Neural Stem Cell Plasticity: Advantages in Therapy for the Injured Central Nervous System

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The physiological and pathological properties of the neural germinal stem cell niche have been well-studied in the past 30 years, mainly in animals and within given limits in humans, and knowledge is available for the cyto-architectonic structure, the cellular components, the timing of development and the energetic maintenance of the niche, as well as for the therapeutic potential and the cross talk between neural and immune cells. In recent years we have gained detailed understanding of the potentiality of neural stem cells (NSCs), although we are only beginning to understand their molecular, metabolic, and epigenetic profile in physiopathology and, further, more can be invested to measure quantitatively the activity of those cells, to model in vitro their therapeutic responses or to predict interactions in silico. Information in this direction has been put forward for other organs but is still limited in the complex and very less accessible context of the brain. A comprehensive understanding of the behavior of endogenous NSCs will help to tune or model them toward a desired response in order to treat complex neurodegenerative diseases. NSCs have the ability to modulate multiple cellular functions and exploiting their plasticity might make them into potent and versatile cellular drugs.

Keywords: neural stem cells, microenvironment, plasticity, metabolism, inflammation, stroke, multiple sclerosis, aging

INTRODUCTION

Although it has been thought for a long time that mammalian neurogenesis occurs only during embryonic and perinatal stages, young neurons are continuously incorporated into the adult brain as demonstrated by Altman and Das already in the early sixties (Altman, 1962; Altman and Das, 1965). Indeed, neural stem cells (NSCs), residing in the brain of most adult mammals in the so-called “neurogenic niches,” sustain neurogenesis throughout life. It is estimated that 700 new neurons are generated every day by the neuropaotetic niche in an adult human hippocampus, outlining one aspect of the plasticity/renewal capacity of NSCs (Knoth et al., 2010; Spalding et al., 2013). As for other stem cells, the specialized microenvironment of the neurogenic niche ensures not only NSC self-renewal but also differentiation, mainly into neurons. However, neurogenesis is not the only activity of NSCs in the adulthood. As a matter of fact, recent studies indicate that adult NSCs residing within the sub-ventricular zone (SVZ) might physiologically exert alternative functions to cell replacement, the so-called non-neurogenic functions (Martino et al., 2014), mainly aimed at protecting CNS homeostasis, in both physiological and pathological conditions. They regulate and are regulated by several signaling pathways (Faigle and Song, 2013) that, tuning...
the evolution of progenitor proliferation, division, and migration, can per se also impact the composition of the niche (Preston and Sherman, 2011; Gattazzo et al., 2014). Neighboring cells, the vasculature and the cerebrospinal fluid constitute the main routes through which molecular signals reach NSCs and affect their behavior.

Overall, knowing the physiological properties of NSCs and what changes in pathological conditions open up the possibility of exploiting NSC plasticity for preventive/therapeutic purposes.

This review will primarily focus on (i) the properties of precursors of the adult neurogenic niches of the central nervous system (CNS); (ii) the mechanisms of inter- and intra-cellular communication of NSCs and other cells, resident or not in the niche, in physio- and patho-logical conditions, with focus on multiple sclerosis (MS) and ischemic stroke, neurodegenerative disorders of the brain that unfold acute and chronic consequences.

WHAT DEFINES A NSC AND A NSC NICHE?

At the onset of murine neurogenesis, at embryonic day 9.5, the precursors in the CNS are neuroepithelial cells (NECs) that form a tube with a central canal (Taverna et al., 2014). NECs are highly proliferative and initially divide symmetrically to expand; afterwards they convert into radial glial cells (RGCs) that divide both symmetrically and asymmetrically. Basal processes of RGCs are used by newborn neurons as guiding scaffolds while they migrate away from the germinal niche toward the pial surface.

