Neuron.* 2001;31(5):727-41.
- [42] Merkle FT, Mirzadeh Z, Alvarez-Buylla A. Mosaic organization of neural stem cells in the adult brain. *Science.* 2007;317(5836):381-4.
- [43] Bonfanti L, Peretto P. Radial glial origin of the adult neural stem cells in the subventricular zone. *Progress in neurobiology.* 2007;83(1):24-36.
- [44] Peretto P, Giachino C, Aimar P, Fasolo A, Bonfanti L. Chain formation and glial tube assembly in the shift from neonatal to adult subventricular zone of the rodent forebrain. *The Journal of comparative neurology.* 2005;487(4):407-27.
- [45] Eckenhoff MF, Rakic P. Radial organization of the hippocampal dentate gyrus: a Golgi, ultrastructural, and immunocytochemical analysis in the developing rhesus monkey. *The Journal of comparative neurology.* 1984;223(1):1-21.
- [46] Martino G, Pluchino S. The therapeutic potential of neural stem cells. *Nat Rev Neurosci.* 2006;7(5):395-406.
- [47] Baizabal JM, Furlan-Magaril M, Santa-Olalla J, Covarrubias L. Neural stem cells in development and regenerative medicine. *Archives of medical research.* 2003;34(6):572-88.
- [48] Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood cells.* 1978;4(1-2):7-25.

- [49] Jones DL, Wagers AJ. No place like home: anatomy and function of the stem cell niche. *Nature reviews Molecular cell biology*. 2008;9(1):11-21.
- [50] Decimo I, Bifari F, Krampera M, Fumagalli G. Neural stem cell niches in health and diseases. *Curr Pharm Des*. 2012;18(13):1755-83.
- [51] Morrison SJ, Spradling AC. Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. *Cell*. 2008;132(4):598-611.
- [52] Jordan JD, Ma DK, Ming GL, Song H. Cellular niches for endogenous neural stem cells in the adult brain. *CNS & neurological disorders drug targets*. 2007;6(5):336-41.
- [53] Bonfanti L, Ponti G. Adult mammalian neurogenesis and the New Zealand white rabbit. *Veterinary journal*. 2008;175(3):310-31.
- [54] Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2002;22(3):629-34.
- [55] Gage FH. Mammalian neural stem cells. *Science*. 2000;287(5457):1433-8.
- [56] 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*. 1999;97(6):703-16.
- [57] Malatesta P, Hartfuss E, Gotz M. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. *Development (Cambridge, England)*. 2000;127(24):5253-63.
- [58] Ponti G, Obernier K, Guinto C, Jose L, Bonfanti L, Alvarez-Buylla A. Cell cycle and lineage progression of neural progenitors in the ventricular-subventricular zones of adult mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;110(11):E1045-54.
- [59] Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. *Annual review of neuroscience*. 2009;32:149-84.
- [60] Altman J. Autoradiographic and histological studies of postnatal neurogenesis. IV. Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. *The Journal of comparative neurology*. 1969;137(4):433-57.
- [61] Lois C, Alvarez-Buylla A. Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia. *Proceedings of the National Academy of Sciences of the United States of America*. 1993;90(5):2074-7.
- [62] Luskin MB. Restricted proliferation and migration of postnatally generated neurons derived from the forebrain subventricular zone. *Neuron*. 1993;11(1):173-89.

- [63] Lois C, Garcia-Verdugo JM, Alvarez-Buylla A. Chain migration of neuronal precursors. *Science*. 1996;271(5251):978-81.
- [64] Merkle FT, Tramontin AD, Garcia-Verdugo JM, Alvarez-Buylla A. Radial glia give rise to adult neural stem cells in the subventricular zone. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(50):17528-32.
- [65] Shen Q, Wang Y, Kokovay E, Lin G, Chuang SM, Goderie SK, et al. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. *Cell stem cell*. 2008;3(3):289-300.
- [66] 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(3):265-78.
- [67] Wang C, Liu F, Liu YY, Zhao CH, You Y, Wang L, et al. Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. *Cell research*. 2011;21(11):1534-50.
- [68] Sanai N, Tramontin AD, Quinones-Hinojosa A, Barbaro NM, Gupta N, Kunwar S, et al. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature*. 2004;427(6976):740-4.
- [69] Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, Wikkelsø C, et al. Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. *Science*. 2007;315(5816):1243-9.
- [70] Sanai N, Nguyen T, Ihrie RA, Mirzadeh Z, Tsai HH, Wong M, et al. Corridors of migrating neurons in the human brain and their decline during infancy. *Nature*. 2011;478(7369):382-6.
- [71] Goritz C, Frisen J. Neural stem cells and neurogenesis in the adult. *Cell stem cell*. 2012;10(6):657-9.
- [72] Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, et al. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. *PloS one*. 2010;5(1):e8809.
- [73] Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, et al. Dynamics of hippocampal neurogenesis in adult humans. *Cell*. 2013;153(6):1219-27.
- [74] Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, et al. Neurogenesis in the Striatum of the Adult Human Brain. *Cell*. 2014.
- [75] Tong CK, Chen J, Cebrian-Silla A, Mirzadeh Z, Obernier K, Guinto CD, et al. Axonal Control of the Adult Neural Stem Cell Niche. *Cell stem cell*. 2014.
- [76] Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. *Trends in neurosciences*. 2004;27(8):447-52.

- [77] Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. Cell types, lineage, and architecture of the germinal zone in the adult dentate gyrus. *The Journal of comparative neurology*. 2004;478(4):359-78.
- [78] Ehninger D, Kempermann G. Neurogenesis in the adult hippocampus. *Cell and tissue research*. 2008;331(1):243-50.
- [79] Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. Neurogenesis in the adult human hippocampus. *Nature medicine*. 1998;4(11):1313-7.
- [80] Gage FH, Kempermann G, Palmer TD, Peterson DA, Ray J. Multipotent progenitor cells in the adult dentate gyrus. *Journal of Neurobiology*. 1998;36(2):249-66.
- [81] Gould E, Cameron HA. Regulation of neuronal birth, migration and death in the rat dentate gyrus. *Dev Neurosci*. 1996;18(1-2):22-35.
- [82] Manganas LN, Zhang X, Li Y, Hazel RD, Smith SD, Wagshul ME, et al. Magnetic resonance spectroscopy identifies neural progenitor cells in the live human brain. *Science*. 2007;318(5852):980-5.
- [83] Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;95(6):3168-71.
- [84] J A, GD D.-Autoradiographic and histological evidence of postnatal hippocampal neurogenesis. D-0406041. (-0021-9967 (Print)):-319-35.
- [85] Sierra A, Encinas JM, Maletic-Savatic M. Adult human neurogenesis: from microscopy to magnetic resonance imaging. *Frontiers in neuroscience*. 2011;5:47.
- [86] Seri B, Garcia-Verdugo JM, McEwen BS, Alvarez-Buylla A. Astrocytes give rise to new neurons in the adult mammalian hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(18):7153-60.
- [87] Martino G, Pluchino S, Bonfanti L, Schwartz M. Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiological reviews*. 2011;91(4):1281-304.
- [88] Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell*. 2008;132(4):645-60.
- [89] Ming GL, Song H. Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron*. 2011;70(4):687-702.
- [90] Palmer TD, Willhoite AR, Gage FH. Vascular niche for adult hippocampal neurogenesis. *The Journal of comparative neurology*. 2000;425(4):479-94.

- [91] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301(5634):805-9.
- [92] Yu TS, Zhang G, Liebl DJ, Kernie SG. Traumatic brain injury-induced hippocampal neurogenesis requires activation of early nestin-expressing progenitors. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28(48):12901-12.
- [93] Bonaguidi MA, Song J, Ming GL, Song H. A unifying hypothesis on mammalian neural stem cell properties in the adult hippocampus. *Current opinion in neurobiology*. 2012;22(5):754-61.
- [94] Filippov V, Kronenberg G, Pivneva T, Reuter K, Steiner B, Wang LP, et al. Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. *Molecular and Cellular Neuroscience*. 2003;23(3):373-82.
- [95] Lagace DC, Whitman MC, Noonan MA, Ables JL, DeCarolus NA, Arguello AA, et al. Dynamic contribution of nestin-expressing stem cells to adult Neurogenesis. *Journal of Neuroscience*. 2007;27(46):12623-9.
- [96] Ahn S, Joyner AL. In vivo analysis of quiescent adult neural stem cells responding to Sonic hedgehog. *Nature*. 2005;437(7060):894-7.
- [97] Denise A, Garcia R, Doan NB, Imura T, Bush TG, Sofroniew MV. GFAP-expressing progenitors are the principal source of constitutive neurogenesis in adult mouse forebrain. *Nature neuroscience*. 2004;7(11):1233-41.
- [98] Dhaliwal J, Lagace DC. Visualization and genetic manipulation of adult neurogenesis using transgenic mice. *The European journal of neuroscience*. 2011;33(6):1025-36.
- [99] Bonaguidi MA, Wheeler MA, Shapiro JS, Stadel RP, Sun GJ, Ming GL, et al. In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. *Cell*. 2011;145(7):1142-55.
- [100] Fuentealba LC, Obernier K, Alvarez-Buylla A. Adult neural stem cells bridge their niche. *Cell stem cell*. 2012;10(6):698-708.
- [101] Ehm O, Goritz C, Covic M, Schaffner I, Schwarz TJ, Karaca E, et al. RBPJkappa-dependent signaling is essential for long-term maintenance of neural stem cells in the adult hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2010;30(41):13794-807.
- [102] Lavado A, Lagutin OV, Chow LM, Baker SJ, Oliver G. Prox1 is required for granule cell maturation and intermediate progenitor maintenance during brain neurogenesis. *PLoS biology*. 2010;8(8).

- [103] Song J, Zhong C, Bonaguidi MA, Sun GJ, Hsu D, Gu Y, et al. Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. *Nature*. 2012;489(7414):150-4.
- [104] Zhao C, Teng EM, Summers RG, Jr., Ming GL, Gage FH. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(1):3-11.
- [105] Ge S, Sailor KA, Ming GL, Song H. Synaptic integration and plasticity of new neurons in the adult hippocampus. *The Journal of physiology*. 2008;586(16):3759-65.
- [106] Dayer AG, Ford AA, Cleaver KM, Yassaee M, Cameron HA. Short-term and long-term survival of new neurons in the rat dentate gyrus. *Journal of Comparative Neurology*. 2003;460(4):563-72.
- [107] Kirshblum S, Campagnolo DI. *Spinal cord medicine*. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. xiv, 688 p. p.
- [108] Holtz A, Levi R. *Spinal cord injury*. New York: Oxford University Press; 2010. vi, 319 p., 4 p. of plates p.
- [109] Smart IH. Proliferative characteristics of the ependymal layer during the early development of the spinal cord in the mouse. *Journal of anatomy*. 1972;111(Pt 3):365-80.
- [110] Del Bigio MR. Ependymal cells: biology and pathology. *Acta neuropathologica*. 2010;119(1):55-73.
- [111] Fu H, Qi Y, Tan M, Cai J, Hu X, Liu Z, et al. Molecular mapping of the origin of postnatal spinal cord ependymal cells: evidence that adult ependymal cells are derived from Nkx6.1+ventral neural progenitor cells. *The Journal of comparative neurology*. 2003;456(3):237-44.
- [112] Sabourin JC, Ackema KB, Ohayon D, Guichet PO, Perrin FE, Garces A, et al. A mesenchymal-like ZEB1(+) niche harbors dorsal radial glial fibrillary acidic protein-positive stem cells in the spinal cord. *Stem cells*. 2009;27(11):2722-33.
- [113] Kehl LJ, Fairbanks CA, Laughlin TM, Wilcox GL. Neurogenesis in postnatal rat spinal cord: a study in primary culture. *Science*. 1997;276(5312):586-9.
- [114] Barnabe-Heider F, Goritz C, Sabelstrom H, Takebayashi H, Pfrieder FW, Meletis K, et al. Origin of new glial cells in intact and injured adult spinal cord. *Cell stem cell*. 2010;7(4):470-82.
- [115] Alfaro-Cervello C, Soriano-Navarro M, Mirzadeh Z, Alvarez-Buylla A, Garcia-Verdugo JM. Biciliated ependymal cell proliferation contributes to spinal cord growth. *The Journal of comparative neurology*. 2012;520(15):3528-52.

- [116] Nolte C, Matyash M, Pivneva T, Schipke CG, Ohlemeyer C, Hanisch UK, et al. GFAP promoter-controlled EGFP-expressing transgenic mice: a tool to visualize astrocytes and astrogliosis in living brain tissue. *Glia*. 2001;33(1):72-86.
- [117] Hamilton LK, Truong MK, Bednarczyk MR, Aumont A, Fernandes KJ. Cellular organization of the central canal ependymal zone, a niche of latent neural stem cells in the adult mammalian spinal cord. *Neuroscience*. 2009;164(3):1044-56.
- [118] Seitz R, Lohler J, Schwendemann G. Ependyma and meninges of the spinal cord of the mouse. A light-and electron-microscopic study. *Cell and tissue research*. 1981;220(1):61-72.
- [119] Meletis K, Barnabe-Heider F, Carlen M, Evergren E, Tomilin N, Shupliakov O, et al. Spinal cord injury reveals multilineage differentiation of ependymal cells. *PLoS biology*. 2008;6(7):e182.
- [120] Bodega G, Suarez I, Rubio M, Fernandez B. Ependyma: phylogenetic evolution of glial fibrillary acidic protein (GFAP) and vimentin expression in vertebrate spinal cord. *Histochemistry*. 1994;102(2):113-22.
- [121] Sabelstrom H, Stenudd M, Reu P, Dias DO, Elfineh M, Zdunek S, et al. Resident neural stem cells restrict tissue damage and neuronal loss after spinal cord injury in mice. *Science*. 2013;342(6158):637-40.
- [122] Rafols JA, Goshgarian HG. Spinal tanycytes in the adult rat: a correlative Golgi gold-toning study. *The Anatomical record*. 1985;211(1):75-86.
- [123] Huang AL, Chen X, Hoon MA, Chandrashekar J, Guo W, Trankner D, et al. The cells and logic for mammalian sour taste detection. *Nature*. 2006;442(7105):934-8.
- [124] Marichal N, Garcia G, Radmilovich M, Trujillo-Cenoz O, Russo RE. Enigmatic central canal contacting cells: immature neurons in "standby mode"? *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009;29(32):10010-24.
- [125] Goritz C, Dias DO, Tomilin N, Barbacid M, Shupliakov O, Frisen J. A pericyte origin of spinal cord scar tissue. *Science*. 2011;333(6039):238-42.
- [126] Moreno-Manzano V, Rodriguez-Jimenez FJ, Garcia-Rosello M, Lainez S, Erceg S, Calvo MT, et al. Activated spinal cord ependymal stem cells rescue neurological function. *Stem cells*. 2009;27(3):733-43.
- [127] Kulbatski I, Tator CH. Region-specific differentiation potential of adult rat spinal cord neural stem/precursors and their plasticity in response to in vitro manipulation. *The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society*. 2009;57(5):405-23.
- [128] Zhao M, Momma S, Delfani K, Carlen M, Cassidy RM, Johansson CB, et al. Evidence for neurogenesis in the adult mammalian substantia nigra. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100(13):7925-30.

