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

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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 homoeostasis 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.

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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-HT2C 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

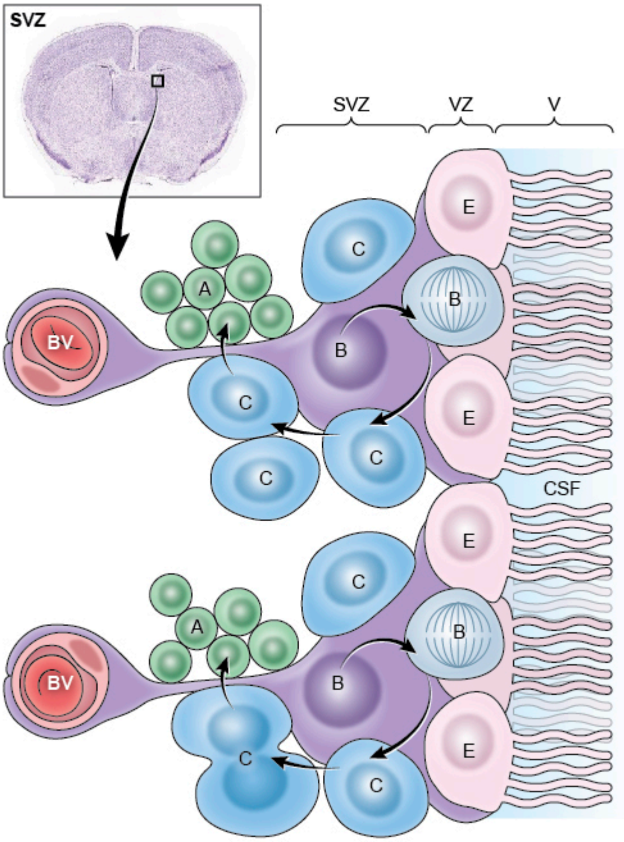

Figure 1. Subventricular Zone Niche. Coronal brain section (Allen Developing Mouse Brain Atlas) shows the location of the neurogenic subventricular zone (SVZ) niche. The SVZ can be found contacting the overlying ventricular zone (VZ), a pseudo-stratified epithelium layer that lines the cerebrospinal 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

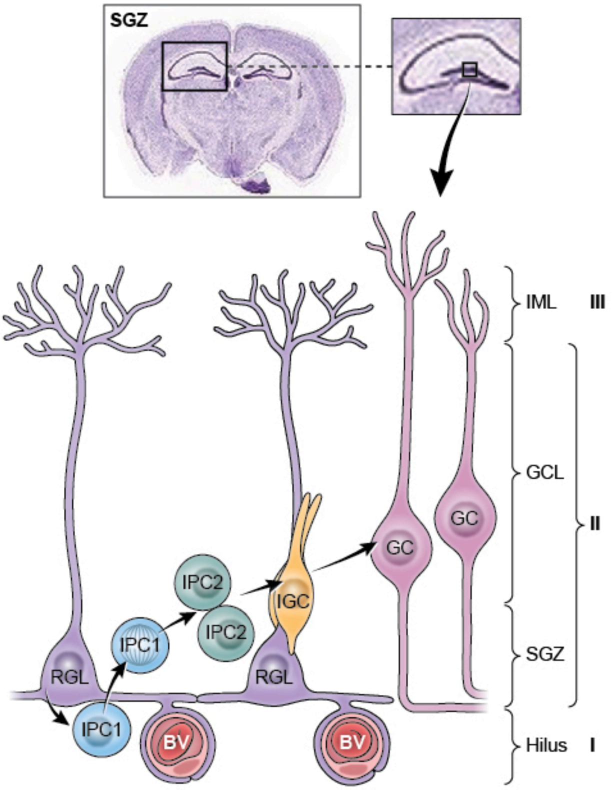

Figure 2. Subgranular Zone Niche. Coronal brain section (Allen Developing Mouse Brain Atlas) shows the location of the subgranular zone (SGZ) niche in the dentate gyrus of the hippocampus. Radial glial-like cells (RGL) are the type of NSC that make up the SGZ. In the proximal domain (I) or hilus, they 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-conducive 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 neurogenenic 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 (PDGFRα) (oligodendrocytic markers) [34]. Only a small number of cells express neuronal markers such as microtubule-associated protein 2 (MAP2) and DCX,