Although most CNS regions largely extinguish their NSC pool after development, discrete areas of the adult brain retain NSCs and active neurogenesis throughout life (Ming and Song, 2005, 2011). Namely, the striatal subventricular zone (SVZ) and the hippocampal dentate gyrus (DG, subgranular zone SGZ) are the most extensively characterized adult neurogenic niches. However, according to the most recent evidences, sites of neurogenesis are present also in the ependyma (Alvarez-Buylla and Lim, 2004; Bjornsson et al., 2015), near the third and fourth ventricle, in the forebrain, in the striatum, in the amygdala, in the hypothalamus, in the substantia nigra and in the subcortical white matter or spinal cord root ganglia (Bernier et al., 2002; Lie et al., 2002; Kokoeva et al., 2005; Chang et al., 2008; Ernst et al., 2014; Muratori et al., 2015; Stolp and Molnar, 2015). Proliferating cells from those regions, namely somatic NSCs, can be isolated and established as virtually perpetual cell lines in response to fibroblast growth factor 2 (FGF-2) and epidermal growth factor (EGF) similar to their embryonic counterparts (Temple, 2001).

In the adult neural stem cell niche, NSCs, immature neurons, supporting astrocytes, blood vessels and epithelial ciliated cells are in close contact and the vasculature with “leaky” features supports adult neurogenesis (Butti et al., 2014). In the mouse, the SVZ contains slowly dividing progenitors that can be subdivided into two types: type B1 cells, in close contact with both the cerebrospinal fluid (CSF) and the blood vessels of the SVZ, and type B2 cells, closer to the striatum (Ihrie et al., 2011). B1 cells give rise to transit amplifying cells (type C cells), located in close proximity to blood vessels, and along with B2 cells, they form a glial supportive sheath around their more differentiated progeny and migrating neuroblasts, type A cells, that originate from type C cells. Type A cells migrate tangentially to form the rostral migratory stream (RMS) to the olfactory bulb for terminal differentiation. Once in the olfactory bulb, the neuroblasts defasciculate from the stream and migrate radially to their site of terminal differentiation into neurons (Alvarez-Buylla et al., 2000). SVZ-NSCs give rise also to oligodendrocyte precursors and mature oligodendrocytes, continuously replenishing cells in the corpus callosum (Menn et al., 2006).

The primary role of the neurogenic SGZ niche instead is to generate new granule cells, primary excitatory neurons that support hippocampus-dependent cognitive functions (Zhao et al., 2008). Stem cells of the SGZ give rise to radial astrocytes that convert into immature progenitors (Type 1, the counterpart of type B in the SVZ) and eventually into neuroblasts (Type 2, the counterpart of Type C-A cells in the SVZ) (Zhao et al., 2008). Complete depletion either of type 2 or type C cells, respectively in the SGZ and SVZ, (non-radial glia like cells) stops neurogenesis (Doetsch et al., 1999; Ahn and Joyner, 2005), although, but infrequently, dividing radial glia could sustain neurogenesis as well (Seri et al., 2004). NSCs of the SGZ are also in close contact with blood vessels and endothelial cells, that act as scaffolding cells for NSCs (Palmer et al., 2000) and play a major role in directing NSC specification (Shen et al., 2004, 2008; Tavaezoie et al., 2008; Kokoyav et al., 2010).

This is the conventional cell classification for the mouse neural germinal center, which has been better characterized.