- [129] Bernier PJ, Bedard A, Vinet J, Levesque M, Parent A. Newly generated neurons in the amygdala and adjoining cortex of adult primates. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(17):11464-9.
- [130] Gould E, Reeves AJ, Graziano MS, Gross CG. Neurogenesis in the neocortex of adult primates. *Science*. 1999;286(5439):548-52.
- [131] Migaud M, Batailler M, Segura S, Duittoz A, Franceschini I, Pillon D. Emerging new sites for adult neurogenesis in the mammalian brain: a comparative study between the hypothalamus and the classical neurogenic zones. *The European journal of neuroscience*. 2010;32(12):2042-52.
- [132] Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. *Current opinion in neurobiology*. 2004;14(2):186-91.
- [133] Lledo PM, Alonso M, Grubb MS. Adult neurogenesis and functional plasticity in neuronal circuits. *Nature reviews Neuroscience*. 2006;7(3):179-93.
- [134] Kokoeva MV, Yin H, Flier JS. Evidence for constitutive neural cell proliferation in the adult murine hypothalamus. *J Comp Neurol*. 2007;505(2):209-20.
- [135] Pencea V, Bingaman KD, Freedman LJ, Luskin MB. Neurogenesis in the subventricular zone and rostral migratory stream of the neonatal and adult primate forebrain. *Experimental neurology*. 2001;172(1):1-16.
- [136] Kokoeva MV, Yin H, Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science*. 2005;310(5748):679-83.
- [137] Bennett L, Yang M, Enikolopov G, Iacovitti L. Circumventricular organs: a novel site of neural stem cells in the adult brain. *Molecular and cellular neurosciences*. 2009;41(3):337-47.
- [138] Mercier F, Kitasako JT, Hatton GI. Anatomy of the brain neurogenic zones revisited: fractones and the fibroblast/macrophage network. *The Journal of comparative neurology*. 2002;451(2):170-88.
- [139] Bifari F, Decimo I, Chiamulera C, Bersan E, Malpeli G, Johansson J, et al. Novel stem/progenitor cells with neuronal differentiation potential reside in the leptomeningeal niche. *Journal of cellular and molecular medicine*. 2009;13(9B):3195-208.
- [140] Itokazu Y, Kitada M, Dezawa M, Mizoguchi A, Matsumoto N, Shimizu A, et al. Choroid plexus ependymal cells host neural progenitor cells in the rat. *Glia*. 2006;53(1):32-42.
- [141] DeGiorgio LA, Sheu KF, Blass JP. Culture from human leptomeninges of cells containing neurofilament protein and neuron-specific enolase. *J Neurol Sci*. 1994;124(2):141-8.
- [142] Petricevic J, Forempoher G, Ostojic L, Mardesic-Brakus S, Andjelinovic S, Vukojevic K, et al. Expression of nestin, mesothelin and epithelial membrane antigen (EMA) in

developing and adult human meninges and meningiomas. *Acta histochemica*. 2011;113(7):703-11.

- [143] Decimo I, Bifari F, Rodriguez FJ, Malpeli G, Dolci S, Lavarini V, et al. Nestin-and doublecortin-positive cells reside in adult spinal cord meninges and participate in injury-induced parenchymal reaction. *Stem cells*. 2011;29(12):2062-76.
- [144] Halfter W, Dong S, Yip YP, Willem M, Mayer U. A critical function of the pial basement membrane in cortical histogenesis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2002;22(14):6029-40.
- [145] Mercier F, Hatton GL. Connexin 26 and basic fibroblast growth factor are expressed primarily in the subpial and subependymal layers in adult brain parenchyma: roles in stem cell proliferation and morphological plasticity? *The Journal of comparative neurology*. 2001;431(1):88-104.
- [146] Stumm R, Kolodziej A, Schulz S, Kohtz JD, Holtt V. Patterns of SDF-1alpha and SDF-1gamma mRNAs, migration pathways, and phenotypes of CXCR4-expressing neurons in the developing rat telencephalon. *The Journal of comparative neurology*. 2007;502(3):382-99.
- [147] Siegenthaler JA, Ashique AM, Zarbalis K, Patterson KP, Hecht JH, Kane MA, et al. Retinoic acid from the meninges regulates cortical neuron generation. *Cell*. 2009;139(3):597-609.
- [148] Lee A, Kessler JD, Read TA, Kaiser C, Corbeil D, Huttner WB, et al. Isolation of neural stem cells from the postnatal cerebellum. *Nature neuroscience*. 2005;8(6):723-9.
- [149] Ponti G, Crociara P, Armentano M, Bonfanti L. Adult neurogenesis without germinal layers: the "atypical" cerebellum of rabbits. *Arch Ital Biol*. 2010;148(2):147-58.
- [150] Ponti G, Peretto P, Bonfanti L. Genesis of neuronal and glial progenitors in the cerebellar cortex of peripuberal and adult rabbits. *PLoS One*. 2008;3(6):e2366.
- [151] Ponti G, Peretto P, Bonfanti L. A subpial, transitory germinal zone forms chains of neuronal precursors in the rabbit cerebellum. *Developmental biology*. 2006;294(1):168-80.
- [152] McDonough A, Martinez-Cerdeno V. Endogenous proliferation after spinal cord injury in animal models. *Stem Cells Int*. 2012;2012:387513.
- [153] Bonfanti L, Peretto P. Adult neurogenesis in mammals--a theme with many variations. *The European journal of neuroscience*. 2011;34(6):930-50.
- [154] Nunes MC, Roy NS, Keyoung HM, Goodman RR, McKhann G, 2nd, Jiang L, et al. Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain. *Nature medicine*. 2003;9(4):439-47.
- [155] Zhu X, Bergles DE, Nishiyama A. NG2 cells generate both oligodendrocytes and gray matter astrocytes. *Development (Cambridge, England)*. 2008;135(1):145-57.

- [156] Horner PJ, Thallmair M, Gage FH. Defining the NG2-expressing cell of the adult CNS. *J Neurocytol.* 2002;31(6-7):469-80.
- [157] Shechter R, Ziv Y, Schwartz M. New GABAergic interneurons supported by myelin-specific T cells are formed in intact adult spinal cord. *Stem Cells.* 2007;25(9):2277-82.
- [158] Kokaia Z, Thored P, Arvidsson A, Lindvall O. Regulation of stroke-induced neurogenesis in adult brain--recent scientific progress. *Cerebral cortex.* 2006;16 Suppl 1:i162-7.
- [159] Jin K, Wang X, Xie L, Mao XO, Zhu W, Wang Y, et al. Evidence for stroke-induced neurogenesis in the human brain. *Proceedings of the National Academy of Sciences of the United States of America.* 2006;103(35):13198-202.
- [160] Jin K, Minami M, Lan JQ, Mao XO, Batteur S, Simon RP, et al. Neurogenesis in dentate subgranular zone and rostral subventricular zone after focal cerebral ischemia in the rat. *Proceedings of the National Academy of Sciences of the United States of America.* 2001;98(8):4710-5.
- [161] Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science.* 2003;302(5651):1760-5.
- [162] Gould E, Tanapat P. Lesion-induced proliferation of neuronal progenitors in the dentate gyrus of the adult. *Neuroscience.* 1997;80(2):427-36.
- [163] Pluchino S, Muzio L, Imitola J, Deleidi M, Alfaro-Cervello C, Salani G, et al. Persistent inflammation alters the function of the endogenous brain stem cell compartment. *Brain : a journal of neurology.* 2008;131:2564-78.
- [164] Zheng WM, Zhuge QC, Zhong M, Chen GR, Shao B, Wang H, et al. Neurogenesis in Adult Human Brain after Traumatic Brain Injury. *J Neurotraum.* 2013;30(22):1872-80.
- [165] Urrea C, Castellanos DA, Sagen J, Tsoulfas P, Bramlett HM, Dietrich WD. Widespread cellular proliferation and focal neurogenesis after traumatic brain injury in the rat. *Restor Neurol Neuros.* 2007;25(1):65-76.
- [166] Brundin L, Brismar H, Danilov AI, Olsson T, Johansson CB. Neural stem cells: A potential source for remyelination in neuroinflammatory disease. *Brain Pathol.* 2003;13(3):322-8.
- [167] Yagita Y, Kitagawa K, Ohtsuki T, Takasawa K, Miyata T, Okano H, et al. Neurogenesis by progenitor cells in the ischemic adult rat hippocampus. *Stroke; a journal of cerebral circulation.* 2001;32(8):1890-6.
- [168] Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet.* 2008;371(9624):1612-23.
- [169] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics-2013 Update A Report From the American Heart Association. *Circulation.* 2013;127(1):E6-E245.

- [170] Endres M, Dirnagl U, Moskowitz MA. The ischemic cascade and mediators of ischemic injury. *Handbook of clinical neurology*. 2009;92:31-41.
- [171] Escuret E. [Cerebral ischemic cascade]. *Annales francaises d'anesthesie et de reanimation*. 1995;14(1):103-13.
- [172] Felberg RA, Burgin WS, Grotta JC. Neuroprotection and the ischemic cascade. *CNS spectrums*. 2000;5(3):52-8.
- [173] Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends in neurosciences*. 1999;22(9):391-7.
- [174] Zhang RL, Zhang ZG, Lu M, Wang Y, Yang JJ, Chopp M. Reduction of the cell cycle length by decreasing G1 phase and cell cycle reentry expand neuronal progenitor cells in the subventricular zone of adult rat after stroke. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2006;26(6):857-63.
- [175] Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nature medicine*. 2002;8(9):963-70.
- [176] Thored P, Arvidsson A, Cacci E, Ahlenius H, Kallur T, Darsalia V, et al. Persistent production of neurons from adult brain stem cells during recovery after stroke. *Stem cells*. 2006;24(3):739-47.
- [177] Nakatomi H, Kuriu T, Okabe S, Yamamoto S, Hatano O, Kawahara N, et al. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. *Cell*. 2002;110(4):429-41.
- [178] Darsalia V, Heldmann U, Lindvall O, Kokaia Z. Stroke-induced neurogenesis in aged brain. *Stroke; a journal of cerebral circulation*. 2005;36(8):1790-5.
- [179] Tanaka R, Yamashiro K, Mochizuki H, Cho N, Onodera M, Mizuno Y, et al. Neurogenesis after transient global ischemia in the adult hippocampus visualized by improved retroviral vector. *Stroke; a journal of cerebral circulation*. 2004;35(6):1454-9.
- [180] Nakagomi T, Taguchi A, Fujimori Y, Saino O, Nakano-Doi A, Kubo S, et al. Isolation and characterization of neural stem/progenitor cells from post-stroke cerebral cortex in mice. *European Journal of Neuroscience*. 2009;29(9):1842-52.
- [181] Zhang RL, Zhang ZG, Chopp M. Neurogenesis in the adult ischemic brain: Generation, migration, survival, and restorative therapy. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*. 2005;11(5):408-16.
- [182] Kawai T, Takagi N, Miyake-Takagi K, Okuyama N, Mochizuki N, Takeo S. Characterization of BrdU-positive neurons induced by transient global ischemia in adult hippocampus. *J Cerebr Blood F Met*. 2004;24(5):548-55.