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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

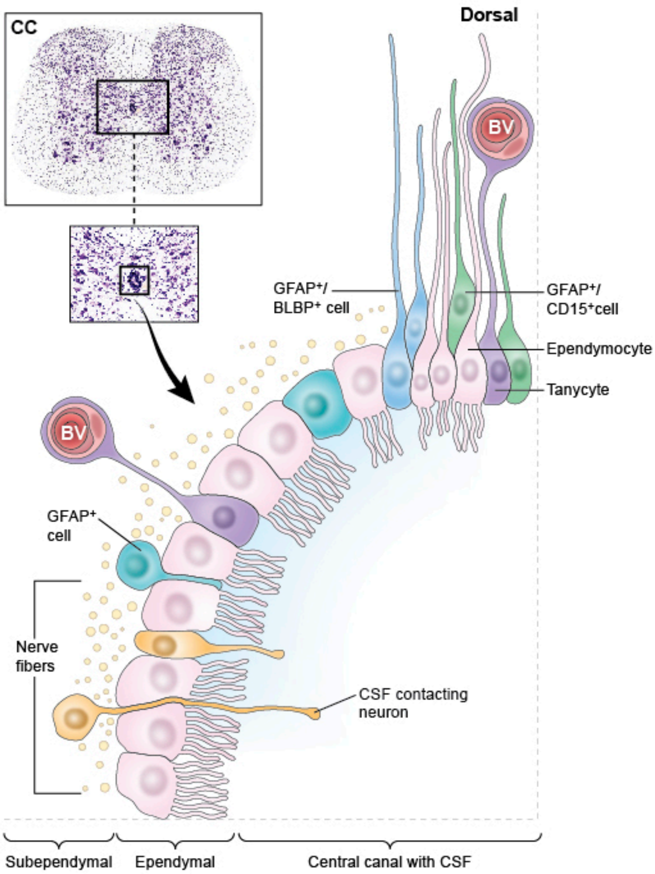

Figure 3. Central Canal Niche. Cross-section through the spinal cord at lumbar level 1 (Allen Developing Mouse Brain Atlas) shows the location of the central canal. Lining the lumen of the cerebrospinal fluid (CSF)-filled central canal is a pseudo-stratified epithelium with interspersed ependymal cells (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-alpha (MIP2-alpha) 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

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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

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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 chemotactic 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

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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/paresthesia, 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 re-growth, 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].

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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 (PDGFRα) on NSC whereby it regulates neurogenesis [327]. PDGF receptor β (PDGFRβ) 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-catentin) 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]. Wbt7b 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-catentin, 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 subendymal 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 (GSKβ) signaling pathway in hippocampal NSC, allowing for accumulation of β-catenin and consequent promotion of proliferation of NSC [358, 359].

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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-1α and IL-1β have both been found to positively regulate neurogenesis [374, 375]. Interestingly, the effect of IL-1β 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, $\alpha6\beta1$ integrins are expressed in high levels on proliferating NSC and progenitors [65, 424, 425]. Quiescent NSC do not express β1 integrins; activation of NSC through daughter cell depletion or administration of CXCL12/SDF-1, however, leads to upregulation of β1 integrins, showing the pivotal role of β1 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-epitheliun derived growth factor; PDGF, platelet-derived growth factors; Wnt, wingless-related integration site; BMP, bone morphogenic proteinss; 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 (*in vivo*).	[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 (*in vitro*)	[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 (*in vitro)*	[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 (*in vitro*)	[465, 470]
IL-4	NSC migration↑ differentiation↑	T cells (Th2), through effect on microglia/macrophages	EAE related chemokines treatment (*in vitro*)	[471, 472]
IL-10	NSC migration↑	Reactivated astrocytes, activated lymphocytes, microglia/macrophages	EAE related chemokines treatment (*in vitro*)	[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. Lipopolysaccaride (LPS)-stimulation (*in vitro*).	[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]

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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 ($\alpha 4$ β1) 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 *Ifng*, *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 tumorgenicity [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-Ooigodendrocyte 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

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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

O_{2} – 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-epitheliun 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

GSKβ-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-lusine-valine-alanine-valine

RGD – tripeptide-Arg-Gly-Asp

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