In humans the SVZ differs from the one in rodents because it organizes into four layers instead: the ependymal layer, the hypocellular gap, the astrocytic ribbon, and the transitional zone to the parenchyma, rich in myelin and oligodendrocytes (Quinones-Hinojosa et al., 2006). Migrating neuron-like cells can occasionally be found in the layers II and III as individual cells (Sanai et al., 2004; Quinones-Hinojosa et al., 2006). In detail, layer I consists of an ependymal monolayer lining the ventricular wall with astrocytic processes contacting the ventricular wall. Layer II, also known as the gap region, is rich in GFAP+ processes, with only some neuroblasts in the anterior regions. Ependymal cells send basal processes into Layer II, making critical contacts with the underlying basal lamina. Layer II may function as the corridor for neuroblast migration. Layer III is the proliferative region of the human SVZ, with GFAP+/Ki67+ and CD133+ cells. Few neuroblasts are present in the human SVZ, compared to the rodent, and are found mainly in Layer III. Some ependymal cells, which typically comprise the epithelial barrier of the ventricles, have motile cilia and are found in small clusters (4–14 cells) in Layer III (Quinones-Hinojosa et al., 2006; Kam et al., 2009). Layer IV represents the first portion of brain parenchyma away from the parietal ventricle and where the first evidence of neurons is found.

EXTRACELLULAR CUES AND INTRINSIC GENETIC PROGRAMS CONTROL THE NSC FUNCTIONS IN PHYSIOLOGICAL CONDITIONS IN THE ADULT BRAIN

Main feature of NSCs is their plasticity (Suh et al., 2009; Martino et al., 2011). The two major adult stem neurogenic niches take
advantage of different mechanisms to exploit this property, which manifests as self renewal capacity, quiescence, metabolic modulation, homing, differentiation capacity, cellular cross-talk, and immune surveillance (Figure 1A, Table 1).

The maintenance of the neurogenic niche itself and the renewal capacity depends on active intrinsic genetic (Tirone et al., 2013) and epigenetic (Liu et al., 2010; Yao et al., 2016) programs along with microenvironment-dependent specific properties. Autocrine regulators of NSC proliferation, such as transforming growth factor α (Tropepe et al., 1997; Guerra-Crespo et al., 2009) and β (Dias et al., 2014), amphyregulin, fibroblast growth factor-2 (FGF-2), insulin-like growth factor 2 (IGF2) (Marques et al., 2011) are released from specific subsets of NSCs along with leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) that promote proliferation (Emsley and Hagg, 2003; Lee et al., 2013) and sphingosine-1-phosphate (S1P) or prostaglandin D2 (PGD2) that instead maintain quiescence (Codega et al., 2014; Chaker et al., 2016). The environment-contribution to NSCs plasticity encompasses several elements as described below.

Close anatomical association between NSCs and the vascular structure (vascular niche) is preserved both in the SVZ and SGZ and vascular endothelial cells of the niche secrete Notch ligands Jagged1, Jagged2, and Delta-like-4, crucial factors for self-renewal and neurogenesis (Shen et al., 2004; Androussellis-Theotokis et al., 2010; Lu et al., 2011). Recent evidence supports the hypothesis that the cross-talk between blood vessels and NSCs is bi-directional: NSCs can indeed provide juxtacrine and paracrine signals to drive endothelial cells (Chou and Modo, 2016) and promote angiogenesis (Hicks et al., 2013). Moreover, vascular endothelial growth factor (VEGF) is a shared cue both for angiogenesis and neurogenesis because on one side it promotes the angiogenic development of capillaries, on the other, the secretion of neurogenic molecules by proximal endothelial cells (Jin et al., 2002; Cao et al., 2004; Kim et al., 2004; Udo et al., 2008; Ruiz de Almodovar et al., 2009). Further, other cues secreted from vascular endothelial cells such as neurotrophin 3 (NT3) or betacellulin (BTC) maintain quiescence or promote proliferation of NSCs, respectively (Gomez-Gaviro et al., 2012; Delgado et al., 2014), although there is evidence of NT3 effect on differentiation (Shimazu et al., 2006), while stromal derived factor-1 (SDF1) stimulates the motility of type A, B, and C neuroblasts (Kokovay et al., 2010).