- [183] Andres RH, Horie N, Slikker W, Keren-Gill H, Zhan K, Sun G, et al. Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. *Brain : a journal of neurology*. 2011;134(Pt 6):1777-89.
- [184] Lichtenwalner RJ, Parent JM. Adult neurogenesis and the ischemic forebrain. *J Cerebr Blood F Met*. 2006;26(1):1-20.
- [185] Kunze A, Grass S, Witte OW, Yamaguchi M, Kempermann G, Redecker C. Proliferative response of distinct hippocampal progenitor cell populations after cortical infarcts in the adult brain. *Neurobiol Dis*. 2006;21(2):324-32.
- [186] Vandenbosch R, Borgs L, Beukelaers P, Belachew S, Moonen G, Nguyen L, et al. Adult neurogenesis and the diseased brain. *Curr Med Chem*. 2009;16(6):652-66.
- [187] Zhang RL, Zhang ZG, Zhang CL, Zhang L, Robin A, Wang Y, et al. Stroke transiently increases subventricular zone cell division from asymmetric to symmetric and increases neuronal differentiation in the adult rat. *Journal of Neuroscience*. 2004;24(25):5810-5.
- [188] Zhang RL, Zhang ZG, Wang Y, LeTourneau Y, Liu XS, Zhang XG, et al. Stroke induces ependymal cell transformation into radial glia in the subventricular zone of the adult rodent brain. *J Cerebr Blood F Met*. 2007;27(6):1201-12.
- [189] Vandenbosch R. Adult Neurogenesis and the Diseased Brain. *Current Medicinal Chemistry*. 2009;16:652-66.
- [190] Parent JM, Vexler ZS, Gong C, Derugin N, Ferriero DM. Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. *Annals of neurology*. 2002;52(6):802-13.
- [191] Zhang R, Zhang Z, Wang L, Wang Y, Goussev A, Zhang L, et al. Activated neural stem cells contribute to stroke-induced neurogenesis and neuroblast migration toward the infarct boundary in adult rats. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2004;24(4):441-8.
- [192] Decimo I, Bifari F, Krampera M, Fumagalli G. Neural Stem Cell Niches in Health and Diseases. *Current Pharmaceutical Design*. 2012;18:1755-83.
- [193] Planas AM, Justicia C, Soriano MA, Ferrer I. Epidermal growth factor receptor in proliferating reactive glia following transient focal ischemia in the rat brain. *Glia*. 1998;23(2):120-9.
- [194] Tureyen K, Vemuganti R, Bowen KK, Sailor KA, Dempsey RJ. EGF and FGF-2 infusion increases post-ischemic neural progenitor cell proliferation in the adult rat brain. *Neurosurgery*. 2005;57(6):1254-62.

- [195] Tokumine J, Kakinohana O, Cizkova D, Smith DW, Marsala M. Changes in spinal GDNF, BDNF, and NT-3 expression after transient ischemia in the rat. *Journal of neuroscience research*. 2003;74(4):552-61.
- [196] Kitagawa H, Sasaki C, Zhang WR, Sakai K, Shiro Y, Warita H, et al. Induction of glial cell line-derived neurotrophic factor receptor proteins in cerebral cortex and striatum after permanent middle cerebral artery occlusion in rats. *Brain research*. 1999;834(1-2):190-5.
- [197] Takami K, Kiyota Y, Iwane M, Miyamoto M, Tsukuda R, Igarashi K, et al. Upregulation of fibroblast growth factor-receptor messenger RNA expression in rat brain following transient forebrain ischemia. *Experimental brain research*. 1993;97(2):185-94.
- [198] Kokaia Z, Zhao Q, Kokaia M, Elmer E, Metsis M, Smith ML, et al. Regulation of Brain-Derived Neurotrophic Factor Gene-Expression after Transient Middle Cerebral-Artery Occlusion with and without Brain-Damage. *Experimental neurology*. 1995;136(1):73-88.
- [199] Lin TN, Te J, Lee M, Sun GY, Hsu CY. Induction of basic fibroblast growth factor (bFGF) expression following focal cerebral ischemia. *Brain research Molecular brain research*. 1997;49(1-2):255-65.
- [200] Lin TN, Wong YP, Chen JJ, Cheng JT, Yu SF, Sun SH, et al. Elevated basic fibroblast growth factor levels in stroke-prone spontaneously hypertensive rats. *Neuroscience*. 1997;76(2):557-70.
- [201] Heldmann U, Thored P, Claassen JH, Arvidsson A, Kokaia Z, Lindvall O. TNF-alpha antibody infusion impairs survival of stroke-generated neuroblasts in adult rat brain. *Experimental neurology*. 2005;196(1):204-8.
- [202] Tsai PT, Ohab JJ, Kertesz N, Groszer M, Matter C, Gao J, et al. A critical role of erythropoietin receptor in neurogenesis and post-stroke recovery. *Journal of Neuroscience*. 2006;26(4):1269-74.
- [203] Chou J, Harvey BK, Chang CF, Shen H, Morales M, Wang Y. Neuroregenerative effects of BMP7 after stroke in rats. *J Neurol Sci*. 2006;240(1-2):21-9.
- [204] Kang SS, Keasey MP, Arnold SA, Reid R, Gerald J, Hagg T. Endogenous CNTF mediates stroke-induced adult CNS neurogenesis in mice. *Neurobiol Dis*. 2012;49C: 68-78.
- [205] Guerra-Crespo M, Gleason D, Sistos A, Toosky T, Solaroglu I, Zhang JH, et al. Transforming growth factor-alpha induces neurogenesis and behavioral improvement in a chronic stroke model. *Neuroscience*. 2009;160(2):470-83.
- [206] Leker RR, Toth ZE, Shahar T, Cassiani-Ingoni R, Szalayova I, Key S, et al. Transforming growth factor alpha induces angiogenesis and neurogenesis following stroke. *Neuroscience*. 2009;163(1):233-43.

- [207] Sun Y, Jin K, Xie L, Childs J, Mao XO, Logvinova A, et al. VEGF-induced neuroprotection, neurogenesis, and angiogenesis after focal cerebral ischemia. *The Journal of clinical investigation*. 2003;111(12):1843-51.
- [208] Jin K, Mao XO, Sun Y, Xie L, Greenberg DA. Stem cell factor stimulates neurogenesis in vitro and in vivo. *The Journal of clinical investigation*. 2002;110(3):311-9.
- [209] Woodbury ME, Ikezu T. Fibroblast Growth Factor-2 Signaling in Neurogenesis and Neurodegeneration. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology*. 2013.
- [210] Shingo T, Sorokan ST, Shimazaki T, Weiss S. Erythropoietin regulates the in vitro and in vivo production of neuronal progenitors by mammalian forebrain neural stem cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(24):9733-43.
- [211] Zhu W, Fan Y, Frenzel T, Gasmi M, Bartus RT, Young WL, et al. Insulin growth factor-1 gene transfer enhances neurovascular remodeling and improves long-term stroke outcome in mice. *Stroke; a journal of cerebral circulation*. 2008;39(4):1254-61.
- [212] Schneider A, Kruger C, Steigleder T, Weber D, Pitzer C, Laage R, et al. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. *Journal of Clinical Investigation*. 2005;115(8):2083-98.
- [213] Plane JM, Andjelkovic AV, Keep RF, Parent JM. Intact and injured endothelial cells differentially modulate postnatal murine forebrain neural stem cells. *Neurobiol Dis*. 2010;37(1):218-27.
- [214] Chen JL, Zacharek A, Zhang CL, Jiang H, Li Y, Roberts C, et al. Endothelial nitric oxide synthase regulates brain-derived neurotrophic factor expression and neurogenesis after stroke in mice. *Journal of Neuroscience*. 2005;25(9):2366-75.
- [215] Wang Q, Tang XN, Yenari MA. The inflammatory response in stroke. *J Neuroimmunol*. 2007;184(1-2):53-68.
- [216] Hoehn BD, Palmer TD, Steinberg GK. Neurogenesis in rats after focal cerebral ischemia is enhanced by indomethacin. *Stroke; a journal of cerebral circulation*. 2005;36(12):2718-24.
- [217] Kluska MM, Witte OW, Bolz J, Redecker C. Neurogenesis in the adult dentate gyrus after cortical infarcts: Effects of infarct location, N-methyl-D-aspartate receptor blockade and anti-inflammatory treatment. *Neuroscience*. 2005;135(3):723-35.
- [218] Rahpeymai Y, Hietala MA, Wilhelmsson U, Fotheringham A, Davies I, Nilsson AK, et al. Complement: a novel factor in basal and ischemia-induced neurogenesis. *Embo Journal*. 2006;25(6):1364-74.
- [219] Kohman RA, Rhodes JS. Neurogenesis, inflammation and behavior. *Brain, behavior, and immunity*. 2013;27(1):22-32.

- [220] Dooley D, Vidal P, Hendrix S. Immunopharmacological intervention for successful neural stem cell therapy: New perspectives in CNS neurogenesis and repair. *Pharmacology & therapeutics*. 2014;141(1):21-31.
- [221] An C, Shi Y, Li P, Hu X, Gan Y, Stetler RA, et al. Molecular dialogs between the ischemic brain and the peripheral immune system: Dualistic roles in injury and repair. *Progress in neurobiology*. 2013.
- [222] Ekdahl CT, Kokaia Z, Lindvall O. Brain inflammation and adult neurogenesis: the dual role of microglia. *Neuroscience*. 2009;158(3):1021-9.
- [223] Bernabeu R, Sharp FR. NMDA and AMPA/kainate glutamate receptors modulate dentate neurogenesis and CA3 synapsin-I in normal and ischemic hippocampus. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2000;20(12):1669-80.
- [224] Arvidsson A, Kokaia Z, Lindvall O. N-methyl-D-aspartate receptor-mediated increase of neurogenesis in adult rat dentate gyrus following stroke. *The European journal of neuroscience*. 2001;14(1):10-8.
- [225] Kojima T, Hirota Y, Ema M, Takahashi S, Miyoshi I, Okano H, et al. Subventricular Zone-Derived Neural Progenitor Cells Migrate Along a Blood Vessel Scaffold Toward the Post-stroke Striatum. *Stem cells*. 2010;28(3):545-54.
- [226] Zhang RL, Zhang ZG, Zhang L, Chopp M. Proliferation and differentiation of progenitor cells in the cortex and the subventricular zone in the adult rat after focal cerebral ischemia. *Neuroscience*. 2001;105(1):33-41.
- [227] Hou SW, Wang YQ, Xu M, Shen DH, Wang JJ, Huang F, et al. Functional integration of newly generated neurons into striatum after cerebral ischemia in the adult rat brain. *Stroke; a journal of cerebral circulation*. 2008;39(10):2837-44.
- [228] Kadam SD, Smith-Hicks CL, Smith DR, Worley PF, Comi AM. Functional integration of new neurons into hippocampal networks and poststroke comorbidities following neonatal stroke in mice. *Epilepsy Behav*. 2010;18(4):344-57.
- [229] Zhang RL, Chopp M, Gregg SR, Toh Y, Roberts C, Letourneau Y, et al. Patterns and dynamics of subventricular zone neuroblast migration in the ischemic striatum of the adult mouse. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2009;29(7):1240-50.
- [230] Jin K, Sun Y, Xie L, Peel A, Mao XO, Batteur S, et al. Directed migration of neuronal precursors into the ischemic cerebral cortex and striatum. *Molecular and Cellular Neuroscience*. 2003;24(1):171-89.
- [231] Wang L, Zhang ZG, Zhang RL, Gregg SR, Hozeska-Solgot A, LeTourneau Y, et al. Matrix metalloproteinase 2 (MMP2) and MMP9 secreted by erythropoietin-activated endothelial cells promote neural progenitor cell migration. *Journal of Neuroscience*. 2006;26(22):5996-6003.

- [232] Hill WD, Hess DC, Martin-Studdard A, Carothers JJ, Zheng JQ, Hale D, et al. SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: Association with bone marrow cell homing to injury. *Journal of neuropathology and experimental neurology*. 2004;63(1):84-96.
- [233] Miller JT, Bartley JH, Wimborne HJC, Walker AL, Hess DC, Hill WD, et al. The neuroblast and angioblast chemotaxic factor SDF-1 (CXCL12) expression is briefly up regulated by reactive astrocytes in brain following neonatal hypoxic-ischemic injury. *Bmc Neurosci*. 2005;6.
- [234] Robin AM, Zhang ZG, Wang L, Zhang RL, Katakowski M, Zhang L, et al. Stromal cell-derived factor 1alpha mediates neural progenitor cell motility after focal cerebral ischemia. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2006;26(1):125-34.
- [235] Wang YT, Huang J, Li YN, Yang GY. Roles of Chemokine CXCL12 and its Receptors in Ischemic Stroke. *Current drug targets*. 2012;13(2):166-72.
- [236] Li M, Chang CJ, Lathia JD, Wang L, Pacenta HL, Cotleur A, et al. Chemokine receptor CXCR4 signaling modulates the growth factor-induced cell cycle of self-renewing and multipotent neural progenitor cells. *Glia*. 2011;59(1):108-18.
- [237] Yan YP, Sailor KA, Lang BT, Park SW, Vemuganti R, Dempsey RJ. Monocyte chemo-attractant protein-1 plays a critical role in neuroblast migration after focal cerebral ischemia. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*. 2007;27(6):1213-24.
- [238] Young CC, Brooks KJ, Buchan AM, Szele FG. Cellular and molecular determinants of stroke-induced changes in subventricular zone cell migration. *Antioxidants & redox signaling*. 2011;14(10):1877-88.
- [239] Jin KL, Wang XM, Xie L, Mao XO, Greenberg DA. Transgenic ablation of doublecortin-expressing cells suppresses adult neurogenesis and worsens stroke outcome in mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(17):7993-8.
- [240] Wang XM, Mao XO, Xie L, Sun F, Greenberg DA, Jin KL. Conditional Depletion of Neurogenesis Inhibits Long-Term Recovery after Experimental Stroke in Mice. *Plos One*. 2012;7(6).
- [241] Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *Lancet neurology*. 2010;9(1):105-18.
- [242] Schaapsmeeders P, Maaijwee NAM, van Dijk EJ, Rutten-Jacobs LCA, Arntz RM, Schoonderwaldt HC, et al. Long-Term Cognitive Impairment After First-Ever Ischemic Stroke in Young Adults. *Stroke; a journal of cerebral circulation*. 2013;44(6):1621-8.