The extracellular matrix (ECM), a dynamic and complex environmental element characterized by biophysical and biochemical properties specific for each tissue and able to regulate cell behavior, represents also an essential player in stem cell niche (Gattazzo et al., 2014). Extensions of the extracellular matrix known as fractones project from the blood vessels of the subventricular plexus as thin, highly branching ECM stalks that expand into bulbs where they contact the basal surface of the ependymal layer (Mercier et al., 2002). Fractones are enriched in laminin, heparan sulfate, perlecan, nidogen, and collagen. Those associations are able to bind several growth factors, suggesting that they may play a role in concentrating, activating, and presenting trophic factors to cells within the niche (Kerever et al., 2007).

NSCs receive inputs also from other cells such as microglia which reside in close proximity to NSCs of the niche. Indeed, resting microglia secrete factors that promote NSC niche maintenance and, at the same time, astrocyte differentiation of striatal NSCs via the Jak/Stat3 pathway (Zhu et al., 2008). Moreover, microglia contribute to the development of cytoarchitectonic and functional differences across cortical areas of the brain, secreting growth factors, and cytokines that tightly regulate the neurogenic process (Kim and de Vellis, 2005; Harry, 2013; Su et al., 2014). Conversely, in vitro, microglia promote neuronal differentiation, but not maintenance or self-renewal (Walton et al., 2006). On the other side, activated microglia inhibit neurogenesis (Sierra et al., 2014) favoring gliogenesis via tumor necrosis factor-α (TNFα) (Carpentier and Palmer, 2009), and when exposed to interleukin 4 (IL4) and interferon-γ (IFNγ), they secrete insulin-like growth factor 1 (IGF1) and promote neuronal differentiation of NSCs (Butovsky et al., 2006). Conversely, NSCs can also influence microglia via VEGF that in turn modulates microglial activation, proliferation and phagocytosis (Mosher et al., 2012).

Stem plasticity is modulated by other cell types as well, namely astrocytes, residing in close proximity with NSCs both in the SVZ and in the SGZ. Their contribution to NSC proliferation is likely exploited via ATP release (Cao et al., 2013) while Wnt3, neurogenesin-1 (NG1), thrombospondin-1 (TSP1) as well as interleukin-1β (IL1β) and interleukin-6 (IL6) promote hippocampal neurodifferentiation (Ueki et al., 2003; Lie et al., 2005; Barkho et al., 2006; Lu and Kipnis, 2010). Of note, when FGF2-producing astrocytes age, neurogenesis is impaired (Shetty et al., 2005).

Signals arising from the ependymal and meningeal cells and released in the CSF may also influence NSC activity (Lim et al., 2000; Siegenthaler et al., 2009). Indeed, NSCs possess primary cilia which sense liquor morphogens, such as FGF2, IGF2 (effective at lower level postnatally), Wnt and Sonic Hedgehog (SHH) (Corbit et al., 2005; Rohatgi et al., 2007; Breunig et al., 2008; Kim et al., 2010; Ihrle et al., 2011; Lehtinen and Walsh, 2011) and, possibly, the CSF flow itself. The latter indeed can, via mechano-sensing signaling, promote proliferation and differentiation (Li et al., 2011; Arulmoli et al., 2015; Jagielska et al., 2017).

Moreover, cytoarchitectonic innervation via GABA (γ-Aminobutyric acid)-, glutamin-, colin-, serotonin-, and dopamine-ergic neurons sustains neurogenesis in the niche (Suh et al., 2009; Song et al., 2012; Paez-Gonzalez et al., 2014; Young et al., 2014; Alumni and Bally-Cuif, 2016; Chaker et al., 2016). Conversely, it is not clear yet whether NSCs have an impact on axons and neuronal circuitry (Zhang Y. et al., 2016).