- [243] Wolfe CDA, Crichton SL, Heuschmann PU, McKeivitt CJ, Toschke AM, Grieve AP, et al. Estimates of Outcomes Up to Ten Years after Stroke: Analysis from the Prospective South London Stroke Register. *PLoS medicine*. 2011;8(5).
- [244] Gemma C, Bachstetter AD. The role of microglia in adult hippocampal neurogenesis. *Frontiers in cellular neuroscience*. 2013;7:229.
- [245] Nadareishvili Z, Hallenbeck J. Neuronal regeneration after stroke. *New Engl J Med*. 2003;348(23):2355-6.
- [246] Kokaia Z, Lindvall O. Stem cell repair of striatal ischemia. *Progress in brain research*. 2012;201:35-53.
- [247] Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. *Neuron*. 2006;52(1):61-76.
- [248] Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clinic proceedings*. 2014;89(2):225-40.
- [249] Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *The New England journal of medicine*. 2000;343(13):938-52.
- [250] Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV. Environmental factors and their timing in adult-onset multiple sclerosis. *Nat Rev Neurol*. 2010;6(3):156-66.
- [251] Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. *The American journal of managed care*. 2013;19(2 Suppl):S15-20.
- [252] Popescu BF, Lucchinetti CF. Pathology of demyelinating diseases. *Annual review of pathology*. 2012;7:185-217.
- [253] Lucchinetti CF, Popescu BF, Bunyan RF, Moll NM, Roemer SF, Lassmann H, et al. Inflammatory cortical demyelination in early multiple sclerosis. *The New England journal of medicine*. 2011;365(23):2188-97.
- [254] Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. *Lancet neurology*. 2008;7(9):841-51.
- [255] 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. *J Neurol Sci*. 2008;265(1-2):26-31.
- [256] Rasmussen S, Imitola J, Ayuso-Sacido A, Wang Y, Starossom SC, Kivisakk P, et al. Reversible neural stem cell niche dysfunction in a model of multiple sclerosis. *Annals of neurology*. 2011;69(5):878-91.
- [257] Franklin RJ. Why does remyelination fail in multiple sclerosis? *Nat Rev Neurosci*. 2002;3(9):705-14.

- [258] Maki T, Liang AC, Miyamoto N, Lo EH, Arai K. Mechanisms of oligodendrocyte re-generation from ventricular-subventricular zone-derived progenitor cells in white matter diseases. *Frontiers in cellular neuroscience*. 2013;7:275.
- [259] Whitney NP, Eidem TM, Peng H, Huang Y, Zheng JC. Inflammation mediates vary-ing effects in neurogenesis: relevance to the pathogenesis of brain injury and neuro-degenerative disorders. *Journal of neurochemistry*. 2009;108(6):1343-59.
- [260] Picard-Riera N, Decker L, Delarasse C, Goude K, Nait-Oumesmar B, Liblau R, et al. Experimental autoimmune encephalomyelitis mobilizes neural progenitors from the subventricular zone to undergo oligodendrogenesis in adult mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(20):13211-6.
- [261] Nait-Oumesmar B, Picard-Riera N, Kerninon C, Decker L, Seilhean D, Hoglinger GU, et al. Activation of the subventricular zone in multiple sclerosis: evidence for early glial progenitors. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;104(11):4694-9.
- [262] Huehnchen P, Prozorovski T, Klaissle P, Lesemann A, Ingwersen J, Wolf SA, et al. Modulation of adult hippocampal neurogenesis during myelin-directed autoimmune neuroinflammation. *Glia*. 2011;59(1):132-42.
- [263] Giannakopoulou A, Grigoriadis N, Bekiari C, Loubopoulos A, Dori I, Tsingotjidou AS, et al. Acute inflammation alters adult hippocampal neurogenesis in a multiple sclerosis mouse model. *Journal of neuroscience research*. 2013;91(7):890-900.
- [264] Geurts JJG, Bo L, Roosendaal SD, Hazes T, Daniels R, Barkhof F, et al. Extensive hip-pocampal demyelination in multiple sclerosis. *Journal of neuropathology and experi-mental neurology*. 2007;66(9):819-27.
- [265] Papadopoulos D, Dukes S, Patel R, Nicholas R, Vora A, Reynolds R. Substantial Ar-chaecortical Atrophy and Neuronal Loss in Multiple Sclerosis. *Brain Pathol*. 2009;19(2):238-53.
- [266] Roosendaal SD, Moraal B, Vrenken H, Castelijns JA, Pouwels PJW, Barkhof F, et al. In vivo MR imaging of hippocampal lesions in multiple sclerosis. *J Magn Reson Imaging*. 2008;27(4):726-31.
- [267] Sicotte NL, Kern KC, Giesser BS, Arshanapalli A, Schultz A, Montag M, et al. Region-al hippocampal atrophy in multiple sclerosis. *Brain : a journal of neurology*. 2008;131:1134-41.
- [268] Danilov AI, Covacu R, Moe MC, Langmoen IA, Johansson CB, Olsson T, et al. Neuro-genesis in the adult spinal cord in an experimental model of multiple sclerosis. *The European journal of neuroscience*. 2006;23(2):394-400.
- [269] Wolswijk G. Oligodendrocyte precursor cells in the demyelinated multiple sclerosis spinal cord. *Brain : a journal of neurology*. 2002;125:338-49.

- [270] Chang A, Nishiyama A, Peterson J, Prineas J, Trapp BD. NG2-positive oligodendrocyte progenitor cells in adult human brain and multiple sclerosis lesions. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(17):6404-12.
- [271] Scolding N, Franklin R, Stevens S, Heldin CH, Compston A, Newcombe J. Oligodendrocyte progenitors are present in the normal adult human CNS and in the lesions of multiple sclerosis. *Brain : a journal of neurology*. 1998;121 (Pt 12):2221-8.
- [272] Snethen H, Love S, Scolding N. Disease-responsive neural precursor cells are present in multiple sclerosis lesions. *Regenerative medicine*. 2008;3(6):835-47.
- [273] Goldman S. Stem and progenitor cell-based therapy of the human central nervous system. *Nature biotechnology*. 2005;23(7):862-71.
- [274] Cripps RA, Lee BB, Wing P, Weerts E, Mackay J, Brown D. A global map for traumatic spinal cord injury epidemiology: towards a living data repository for injury prevention. *Spinal cord*. 2011;49(4):493-501.
- [275] Karlsson AK. Autonomic dysfunction in spinal cord injury: clinical presentation of symptoms and signs. *Autonomic Dysfunction after Spinal Cord Injury*. 2006;152:1-8.
- [276] Oyinbo CA. Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this multiply cascade. *Acta neurobiologiae experimentalis*. 2011;71(2):281-99.
- [277] Tator CH. Biology of neurological recovery and functional restoration after spinal cord injury. *Neurosurgery*. 1998;42(4):696-707; discussion-8.
- [278] Bareyre FM, Schwab ME. Inflammation, degeneration and regeneration in the injured spinal cord: insights from DNA microarrays. *Trends in neurosciences*. 2003;26(10):555-63.
- [279] Schnell L, Fearn S, Klassen H, Schwab ME, Perry VH. Acute inflammatory responses to mechanical lesions in the CNS: differences between brain and spinal cord. *The European journal of neuroscience*. 1999;11(10):3648-58.
- [280] Cao HQ, Dong ED. An update on spinal cord injury research. *Neuroscience bulletin*. 2013;29(1):94-102.
- [281] Beattie MS, Hermann GE, Rogers RC, Bresnahan JC. Cell death in models of spinal cord injury. *Progress in brain research*. 2002;137:37-47.
- [282] Fitch MT, Silver J. Activated macrophages and the blood-brain barrier: inflammation after CNS injury leads to increases in putative inhibitory molecules. *Exp Neurol*. 1997;148:587-603.
- [283] Reier PJ, Houle JD. The glial scar: its bearing on axonal elongation and transplantation approaches to CNS repair. *Adv Neurol*. 1988;47:87-138.

- [284] Rolls A, Shechter R, Schwartz M. The bright side of the glial scar in CNS repair. *Nature reviews Neuroscience*. 2009;10(3):235-41.
- [285] Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. *Neuroscience letters*. 2014.
- [286] Yuan YM, He C. The glial scar in spinal cord injury and repair. *Neuroscience bulletin*. 2013;29(4):421-35.
- [287] Yiu G, He Z. Glial inhibition of CNS axon regeneration. *Nature reviews Neuroscience*. 2006;7(8):617-27.
- [288] Silver J, Miller JH. Regeneration beyond the glial scar. *Nature reviews Neuroscience*. 2004;5(2):146-56.
- [289] Faulkner JR. Reactive astrocytes protect tissue and preserve function after spinal cord injury. *J Neurosci*. 2004;24:2143-55.
- [290] Sofroniew MV. Reactive astrocytes in neural repair and protection. *Neuroscientist*. 2005;11:400-7.
- [291] Fawcett JW. Overcoming inhibition in the damaged spinal cord. *Journal of neurotrauma*. 2006;23(3-4):371-83.
- [292] do Carmo Cunha J. Responses of reactive astrocytes containing S100[beta] protein and fibroblast growth factor-2 in the border and in the adjacent preserved tissue after a contusion injury of the spinal cord in rats: implications for wound repair and neuroregeneration. *Wound Repair Regen*. 2007;15:134-46.
- [293] White RE, Yin FQ, Jakeman LB. TGF- α increases astrocyte invasion and promotes axonal growth into the lesion following spinal cord injury in mice. *Exp Neurol*. 2008;214:10-24.
- [294] Wu VW, Nishiyama N, Schwartz JP. A culture model of reactive astrocytes: increased nerve growth factor synthesis and reexpression of cytokine responsiveness. *J Neurochem*. 1998;71:749-56.
- [295] Schwartz JP, Nishiyama N. Neurotrophic factor gene expression in astrocytes during development and following injury. *Brain Res Bull*. 1994;35:403-7.
- [296] Hagg T, Oudega M. Degenerative and spontaneous regenerative processes after spinal cord injury. *J Neurotrauma*. 2006;23(3-4):264-80.
- [297] Horky LL, Galimi F, Gage FH, Horner PJ. Fate of endogenous stem/progenitor cells following spinal cord injury. *The Journal of comparative neurology*. 2006;498(4):525-38.
- [298] Takahashi M, Arai Y, Kurosawa H, Sueyoshi N, Shirai S. Ependymal cell reactions in spinal cord segments after compression injury in adult rat. *Journal of neuropathology and experimental neurology*. 2003;62(2):185-94.

- [299] Hofstetter CP, Holmstrom NA, Lilja JA, Schweinhardt P, Hao J, Spenger C, et al. Al-lodynia limits the usefulness of intraspinal neural stem cell grafts; directed differen-tiation improves outcome. *Nature neuroscience*. 2005;8(3):346-53.
- [300] Ramasamy S, Narayanan G, Sankaran S, Yu YH, Ahmed S. Neural stem cell survival factors. *Archives of biochemistry and biophysics*. 2013;534(1-2):71-87.
- [301] Pluchino S, Cossetti C. How stem cells speak with host immune cells in inflammato-ry brain diseases. *Glia*. 2013;61(9):1379-401.
- [302] Gritti A, Frolichsthal-Schoeller P, Galli R, Parati EA, Cova L, Pagano SF, et al. Epider-mal and fibroblast growth factors behave as mitogenic regulators for a single multi-potent stem cell-like population from the subventricular region of the adult mouse forebrain. *The Journal of neuroscience : the official journal of the Society for Neuro-science*. 1999;19(9):3287-97.
- [303] Morshead CM, Reynolds BA, Craig CG, McBurney MW, Staines WA, Morassutti D, et al. Neural stem cells in the adult mammalian forebrain: a relatively quiescent sub-population of subependymal cells. *Neuron*. 1994;13(5):1071-82.
- [304] Maina F, Klein R. Hepatocyte growth factor, a versatile signal for developing neu-rons. *Nature neuroscience*. 1999;2(3):213-7.
- [305] Wang TW, Zhang H, Gyetko MR, Parent JM. Hepatocyte growth factor acts as a mi-togen and chemoattractant for postnatal subventricular zone-olfactory bulb neuro-genesis. *Molecular and cellular neurosciences*. 2011;48(1):38-50.
- [306] Hu ZX, Geng JM, Liang DM, Luo M, Li ML. Hepatocyte growth factor protects hu-man embryonic stem cell derived-neural progenitors from hydrogen peroxide-in-duced apoptosis. *European journal of pharmacology*. 2010;645(1-3):23-31.
- [307] Doeppner TR, Kaltwasser B, ElAli A, Zechariah A, Hermann DM, Bahr M. Acute hepatocyte growth factor treatment induces long-term neuroprotection and stroke recovery via mechanisms involving neural precursor cell proliferation and differen-tiation. *Journal of cerebral blood flow and metabolism : official journal of the Interna-tional Society of Cerebral Blood Flow and Metabolism*. 2011;31(5):1251-62.
- [308] Shalaby F, Rossant J, Yamaguchi TP, Gertsenstein M, Wu XF, Breitman ML, et al. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice. *Nature*. 1995;376(6535):62-6.
- [309] Shalaby F, Ho J, Stanford WL, Fischer KD, Schuh AC, Schwartz L, et al. A require-ment for Flk1 in primitive and definitive hematopoiesis and vasculogenesis. *Cell*. 1997;89(6):981-90.
- [310] Ema M, Faloon P, Zhang WJ, Hirashima M, Reid T, Stanford WL, et al. Combinatori-al effects of Flk1 and Tal1 on vascular and hematopoietic development in the mouse. *Genes & development*. 2003;17(3):380-93.

- [311] Jin K, Zhu Y, Sun Y, Mao XO, Xie L, Greenberg DA. Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(18):11946-50.
- [312] Calvo CF, Fontaine RH, Soueid J, Tammela T, Makinen T, Alfaro-Cervello C, et al. Vascular endothelial growth factor receptor 3 directly regulates murine neurogenesis. *Genes & development*. 2011;25(8):831-44.
- [313] Mackenzie F, Ruhrberg C. Diverse roles for VEGF-A in the nervous system. *Development*. 2012;139(8):1371-80.
- [314] Wada T, Haigh JJ, Ema M, Hitoshi S, Chaddah R, Rossant J, et al. Vascular endothelial growth factor directly inhibits primitive neural stem cell survival but promotes definitive neural stem cell survival. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(25):6803-12.
- [315] Darland DC, Cain JT, Berosik MA, Saint-Geniez M, Odens PW, Schaubhut GJ, et al. Vascular endothelial growth factor (VEGF) isoform regulation of early forebrain development. *Developmental biology*. 2011;358(1):9-22.
- [316] Zheng XR, Zhang SS, Yin F, Tang JL, Yang YJ, Wang X, et al. Neuroprotection of VEGF-expression neural stem cells in neonatal cerebral palsy rats. *Behavioural brain research*. 2012;230(1):108-15.
- [317] Lian Jin H, Pennant WA, Hyung Lee M, Su S, Ah Kim H, Lu Liu M, et al. Neural stem cells modified by a hypoxia-inducible VEGF gene expression system improve cell viability under hypoxic conditions and spinal cord injury. *Spine*. 2011;36(11):857-64.
- [318] Goberdhan DC, Wilson C. The functions of insulin signaling: size isn't everything, even in *Drosophila*. *Differentiation; research in biological diversity*. 2003;71(7):375-97.
- [319] Rotwein P, Burgess SK, Milbrandt JD, Krause JE. Differential expression of insulin-like growth factor genes in rat central nervous system. *Proceedings of the National Academy of Sciences of the United States of America*. 1988;85(1):265-9.
- [320] Werther GA, Abate M, Hogg A, Cheesman H, Oldfield B, Hards D, et al. Localization of insulin-like growth factor-I mRNA in rat brain by in situ hybridization--relationship to IGF-I receptors. *Molecular endocrinology*. 1990;4(5):773-8.
- [321] D'Ercole AJ, Ye P, O'Kusky JR. Mutant mouse models of insulin-like growth factor actions in the central nervous system. *Neuropeptides*. 2002;36(2-3):209-20.
- [322] Renault VM, Rafalski VA, Morgan AA, Salih DA, Brett JO, Webb AE, et al. FoxO3 regulates neural stem cell homeostasis. *Cell stem cell*. 2009;5(5):527-39.

- [323] Tombran-Tink J, Chader GG, Johnson LV. PEDF: a pigment epithelium-derived factor with potent neuronal differentiative activity. *Experimental eye research*. 1991;53(3):411-4.
- [324] Tombran-Tink J, Johnson LV. Neuronal differentiation of retinoblastoma cells induced by medium conditioned by human RPE cells. *Investigative ophthalmology & visual science*. 1989;30(8):1700-7.
- [325] Ramirez-Castillejo C, Sanchez-Sanchez F, Andreu-Agullo C, Ferron SR, Aroca-Aguilar JD, Sanchez P, et al. Pigment epithelium-derived factor is a niche signal for neural stem cell renewal. *Nature neuroscience*. 2006;9(3):331-9.
- [326] Andreu-Agullo C, Morante-Redolat JM, Delgado AC, Farinas I. Vascular niche factor PEDF modulates Notch-dependent stemness in the adult subependymal zone. *Nature neuroscience*. 2009;12(12):1514-23.
- [327] Jackson EL, Garcia-Verdugo JM, Gil-Perotin S, Roy M, Quinones-Hinojosa A, VandenBerg 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(2):187-99.
- [328] Arimura K, Ago T, Kamouchi M, Nakamura K, Ishitsuka K, Kuroda J, et al. PDGF receptor beta signaling in pericytes following ischemic brain injury. *Current neurovascular research*. 2012;9(1):1-9.
- [329] McMahon AP, Joyner AL, Bradley A, McMahon JA. The midbrain-hindbrain phenotype of Wnt-1-/Wnt-1-mice results from stepwise deletion of engrailed-expressing cells by 9.5 days postcoitum. *Cell*. 1992;69(4):581-95.
- [330] Lee SM, Tole S, Grove E, McMahon AP. A local Wnt-3a signal is required for development of the mammalian hippocampus. *Development*. 2000;127(3):457-67.
- [331] Brault V, Moore R, Kutsch S, Ishibashi M, Rowitch DH, McMahon AP, et al. Inactivation of the beta-catenin gene by Wnt1-Cre-mediated deletion results in dramatic brain malformation and failure of craniofacial development. *Development (Cambridge, England)*. 2001;128(8):1253-64.
- [332] Chenn A, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science*. 2002;297(5580):365-9.
- [333] Lie DC, Colamarino SA, Song HJ, Desire L, Mira H, Consiglio A, et al. Wnt signalling regulates adult hippocampal neurogenesis. *Nature*. 2005;437(7063):1370-5.
- [334] Nusse R. Wnt signaling and stem cell control. *Cell research*. 2008;18(5):523-7.
- [335] Andersson ER, Bryjova L, Biris K, Yamaguchi TP, Arenas E, Bryja V. Genetic interaction between Lrp6 and Wnt5a during mouse development. *Developmental dynamics : an official publication of the American Association of Anatomists*. 2010;239(1):237-45.

- [336] Wang TW, Zhang H, Parent JM. Retinoic acid regulates postnatal neurogenesis in the murine subventricular zone-olfactory bulb pathway. *Development (Cambridge, England)*. 2005;132(12):2721-32.
- [337] Jacobs S, Lie DC, DeCicco KL, Shi Y, DeLuca LM, Gage FH, et al. Retinoic acid is required early during adult neurogenesis in the dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(10):3902-7.
- [338] Marinaro C, Pannese M, Weinandy F, Sessa A, Bergamaschi A, Taketo MM, et al. Wnt signaling has opposing roles in the developing and the adult brain that are modulated by Hipk1. *Cerebral cortex*. 2012;22(10):2415-27.
- [339] Mazumdar J, O'Brien WT, Johnson RS, LaManna JC, Chavez JC, Klein PS, et al. O2 regulates stem cells through Wnt/beta-catenin signalling. *Nature cell biology*. 2010;12(10):1007-13.
- [340] Lim DA, Tramontin AD, Trevejo JM, Herrera DG, Garcia-Verdugo JM, Alvarez-Buylla A. Noggin antagonizes BMP signaling to create a niche for adult neurogenesis. *Neuron*. 2000;28(3):713-26.
- [341] Zimmerman LB, De Jesus-Escobar JM, Harland RM. The Spemann organizer signal noggin binds and inactivates bone morphogenetic protein 4. *Cell*. 1996;86(4):599-606.
- [342] Bonaguidi MA, Peng CY, McGuire T, Falciglia G, Gobeske KT, Czeisler C, et al. Noggin expands neural stem cells in the adult hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28(37):9194-204.
- [343] Lai K, Kaspar BK, Gage FH, Schaffer DV. Sonic hedgehog regulates adult neural progenitor proliferation in vitro and in vivo. *Nature neuroscience*. 2003;6(1):21-7.
- [344] Machold R, Hayashi S, Rutlin M, Muzumdar MD, Nery S, Corbin JG, et al. Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. *Neuron*. 2003;39(6):937-50.
- [345] Diederich K, Schabitz WR, Minnerup J. Seeing old friends from a different angle: novel properties of hematopoietic growth factors in the healthy and diseased brain. *Hippocampus*. 2012;22(5):1051-7.
- [346] Tan CC, Eckardt KU, Firth JD, Ratcliffe PJ. Feedback modulation of renal and hepatic erythropoietin mRNA in response to graded anemia and hypoxia. *The American journal of physiology*. 1992;263(3 Pt 2):F474-81.
- [347] Wang Y, Yao M, Zhou C, Dong D, Jiang Y, Wei G, et al. Erythropoietin promotes spinal cord-derived neural progenitor cell proliferation by regulating cell cycle. *Neuroscience*. 2010;167(3):750-7.
- [348] Ransome MJ, Turnley AM. Systemically delivered Erythropoietin transiently enhances adult hippocampal neurogenesis. *Journal of neurochemistry*. 2007;102(6):1953-65.

- [349] Pavlica S, Milosevic J, Keller M, Schulze M, Peinemann F, Piscioneri A, et al. Erythropoietin enhances cell proliferation and survival of human fetal neuronal progenitors in normoxia. *Brain research*. 2012;1452:18-28.
- [350] Giese AK, Frahm J, Hubner R, Luo J, Wree A, Frech MJ, et al. Erythropoietin and the effect of oxygen during proliferation and differentiation of human neural progenitor cells. *BMC cell biology*. 2010;11:94.
- [351] Wang L, Zhang ZG, Gregg SR, Zhang RL, Jiao Z, LeTourneau Y, et al. The Sonic hedgehog pathway mediates carbamylated erythropoietin-enhanced proliferation and differentiation of adult neural progenitor cells. *The Journal of biological chemistry*. 2007;282(44):32462-70.
- [352] Yu X, Shacka JJ, Eells JB, Suarez-Quian C, Przygodzki RM, Beleslin-Cokic B, et al. Erythropoietin receptor signalling is required for normal brain development. *Development (Cambridge, England)*. 2002;129(2):505-16.
- [353] Kuwabara T, Asashima M. Regenerative medicine using adult neural stem cells: the potential for diabetes therapy and other pharmaceutical applications. *Journal of molecular cell biology*. 2012;4(3):133-9.
- [354] Erickson RI, Paucar AA, Jackson RL, Visnyei K, Kornblum H. Roles of insulin and transferrin in neural progenitor survival and proliferation. *Journal of neuroscience research*. 2008;86(8):1884-94.
- [355] Zhao Y, Xiao Z, Gao Y, Chen B, Zhao Y, Zhang J, et al. Insulin rescues ES cell-derived neural progenitor cells from apoptosis by differential regulation of Akt and ERK pathways. *Neuroscience letters*. 2007;429(1):49-54.
- [356] Yu SW, Baek SH, Brennan RT, Bradley CJ, Park SK, Lee YS, et al. Autophagic death of adult hippocampal neural stem cells following insulin withdrawal. *Stem cells*. 2008;26(10):2602-10.
- [357] Shiraishi H, Okamoto H, Hara H, Yoshida H. Alternative cell death of Apaf1-deficient neural progenitor cells induced by withdrawal of EGF or insulin. *Biochimica et biophysica acta*. 2010;1800(3):405-15.
- [358] Zhang D, Guo M, Zhang W, Lu XY. Adiponectin stimulates proliferation of adult hippocampal neural stem/progenitor cells through activation of p38 mitogen-activated protein kinase (p38MAPK)/glycogen synthase kinase 3beta (GSK-3beta)/beta-catenin signaling cascade. *The Journal of biological chemistry*. 2011;286(52):44913-20.
- [359] Garza JC, Guo M, Zhang W, Lu XY. Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3beta/beta-catenin signaling. *Molecular psychiatry*. 2012;17(8):790-808.

- [360] Avraham Y, Davidi N, Lassri V, Vorobiev L, Kabesa M, Dayan M, et al. Leptin induces neuroprotection neurogenesis and angiogenesis after stroke. *Current neurovascular research*. 2011;8(4):313-22.
- [361] Udagawa J, Ono A, Kawamoto M, Otani H. Leptin and its intracellular signaling pathway maintains the neurosphere. *Neuroreport*. 2010;21(18):1140-5.
- [362] Udagawa J, Hashimoto R, Suzuki H, Hatta T, Sotomaru Y, Hioki K, et al. The role of leptin in the development of the cerebral cortex in mouse embryos. *Endocrinology*. 2006;147(2):647-58.
- [363] Bauer S, Rasika S, Han J, Mauduit C, Raccurt M, Morel G, et al. Leukemia inhibitory factor is a key signal for injury-induced neurogenesis in the adult mouse olfactory epithelium. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2003;23(5):1792-803.
- [364] Bauer S, Patterson PH. Leukemia inhibitory factor promotes neural stem cell self-renewal in the adult brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(46):12089-99.
- [365] Bauer S. Cytokine control of adult neural stem cells. *Annals of the New York Academy of Sciences*. 2009;1153:48-56.
- [366] Shimazaki T, Shingo T, Weiss S. The ciliary neurotrophic factor/leukemia inhibitory factor/gp130 receptor complex operates in the maintenance of mammalian forebrain neural stem cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(19):7642-53.
- [367] Muller S, Chakrapani BP, Schwegler H, Hofmann HD, Kirsch M. Neurogenesis in the dentate gyrus depends on ciliary neurotrophic factor and signal transducer and activator of transcription 3 signaling. *Stem cells*. 2009;27(2):431-41.
- [368] Toda H, Tsuji M, Nakano I, Kobuke K, Hayashi T, Kasahara H, et al. Stem cell-derived neural stem/progenitor cell supporting factor is an autocrine/paracrine survival factor for adult neural stem/progenitor cells. *The Journal of biological chemistry*. 2003;278(37):35491-500.
- [369] Dziembowska M, Tham TN, Lau P, Vitry S, Lazarini F, Dubois-Dalcq M. A role for CXCR4 signaling in survival and migration of neural and oligodendrocyte precursors. *Glia*. 2005;50(3):258-69.
- [370] Kokovay E, Goderie S, Wang Y, Lotz S, Lin G, Sun Y, et al. Adult SVZ lineage cells home to and leave the vascular niche via differential responses to SDF1/CXCR4 signaling. *Cell stem cell*. 2010;7(2):163-73.
- [371] Cui X, Chen J, Zacharek A, Roberts C, Yang Y, Chopp M. Nitric oxide donor up-regulation of SDF1/CXCR4 and Ang1/Tie2 promotes neuroblast cell migration after stroke. *Journal of neuroscience research*. 2009;87(1):86-95.

- [372] Ohta S, Misawa A, Fukaya R, Inoue S, Kanemura Y, Okano H, et al. Macrophage migration inhibitory factor (MIF) promotes cell survival and proliferation of neural stem/progenitor cells. *Journal of cell science*. 2012;125(Pt 13):3210-20.
- [373] Mikami Y, Okano H, Sakaguchi M, Nakamura M, Shimazaki T, Okano HJ, et al. Implantation of dendritic cells in injured adult spinal cord results in activation of endogenous neural stem/progenitor cells leading to de novo neurogenesis and functional recovery. *Journal of neuroscience research*. 2004;76(4):453-65.
- [374] de la Mano A, Gato A, Alonso MI, Carnicero E, Martin C, Moro JA. Role of interleukin-1beta in the control of neuroepithelial proliferation and differentiation of the spinal cord during development. *Cytokine*. 2007;37(2):128-37.
- [375] Ben Menachem-Zidon O, Goshen I, Kreisel T, Ben Menahem Y, Reinhartz E, Ben Hur T, et al. Intrahippocampal transplantation of transgenic neural precursor cells overexpressing interleukin-1 receptor antagonist blocks chronic isolation-induced impairment in memory and neurogenesis. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2008;33(9):2251-62.
- [376] Vawter MP, Basaric-Keys J, Li Y, Lester DS, Lebovics RS, Lesch KP, et al. Human olfactory neuroepithelial cells: tyrosine phosphorylation and process extension are increased by the combination of IL-1beta, IL-6, NGF, and bFGF. *Experimental neurology*. 1996;142(1):179-94.
- [377] Koo JW, Duman RS. IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proceedings of the National Academy of Sciences of the United States of America*. 2008;105(2):751-6.
- [378] Kim TS, Misumi S, Jung CG, Masuda T, Isobe Y, Furuyama F, et al. Increase in dopaminergic neurons from mouse embryonic stem cell-derived neural progenitor/stem cells is mediated by hypoxia inducible factor-1alpha. *Journal of neuroscience research*. 2008;86(11):2353-62.
- [379] Barkho BZ, Song H, Aimone JB, Smrt RD, Kuwabara T, Nakashima K, et al. Identification of astrocyte-expressed factors that modulate neural stem/progenitor cell differentiation. *Stem Cells Dev*. 2006;15(3):407-21.
- [380] Kahn MA, De Vellis J. Regulation of an oligodendrocyte progenitor cell line by the interleukin-6 family of cytokines. *Glia*. 1994;12(2):87-98.
- [381] Murphy M, Dutton R, Koblar S, Cheema S, Bartlett P. Cytokines which signal through the LIF receptor and their actions in the nervous system. *Progress in neurobiology*. 1997;52(5):355-78.
- [382] Martino G, Pluchino S. The therapeutic potential of neural stem cells. *Nat Rev Neurosci*. 2006;7(5):395-406.

- [383] Kokaia Z, Martino G, Schwartz M, Lindvall O. Cross-talk between neural stem cells and immune cells: the key to better brain repair? *Nature neuroscience*. 2012;15(8):1078-87.
- [384] Brazel CY, Nunez JL, Yang Z, Levison SW. Glutamate enhances survival and proliferation of neural progenitors derived from the subventricular zone. *Neuroscience*. 2005;131(1):55-65.
- [385] Castiglione M, Calafiore M, Costa L, Sortino MA, Nicoletti F, Copani A. Group I metabotropic glutamate receptors control proliferation, survival and differentiation of cultured neural progenitor cells isolated from the subventricular zone of adult mice. *Neuropharmacology*. 2008;55(4):560-7.
- [386] Tian Y, Liu Y, Chen X, Kang Q, Zhang J, Shi Q, et al. AMN082 promotes the proliferation and differentiation of neural progenitor cells with influence on phosphorylation of MAPK signaling pathways. *Neurochemistry international*. 2010;57(1):8-15.
- [387] Zhao L, Jiao Q, Yang P, Chen X, Zhang J, Zhao B, et al. Metabotropic glutamate receptor 5 promotes proliferation of human neural stem/progenitor cells with activation of mitogen-activated protein kinases signaling pathway in vitro. *Neuroscience*. 2011;192:185-94.
- [388] Di Giorgi-Gerevini V, Melchiorri D, Battaglia G, Ricci-Vitiani L, Ciceroni C, Busceti CL, et al. Endogenous activation of metabotropic glutamate receptors supports the proliferation and survival of neural progenitor cells. *Cell death and differentiation*. 2005;12(8):1124-33.
- [389] Nochi R, Kato T, Kaneko J, Itou Y, Kuribayashi H, Fukuda S, et al. Involvement of metabotropic glutamate receptor 5 signaling in activity-related proliferation of adult hippocampal neural stem cells. *The European journal of neuroscience*. 2012;36(3):2273-83.
- [390] Liu XX, Wang Q, Haydar TF, Bordey A. Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. *Nature neuroscience*. 2005;8(9):1179-87.
- [391] Fernando RN, Eleuteri B, Abdelhady S, Nussenzweig A, Andang M, Ernfors P. Cell cycle restriction by histone H2AX limits proliferation of adult neural stem cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;108(14):5837-42.
- [392] Banasr M, Hery M, Printemps R, Daszuta A. Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2004;29(3):450-60.

- [393] Brezun JM, Daszuta A. Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. *Neuroscience*. 1999;89(4):999-1002.
- [394] Brezun JM, Daszuta A. Serotonin depletion in the adult rat produces differential changes in highly polysialylated form of neural cell adhesion molecule and tenascin-C immunoreactivity. *Journal of neuroscience research*. 1999;55(1):54-70.
- [395] Encinas JM, Vaahtokari A, Enikolopov G. Fluoxetine targets early progenitor cells in the adult brain. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(21):8233-8.
- [396] Benninghoff J, Gritti A, Rizzi M, Lamorte G, Schloesser RJ, Schmitt A, et al. Serotonin depletion hampers survival and proliferation in neurospheres derived from adult neural stem cells. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2010;35(4):893-903.
- [397] O'Keeffe GC, Barker RA. Dopamine stimulates epidermal growth factor release from adult neural precursor cells derived from the subventricular zone by a disintegrin and metalloprotease. *Neuroreport*. 2011;22(18):956-8.
- [398] Blobel CP. ADAMs: key components in EGFR signalling and development. *Nature reviews Molecular cell biology*. 2005;6(1):32-43.
- [399] Kippin TE, Kapur S, van der Kooy D. Dopamine specifically inhibits forebrain neural stem cell proliferation, suggesting a novel effect of antipsychotic drugs. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2005;25(24):5815-23.
- [400] Yang P, Arnold SA, Habas A, Hetman M, Hagg T. Ciliary neurotrophic factor mediates dopamine D2 receptor-induced CNS neurogenesis in adult mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28(9):2231-41.
- [401] Wolosker H, Panizzutti R, De Miranda J. Neurobiology through the looking-glass: D-serine as a new glial-derived transmitter. *Neurochemistry international*. 2002;41(5):327-32.
- [402] Schell MJ, Molliver ME, Snyder SH. D-serine, an endogenous synaptic modulator: localization to astrocytes and glutamate-stimulated release. *Proceedings of the National Academy of Sciences of the United States of America*. 1995;92(9):3948-52.
- [403] Schell MJ, Brady RO, Jr., Molliver ME, Snyder SH. D-serine as a neuromodulator: regional and developmental localizations in rat brain glia resemble NMDA receptors. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1997;17(5):1604-15.
- [404] Mothet JP, Pollegioni L, Ouanounou G, Martineau M, Fossier P, Baux G. Glutamate receptor activation triggers a calcium-dependent and SNARE protein-dependent release of the gliotransmitter D-serine. *Proceedings of the National Academy of Sciences of the United States of America*. 2005;102(15):5606-11.

- [405] Kartvelishvily E, Shleper M, Balan L, Dumin E, Wolosker H. Neuron-derived D-serine release provides a novel means to activate N-methyl-D-aspartate receptors. *The Journal of biological chemistry*. 2006;281(20):14151-62.
- [406] Yasuda E, Ma N, Semba R. Immunohistochemical evidences for localization and production of D-serine in some neurons in the rat brain. *Neuroscience letters*. 2001;299(1-2):162-4.
- [407] Yoshikawa M, Takayasu N, Hashimoto A, Sato Y, Tamaki R, Tsukamoto H, et al. The serine racemase mRNA is predominantly expressed in rat brain neurons. *Archives of histology and cytology*. 2007;70(2):127-34.
- [408] Yoshikawa M, Nakajima K, Takayasu N, Noda S, Sato Y, Kawaguchi M, et al. Expression of the mRNA and protein of serine racemase in primary cultures of rat neurons. *European journal of pharmacology*. 2006;548(1-3):74-6.
- [409] Maeda K, Sugino H, Hirose T, Kitagawa H, Nagai T, Mizoguchi H, et al. Clozapine prevents a decrease in neurogenesis in mice repeatedly treated with phencyclidine. *Journal of pharmacological sciences*. 2007;103(3):299-308.
- [410] Huang X, Kong H, Tang M, Lu M, Ding JH, Hu G. D-Serine regulates proliferation and neuronal differentiation of neural stem cells from postnatal mouse forebrain. *CNS neuroscience & therapeutics*. 2012;18(1):4-13.
- [411] Packer MA, Stasiv Y, Benraiss A, Chmielnicki E, Grinberg A, Westphal H, et al. Nitric oxide negatively regulates mammalian adult neurogenesis. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100(16):9566-71.
- [412] Moreno-Lopez B, Romero-Grimaldi C, Noval JA, Murillo-Carretero M, Matarredona ER, Estrada C. Nitric oxide is a physiological inhibitor of neurogenesis in the adult mouse subventricular zone and olfactory bulb. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004;24(1):85-95.
- [413] Carreira BP, Morte MI, Inacio A, Costa G, Rosmaninho-Salgado J, Agasse F, et al. Nitric oxide stimulates the proliferation of neural stem cells bypassing the epidermal growth factor receptor. *Stem cells*. 2010;28(7):1219-30.
- [414] Maeda N. Structural variation of chondroitin sulfate and its roles in the central nervous system. *Central nervous system agents in medicinal chemistry*. 2010;10(1):22-31.
- [415] von Holst A, Sirko S, Faissner A. The unique 473HD-Chondroitinsulfate epitope is expressed by radial glia and involved in neural precursor cell proliferation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(15):4082-94.
- [416] Sirko S, Akita K, Von Holst A, Faissner A. Structural and functional analysis of chondroitin sulfate proteoglycans in the neural stem cell niche. *Methods in enzymology*. 2010;479:37-71.

- [417] Sirko S, von Holst A, Wizenmann A, Gotz M, Faissner A. Chondroitin sulfate glycosaminoglycans control proliferation, radial glia cell differentiation and neurogenesis in neural stem/progenitor cells. *Development*. 2007;134(15):2727-38.
- [418] Gu WL, Fu SL, Wang YX, Li Y, Lu HZ, Xu XM, et al. Chondroitin sulfate proteoglycans regulate the growth, differentiation and migration of multipotent neural precursor cells through the integrin signaling pathway. *BMC neuroscience*. 2009;10:128.
- [419] Joseph SJ, Ford MD, Barth C, Portbury S, Bartlett PF, Nurcombe V, et al. A proteoglycan that activates fibroblast growth factors during early neuronal development is a perlecan variant. *Development*. 1996;122(11):3443-52.
- [420] Inatani M, Irie F, Plump AS, Tessier-Lavigne M, Yamaguchi Y. Mammalian brain morphogenesis and midline axon guidance require heparan sulfate. *Science*. 2003;302(5647):1044-6.
- [421] Akita K, von Holst A, Furukawa Y, Mikami T, Sugahara K, Faissner A. Expression of multiple chondroitin/dermatan sulfotransferases in the neurogenic regions of the embryonic and adult central nervous system implies that complex chondroitin sulfates have a role in neural stem cell maintenance. *Stem cells*. 2008;26(3):798-809.
- [422] Kazanis I, Ffrench-Constant C. Extracellular matrix and the neural stem cell niche. *Developmental neurobiology*. 2011;71(11):1006-17.
- [423] Lathia JD, Rao MS, Mattson MP, Ffrench-Constant C. The microenvironment of the embryonic neural stem cell: lessons from adult niches? *Developmental dynamics : an official publication of the American Association of Anatomists*. 2007;236(12):3267-82.
- [424] Staquicini FI, Dias-Neto E, Li J, Snyder EY, Sidman RL, Pasqualini R, et al. Discovery of a functional protein complex of netrin-4, laminin gamma1 chain, and integrin alpha6beta1 in mouse neural stem cells. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;106(8):2903-8.
- [425] Kazanis I, Lathia JD, Vadakkan TJ, Raborn E, Wan R, Mughal MR, et al. Quiescence and activation of stem and precursor cell populations in the subependymal zone of the mammalian brain are associated with distinct cellular and extracellular matrix signals. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2010;30(29):9771-81.
- [426] Hitoshi S, Alexson T, Tropepe V, Donoviel D, Elia AJ, Nye JS, et al. Notch pathway molecules are essential for the maintenance, but not the generation, of mammalian neural stem cells. *Genes & development*. 2002;16(7):846-58.
- [427] Nakamura Y, Sakakibara S, Miyata T, Ogawa M, Shimazaki T, Weiss S, et al. The bHLH gene *hes1* as a repressor of the neuronal commitment of CNS stem cells. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(1):283-93.

- [428] Nyfeler Y, Kirch RD, Mantei N, Leone DP, Radtke F, Suter U, et al. Jagged1 signals in the postnatal subventricular zone are required for neural stem cell self-renewal. *The EMBO journal*. 2005;24(19):3504-15.
- [429] Androutsellis-Theotokis A, Leker RR, Soldner F, Hoepfner DJ, Ravin R, Poser SW, et al. Notch signalling regulates stem cell numbers in vitro and in vivo. *Nature*. 2006;442(7104):823-6.
- [430] Mizutani K, Yoon K, Dang L, Tokunaga A, Gaiano N. Differential Notch signalling distinguishes neural stem cells from intermediate progenitors. *Nature*. 2007;449(7160):351-5.
- [431] Aguirre A, Rubio ME, Gallo V. Notch and EGFR pathway interaction regulates neural stem cell number and self-renewal. *Nature*. 2010;467(7313):323-7.
- [432] Dave RK, Ellis T, Toumpas MC, Robson JP, Julian E, Adolphe C, et al. Sonic hedgehog and notch signaling can cooperate to regulate neurogenic divisions of neocortical progenitors. *PloS one*. 2011;6(2):e14680.
- [433] Conover JC, Doetsch F, Garcia-Verdugo JM, Gale NW, Yancopoulos GD, Alvarez-Buylla A. Disruption of Eph/ephrin signaling affects migration and proliferation in the adult subventricular zone. *Nature neuroscience*. 2000;3(11):1091-7.
- [434] Khodosevich K, Watanabe Y, Monyer H. EphA4 preserves postnatal and adult neural stem cells in an undifferentiated state in vivo. *Journal of cell science*. 2011;124(Pt 8):1268-79.
- [435] Theus MH, Ricard J, Bethea JR, Liebl DJ. EphB3 limits the expansion of neural progenitor cells in the subventricular zone by regulating p53 during homeostasis and following traumatic brain injury. *Stem cells*. 2010;28(7):1231-42.
- [436] Doeppner TR, Bretschneider E, Doehring M, Segura I, Senturk A, Acker-Palmer A, et al. Enhancement of endogenous neurogenesis in ephrin-B3 deficient mice after transient focal cerebral ischemia. *Acta neuropathologica*. 2011;122(4):429-42.
- [437] Depaepe V, Suarez-Gonzalez N, Dufour A, Passante L, Gorski JA, Jones KR, et al. Ephrin signalling controls brain size by regulating apoptosis of neural progenitors. *Nature*. 2005;435(7046):1244-50.
- [438] Wu C, Qiu R, Wang J, Zhang H, Murai K, Lu Q. ZHX2 Interacts with Ephrin-B and regulates neural progenitor maintenance in the developing cerebral cortex. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009;29(23):7404-12.
- [439] Murai K, Qiu R, Zhang H, Wang J, Wu C, Neubig RR, et al. Galpha subunit coordinates with ephrin-B to balance self-renewal and differentiation in neural progenitor cells. *Stem cells*. 2010;28(9):1581-9.

- [440] Qiu R, Wang J, Tsark W, Lu Q. Essential role of PDZ-RGS3 in the maintenance of neural progenitor cells. *Stem cells*. 2010;28(9):1602-10.
- [441] Qiu R, Wang X, Davy A, Wu C, Murai K, Zhang H, et al. Regulation of neural progenitor cell state by ephrin-B. *The Journal of cell biology*. 2008;181(6):973-83.
- [442] Islam O, Loo TX, Heese K. Brain-derived neurotrophic factor (BDNF) has proliferative effects on neural stem cells through the truncated TRK-B receptor, MAP kinase, AKT, and STAT-3 signaling pathways. *Current neurovascular research*. 2009;6(1):42-53.
- [443] Llado J, Haenggeli C, Maragakis NJ, Snyder EY, Rothstein JD. Neural stem cells protect against glutamate-induced excitotoxicity and promote survival of injured motor neurons through the secretion of neurotrophic factors. *Molecular and cellular neurosciences*. 2004;27(3):322-31.
- [444] Wang F, Kameda M, Yasuhara T, Tajiri N, Kikuchi Y, Liang HB, et al. GDNF-preatment enhances the survival of neural stem cells following transplantation in a rat model of Parkinson's disease. *Neurosci Res*. 2011;71(1):92-8.
- [445] Nguyen L, Malgrange B, Belachew S, Rogister B, Rocher V, Moonen G, et al. Functional glycine receptors are expressed by postnatal nestin-positive neural stem/progenitor cells. *The European journal of neuroscience*. 2002;15(8):1299-305.
- [446] Pitas RE, Boyles JK, Lee SH, Foss D, Mahley RW. Astrocytes synthesize apolipoprotein E and metabolize apolipoprotein E-containing lipoproteins. *Biochimica et biophysica acta*. 1987;917(1):148-61.
- [447] Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. *Science*. 1994;264(5160):850-2.
- [448] Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, et al. GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. *Cell stem cell*. 2009;5(6):634-45.
- [449] Yang CP, Gilley JA, Zhang G, Kernie SG. ApoE is required for maintenance of the dentate gyrus neural progenitor pool. *Development (Cambridge, England)*. 2011;138(20):4351-62.
- [450] Gan HT, Tham M, Hariharan S, Ramasamy S, Yu YH, Ahmed S. Identification of ApoE as an autocrine/paracrine factor that stimulates neural stem cell survival via MAPK/ERK signaling pathway. *Journal of neurochemistry*. 2011;117(3):565-78.
- [451] Tsai PT, Ohab JJ, Kertesz N, Groszer M, Matter C, Gao J, et al. A critical role of erythropoietin receptor in neurogenesis and post-stroke recovery. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(4):1269-74.

- [452] Noguchi CT, Asavaritikrai P, Teng R, Jia Y. Role of erythropoietin in the brain. *Critical reviews in oncology/hematology*. 2007;64(2):159-71.
- [453] Liu X, Wang Q, Haydar TF, Bordey A. Nonsynaptic GABA signaling in postnatal subventricular zone controls proliferation of GFAP-expressing progenitors. *Nature neuroscience*. 2005;8(9):1179-87.
- [454] Tham M, Ramasamy S, Gan HT, Ramachandran A, Poonepalli A, Yu YH, et al. CSPG Is a Secreted Factor that Stimulates Neural Stem Cell Survival Possibly by Enhanced EGFR Signaling. *Plos One*. 2010;5(12):e15341.
- [455] Jones LL, Yamaguchi Y, Stallcup WB, Tuszynski MH. NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2002;22(7):2792-803.
- [456] Babcock AA, Kuziel WA, Rivest S, Owens T. Chemokine expression by glial cells directs leukocytes to sites of axonal injury in the CNS. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2003;23(21):7922-30.
- [457] Owens T, Babcock AA, Millward JM, Toft-Hansen H. Cytokine and chemokine inter-regulation in the inflamed or injured CNS. *Brain research Brain research reviews*. 2005;48(2):178-84.
- [458] Krathwohl MD, Kaiser JL. Chemokines promote quiescence and survival of human neural progenitor cells. *Stem cells*. 2004;22(1):109-18.
- [459] Imitola J, Raddassi K, Park KI, Mueller FJ, Nieto M, Teng YD, et al. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1 α /CXC chemokine receptor 4 pathway. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(52):18117-22.
- [460] Reiss K, Mentlein R, Sievers J, Hartmann D. Stromal cell-derived factor 1 is secreted by meningeal cells and acts as chemotactic factor on neuronal stem cells of the cerebellar external granular layer. *Neuroscience*. 2002;115(1):295-305.
- [461] Krumbholz M, Theil D, Cepok S, Hemmer B, Kivisakk P, Ransohoff RM, et al. Chemokines in multiple sclerosis: CXCL12 and CXCL13 up-regulation is differentially linked to CNS immune cell recruitment. *Brain : a journal of neurology*. 2006;129(Pt 1):200-11.
- [462] Hill WD, Hess DC, Martin-Studdard A, Carothers JJ, Zheng J, Hale D, et al. SDF-1 (CXCL12) is upregulated in the ischemic penumbra following stroke: association with bone marrow cell homing to injury. *Journal of neuropathology and experimental neurology*. 2004;63(1):84-96.
- [463] Villeda SA, Luo J, Mosher KI, Zou B, Britschgi M, Bieri G, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*. 2011;477(7362):90-4.

- [464] Moriyama M, Fukuhara T, Britschgi M, He Y, Narasimhan R, Villeda S, et al. Complement receptor 2 is expressed in neural progenitor cells and regulates adult hippocampal neurogenesis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011;31(11):3981-9.
- [465] Aloisi F, Ria F, Adorini L. Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. *Immunology today*. 2000;21(3):141-7.
- [466] Storch A, Paul G, Csete M, Boehm BO, Carvey PM, Kupsch A, et al. Long-term proliferation and dopaminergic differentiation of human mesencephalic neural precursor cells. *Experimental neurology*. 2001;170(2):317-25.
- [467] Riaz SS, Theofilopoulos S, Jauniaux E, Stern GM, Bradford HF. The differentiation potential of human foetal neuronal progenitor cells in vitro. *Brain research Developmental brain research*. 2004;153(1):39-51.
- [468] Ben-Hur T, Ben-Menachem O, Furer V, Einstein O, Mizrahi-Kol R, Grigoriadis N. Effects of proinflammatory cytokines on the growth, fate, and motility of multipotential neural precursor cells. *Molecular and cellular neurosciences*. 2003;24(3):623-31.
- [469] Pluchino S, Muzio L, Imitola J, Deleidi M, Alfaro-Cervello C, Salani G, et al. Persistent inflammation alters the function of the endogenous brain stem cell compartment. *Brain : a journal of neurology*. 2008;131(Pt 10):2564-78.
- [470] Barnabe-Heider F, Wasylnka JA, Fernandes KJ, Porsche C, Sendtner M, Kaplan DR, et al. Evidence that embryonic neurons regulate the onset of cortical gliogenesis via cardiotrophin-1. *Neuron*. 2005;48(2):253-65.
- [471] Butovsky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, et al. Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Molecular and cellular neurosciences*. 2006;31(1):149-60.
- [472] Guan Y, Jiang Z, Ciric B, Rostami AM, Zhang GX. Upregulation of chemokine receptor expression by IL-10/IL-4 in adult neural stem cells. *Experimental and molecular pathology*. 2008;85(3):232-6.
- [473] Gomez-Nicola D, Valle-Argos B, Pallas-Bazarra N, Nieto-Sampedro M. Interleukin-15 regulates proliferation and self-renewal of adult neural stem cells. *Molecular biology of the cell*. 2011;22(12):1960-70.
- [474] Iosif RE, Ekdahl CT, Ahlenius H, Pronk CJ, Bonde S, Kokaia Z, et al. Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2006;26(38):9703-12.

- [475] Cacci E, Ajmone-Cat MA, Anelli T, Biagioni S, Minghetti L. In vitro neuronal and glial differentiation from embryonic or adult neural precursor cells are differently affected by chronic or acute activation of microglia. *Glia*. 2008;56(4):412-25.
- [476] Williams CA, Lavik EB. Engineering the CNS stem cell microenvironment. *Regenerative medicine*. 2009;4(6):865-77.
- [477] Craig CG, Tropepe V, Morshead CM, Reynolds BA, Weiss S, van der Kooy D. In vivo growth factor expansion of endogenous subependymal neural precursor cell populations in the adult mouse brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1996;16(8):2649-58.
- [478] Kaneko N, Kako E, Sawamoto K. Enhancement of ventricular-subventricular zone-derived neurogenesis and oligodendrogenesis by erythropoietin and its derivatives. *Frontiers in cellular neuroscience*. 2013;7:235.
- [479] Yoshimura S, Takagi Y, Harada J, Teramoto T, Thomas SS, Waeber C, et al. FGF-2 regulation of neurogenesis in adult hippocampus after brain injury. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(10):5874-9.
- [480] Teramoto T, Qiu J, Plumier JC, Moskowitz MA. EGF amplifies the replacement of parvalbumin-expressing striatal interneurons after ischemia. *The Journal of clinical investigation*. 2003;111(8):1125-32.
- [481] Pencea V, Bingaman KD, Wiegand SJ, Luskin MB. Infusion of brain-derived neurotrophic factor into the lateral ventricle of the adult rat leads to new neurons in the parenchyma of the striatum, septum, thalamus, and hypothalamus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(17):6706-17.
- [482] Benraiss A, Chmielnicki E, Lerner K, Roh D, Goldman SA. Adenoviral brain-derived neurotrophic factor induces both neostriatal and olfactory neuronal recruitment from endogenous progenitor cells in the adult forebrain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2001;21(17):6718-31.
- [483] Zhang ZG, Zhang L, Jiang Q, Zhang R, Davies K, Powers C, et al. VEGF enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. *The Journal of clinical investigation*. 2000;106(7):829-38.
- [484] Surget A, Tanti A, Leonardo ED, Laugeray A, Rainer Q, Touma C, et al. Antidepressants recruit new neurons to improve stress response regulation. *Molecular psychiatry*. 2011;16(12):1177-88.
- [485] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000;20(24):9104-10.
- [486] Wang HD, Dunnavant FD, Jarman T, Deutch AY. Effects of antipsychotic drugs on neurogenesis in the forebrain of the adult rat. *Neuropsychopharmacology : official*

publication of the American College of Neuropsychopharmacology. 2004;29(7):1230-8.

- [487] Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Molecular psychiatry*. 2009;14(8):764-73, 39.
- [488] Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. 2004;29(6):1063-9.
- [489] Selemon LD, Lidow MS, Goldman-Rakic PS. Increased volume and glial density in primate prefrontal cortex associated with chronic antipsychotic drug exposure. *Biological psychiatry*. 1999;46(2):161-72.
- [490] Green W, Patil P, Marsden CA, Bennett GW, Wigmore PM. Treatment with olanzapine increases cell proliferation in the subventricular zone and prefrontal cortex. *Brain research*. 2006;1070(1):242-5.
- [491] Wang DD, Krueger DD, Bordey A. GABA depolarizes neuronal progenitors of the postnatal subventricular zone via GABAA receptor activation. *The Journal of physiology*. 2003;550(Pt 3):785-800.
- [492] Nguyen L, Malgrange B, Breuskin I, Bettendorff L, Moonen G, Belachew S, et al. Autocrine/paracrine activation of the GABA(A) receptor inhibits the proliferation of neurogenic polysialylated neural cell adhesion molecule-positive (PSA-NCAM+) precursor cells from postnatal striatum. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2003;23(8):3278-94.
- [493] Bolteus AJ, Bordey A. GABA release and uptake regulate neuronal precursor migration in the postnatal subventricular zone. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2004;24(35):7623-31.
- [494] Wu X, Castren E. Co-treatment with diazepam prevents the effects of fluoxetine on the proliferation and survival of hippocampal dentate granule cells. *Biological psychiatry*. 2009;66(1):5-8.
- [495] Petrus DS, Fabel K, Kronenberg G, Winter C, Steiner B, Kempermann G. NMDA and benzodiazepine receptors have synergistic and antagonistic effects on precursor cells in adult hippocampal neurogenesis. *The European journal of neuroscience*. 2009;29(2):244-52.
- [496] Cossetti C, Alfaro-Cervello C, Donega M, Tyzack G, Pluchino S. New perspectives of tissue remodelling with neural stem and progenitor cell-based therapies. *Cell and tissue research*. 2012;349(1):321-9.
- [497] Marchetti B, Pluchino S. Wnt your brain be inflamed? Yes, it Wnt! *Trends in molecular medicine*. 2013;19(3):144-56.

- [498] Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nature reviews Immunology*. 2008;8(9):726-36.
- [499] Chu K, Kim M, Park KI, Jeong SW, Park HK, Jung KH, et al. Human neural stem cells improve sensorimotor deficits in the adult rat brain with experimental focal ischemia. *Brain research*. 2004;1016(2):145-53.
- [500] Ziv Y, Avidan H, Pluchino S, Martino G, Schwartz M. Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(35):13174-9.
- [501] Gerdoni E, Gallo B, Casazza S, Musio S, Bonanni I, Pedemonte E, et al. Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis. *Annals of neurology*. 2007;61(3):219-27.
- [502] Bacigaluppi M, Pluchino S, Peruzzotti-Jametti L, Kilic E, Kilic U, Salani G, et al. Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. *Brain : a journal of neurology*. 2009;132(Pt 8):2239-51.
- [503] Pluchino S, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, et al. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature*. 2005;436(7048):266-71.
- [504] Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C, Hamner B, et al. A perivascular niche for brain tumor stem cells. *Cancer cell*. 2007;11(1):69-82.
- [505] Pluchino S, Gritti A, Blezer E, Amadio S, Brambilla E, Borsellino G, et al. Human neural stem cells ameliorate autoimmune encephalomyelitis in non-human primates. *Annals of neurology*. 2009;66(3):343-54.
- [506] Pluchino S, Zanotti L, Brambilla E, Rovere-Querini P, Capobianco A, Alfaro-Cervello C, et al. Immune regulatory neural stem/precursor cells protect from central nervous system autoimmunity by restraining dendritic cell function. *Plos One*. 2009;4(6):e5959.
- [507] Pluchino S, Martino G. The therapeutic plasticity of neural stem/precursor cells in multiple sclerosis. *J Neurol Sci*. 2008;265(1-2):105-10.
- [508] Jeong SW, Chu K, Jung KH, Kim SU, Kim M, Roh JK. Human neural stem cell transplantation promotes functional recovery in rats with experimental intracerebral hemorrhage. *Stroke; a journal of cerebral circulation*. 2003;34(9):2258-63.
- [509] Fujiwara Y, Tanaka N, Ishida O, Fujimoto Y, Murakami T, Kajihara H, et al. Intravenously injected neural progenitor cells of transgenic rats can migrate to the injured spinal cord and differentiate into neurons, astrocytes and oligodendrocytes. *Neuroscience letters*. 2004;366(3):287-91.

- [510] Muller FJ, Snyder EY, Loring JF. Gene therapy: can neural stem cells deliver? *Nat Rev Neurosci.* 2006;7(1):75-84.
- [511] Soares S, Sotelo C. Adult neural stem cells from the mouse subventricular zone are limited in migratory ability compared to progenitor cells of similar origin. *Neuroscience.* 2004;128(4):807-17.
- [512] Doetsch F, Petreanu L, Caille I, Garcia-Verdugo JM, Alvarez-Buylla A. EGF converts transit-amplifying neurogenic precursors in the adult brain into multipotent stem cells. *Neuron.* 2002;36(6):1021-34.
- [513] Maslov AY, Barone TA, Plunkett RJ, Pruitt SC. Neural stem cell detection, characterization, and age-related changes in the subventricular zone of mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2004;24(7):1726-33.
- [514] Mi R, Luo Y, Cai J, Limke TL, Rao MS, Hoke A. Immortalized neural stem cells differ from nonimmortalized cortical neurospheres and cerebellar granule cell progenitors. *Experimental neurology.* 2005;194(2):301-19.
- [515] Pluchino S, Quattrini A, Brambilla E, Gritti A, Salani G, Dina G, et al. Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature.* 2003;422(6933):688-94.
- [516] Mueller FJ, Seroby N, Schraufstatter IU, DiScipio R, Wakeman D, Loring JF, et al. Adhesive interactions between human neural stem cells and inflamed human vascular endothelium are mediated by integrins. *Stem cells.* 2006;24(11):2367-72.
- [517] Darsalia V, Kallur T, Kokaia Z. Survival, migration and neuronal differentiation of human fetal striatal and cortical neural stem cells grafted in stroke-damaged rat striatum. *The European journal of neuroscience.* 2007;26(3):605-14.
- [518] Lie DC, Song H, Colamarino SA, Ming GL, Gage FH. Neurogenesis in the adult brain: new strategies for central nervous system diseases. *Annual review of pharmacology and toxicology.* 2004;44:399-421.
- [519] Emsley JG, Mitchell BD, Kempermann G, Macklis JD. Adult neurogenesis and repair of the adult CNS with neural progenitors, precursors, and stem cells. *Progress in neurobiology.* 2005;75(5):321-41.
- [520] Benedetti S, Pirola B, Pollo B, Magrassi L, Bruzzone MG, Rigamonti D, et al. Gene therapy of experimental brain tumors using neural progenitor cells. *Nature medicine.* 2000;6(4):447-50.
- [521] Sun C, Zhang H, Li J, Huang H, Cheng H, Wang Y, et al. Modulation of the major histocompatibility complex by neural stem cell-derived neurotrophic factors used for regenerative therapy in a rat model of stroke. *Journal of translational medicine.* 2010;8:77.
- [522] Cusimano M, Bizziato D, Brambilla E, Donega M, Alfaro-Cervello C, Snider S, et al. Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary

tissue damage in the injured spinal cord. *Brain : a journal of neurology*. 2012;135(Pt 2):447-60.

- [523] Cao QL, Howard RM, Dennison JB, Whittemore SR. Differentiation of engrafted neuronal-restricted precursor cells is inhibited in the traumatically injured spinal cord. *Experimental neurology*. 2002;177(2):349-59.
- [524] Ben-Hur T. Immunomodulation by neural stem cells. *J Neurol Sci*. 2008;265(1-2):102-4.
- [525] Lee HJ, Kim KS, Kim EJ, Choi HB, Lee KH, Park IH, et al. Brain transplantation of immortalized human neural stem cells promotes functional recovery in mouse intracerebral hemorrhage stroke model. *Stem cells*. 2007;25(5):1204-12.
- [526] Lee HJ, Kim KS, Park IH, Kim SU. Human neural stem cells over-expressing VEGF provide neuroprotection, angiogenesis and functional recovery in mouse stroke model. *Plos One*. 2007;2(1):e156.
- [527] Lindvall O, Kokaia Z. Stem cells in human neurodegenerative disorders--time for clinical translation? *The Journal of clinical investigation*. 2010;120(1):29-40.
- [528] Einstein O, Friedman-Levi Y, Grigoriadis N, Ben-Hur T. Transplanted neural precursors enhance host brain-derived myelin regeneration. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009;29(50):15694-702.
- [529] Capone C, Frigerio S, Fumagalli S, Gelati M, Principato MC, Storini C, et al. Neurosphere-derived cells exert a neuroprotective action by changing the ischemic microenvironment. *Plos One*. 2007;2(4):e373.
- [530] Daadi MM, Davis AS, Arac A, Li Z, Maag AL, Bhatnagar R, et al. Human neural stem cell grafts modify microglial response and enhance axonal sprouting in neonatal hypoxic-ischemic brain injury. *Stroke; a journal of cerebral circulation*. 2010;41(3):516-23.
- [531] Lalancette-Hebert M, Gowing G, Simard A, Weng YC, Kriz J. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2007;27(10):2596-605.
- [532] Lu P, Jones LL, Snyder EY, Tuszynski MH. Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. *Experimental neurology*. 2003;181(2):115-29.
- [533] Einstein O, Karussis D, Grigoriadis N, Mizrachi-Kol R, Reinhartz E, Abramsky O, et al. Intraventricular transplantation of neural precursor cell spheres attenuates acute experimental allergic encephalomyelitis. *Molecular and cellular neurosciences*. 2003;24(4):1074-82.

- [534] Fainstein N, Vaknin I, Einstein O, Zisman P, Ben Sasson SZ, Baniyash M, et al. Neural precursor cells inhibit multiple inflammatory signals. *Molecular and cellular neurosciences*. 2008;39(3):335-41.
- [535] Knight JC, Scharf EL, Mao-Draayer Y. Fas activation increases neural progenitor cell survival. *Journal of neuroscience research*. 2010;88(4):746-57.
- [536] Wang L, Shi J, van Ginkel FW, Lan L, Niemeyer G, Martin DR, et al. Neural stem/progenitor cells modulate immune responses by suppressing T lymphocytes with nitric oxide and prostaglandin E2. *Experimental neurology*. 2009;216(1):177-83.
- [537] Kim HM, Hwang DH, Lee JE, Kim SU, Kim BG. Ex vivo VEGF delivery by neural stem cells enhances proliferation of glial progenitors, angiogenesis, and tissue sparing after spinal cord injury. *Plos One*. 2009;4(3):e4987.
- [538] Kim SY, Cho HS, Yang SH, Shin JY, Kim JS, Lee ST, et al. Soluble mediators from human neural stem cells play a critical role in suppression of T-cell activation and proliferation. *Journal of neuroscience research*. 2009;87(10):2264-72.
- [539] Ricci-Vitiani L, Lombardi DG, Signore M, Biffoni M, Pallini R, Parati E, et al. Human neural progenitor cells display limited cytotoxicity and increased oligodendrogenesis during inflammation. *Cell death and differentiation*. 2007;14(4):876-8.
- [540] Lee ST, Chu K, Jung KH, Kim SJ, Kim DH, Kang KM, et al. Anti-inflammatory mechanism of intravascular neural stem cell transplantation in haemorrhagic stroke. *Brain : a journal of neurology*. 2008;131(Pt 3):616-29.
- [541] Einstein O, Fainstein N, Vaknin I, Mizrachi-Kol R, Reihartz E, Grigoriadis N, et al. Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression. *Annals of neurology*. 2007;61(3):209-18.
- [542] Yoo J, Kim HS, Hwang DY. Stem cells as promising therapeutic options for neurological disorders. *Journal of cellular biochemistry*. 2013;114(4):743-53.
- [543] Tsuji O, Miura K, Fujiyoshi K, Momoshima S, Nakamura M, Okano H. Cell therapy for spinal cord injury by neural stem/progenitor cells derived from iPS/ES cells. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2011;8(4):668-76.
- [544] Ben-Hur T. Cell therapy for multiple sclerosis. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2011;8(4):625-42.
- [545] Willerth SM. Neural tissue engineering using embryonic and induced pluripotent stem cells. *Stem cell research & therapy*. 2011;2(2):17.
- [546] Ellis-Behnke RG, Liang YX, You SW, Tay DK, Zhang S, So KF, et al. Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(13):5054-9.

- [547] Guo J, Su H, Zeng Y, Liang YX, Wong WM, Ellis-Behnke RG, et al. Reknitting the injured spinal cord by self-assembling peptide nanofiber scaffold. *Nanomedicine : nanotechnology, biology, and medicine*. 2007;3(4):311-21.
- [548] Christopherson GT, Song H, Mao HQ. The influence of fiber diameter of electrospun substrates on neural stem cell differentiation and proliferation. *Biomaterials*. 2009;30(4):556-64.
- [549] Discher DE, Janmey P, Wang YL. Tissue cells feel and respond to the stiffness of their substrate. *Science*. 2005;310(5751):1139-43.
- [550] Hynes SR, Rauch MF, Bertram JP, Lavik EB. A library of tunable poly(ethylene glycol)/poly(L-lysine) hydrogels to investigate the material cues that influence neural stem cell differentiation. *Journal of biomedical materials research Part A*. 2009;89(2):499-509.
- [551] Soen Y, Mori A, Palmer TD, Brown PO. Exploring the regulation of human neural precursor cell differentiation using arrays of signaling microenvironments. *Molecular systems biology*. 2006;2:37.
- [552] Silva GA, Czeisler C, Niece KL, Beniash E, Harrington DA, Kessler JA, et al. Selective differentiation of neural progenitor cells by high-epitope density nanofibers. *Science*. 2004;303(5662):1352-5.
- [553] Tysseling-Mattiace VM, Sahni V, Niece KL, Birch D, Czeisler C, Fehlings MG, et al. Self-assembling nanofibers inhibit glial scar formation and promote axon elongation after spinal cord injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2008;28(14):3814-23.
- [554] Saha K, Irwin EF, Kozhukh J, Schaffer DV, Healy KE. Biomimetic interfacial interpenetrating polymer networks control neural stem cell behavior. *Journal of biomedical materials research Part A*. 2007;81(1):240-9.
- [555] Nakajima M, Ishimuro T, Kato K, Ko IK, Hirata I, Arima Y, et al. Combinatorial protein display for the cell-based screening of biomaterials that direct neural stem cell differentiation. *Biomaterials*. 2007;28(6):1048-60.