The niche is also very much dependent on and prompt to metabolic changes. While lipid metabolism maintains proliferation and neurogenesis (structural and energy support), glycolysis regulates NSCs development and differentiation (Knobloch et al., 2013). The metabolic activity strongly depends on oxidative saturation because in mammalian CNS oxygen regulates the growth and differentiation state of stem cells (De Filippis and Delia, 2011; Ivanovic and Vlaski-Lafarge, 2016; Sandvig et al., 2017). Dividing progenitor cells depend more on glycolysis, whereas differentiated progeny relies on energetically efficient oxidative phosphorylation occurring at low oxygen concentration. Apart from those, other important
FIGURE 1 | Schematic representation of the interplay among cells of the neural stem cell niche of the subventricular zone (A, B, C). Vascular endothelial cells (EC), ependymal cells (E), differentiated oligodendrocytes (O), astrocytes (As), and neurons (N). Green is used for positive regulators of neural stem cell function, red for inhibitory regulators. Mechanisms are in italic. (A) depicts mechanisms and factors in physiological conditions: in steady-state, B cells self renewal is promoted by niche-derived factors such as CNTF, EGF, FGF2, LIF, PGD2, S1P, and TGFα, as well as by systemic-derived factors as VEGF, BDNF and SDF1. The cerebrospinal fluid also contributes actively to niche homeostasis via IGF1, Wnt and Shh that signal to B cells via their apical cilium. Aging increases neurogenesis-inhibitory factors such as B2M, CCL2, CCL11, CCL19, while pro-neurogenic factors as GDF11 decrease. The hypoxic milieu of the niche favors B cell quiescence, while C and A precursors rely on oxidative phosphorylation. In steady-state, astrogliogenesis is generally inhibited, while growing astrocytes secrete both pro-neurogenic and anti-neurogenic mediators. Nonetheless, a basal level of oligodendrogenesis and in particular neurogenesis occurs also during the steady state. (B) depicts mechanisms and factors that are altered in the SVZ niche in the context of stroke. Ischemia increases Epo, Ang2 and VEGF as well as morphogens BMP, RA and SHH, which stimulate neurogenesis. Moreover, chemotactic and growth factors produced within the lesion (e.g. CXCL12, CCL2) guide newly formed glial and neuronal cells toward the ischemic area. Hypoxia and increased nitric oxide inhibit B cell cycling while low O2 promotes precursor differentiation. Direct (Continued)
metabolic pathways are active in neural stem cells, such as (i) glycogen synthesis or glutamine/folate metabolism (Goodman and Hajihosseini, 2015); (ii) phosphatidylinositol 3-kinase/AKT (PI3K/AKT) growth factor pathway insulin-dependent; (iii) mTOR pathway nutrient-dependent (Rafalski et al., 2012); (iv) AMP-activated protein kinase (AMPK)/LKB1 pathway, sensor of intracellular adenosine monophosphate (AMP) to ATP ratios, and (v) the sirtuin pathway, metabolic sensors of NAD (nicotinamide adenine dinucleotide) level and epigenetic repressors (Folmes et al., 2012; Shyh-Chang et al., 2013).

Cell to cell contact has also been shown to play a role in exploiting the plasticity of NSCs. Astrocytes of the niche negatively control neuronal differentiation through astrocyte-secreted factors such as insulin like growth factor binding protein 6 (IGFBP6) and decorin (Barkho et al., 2006; Wilhelmsson et al., 2012), while astrocytic ephrin-B2 positively regulates proliferation (Ashton et al., 2012).

Another peculiar property of NSCs consists in their capacity to migrate where their replacement or bystander effect is needed. Indeed, endogenous NSCs migrate out of the niche at physiological rate to maintain brain homeostasis, either differentiating or releasing tropic factors (Shen et al., 2004; Kokaia et al., 2012). When transplanted during acute or chronic neuroinflammatory disorders, NSCs show remarkable pathotropism: they follow the molecular gradient of chemotactic inflammatory factors (Muller et al., 2006) and reach the damaged site where they start secreting a series of molecules (i.e., bone morphogenetic protein 4, noggin, Notch, Jagged, and SHH) to recapitulate the microenvironment of the SVZ niche (typical eptopic perivascular niche) (Pluchino et al., 2003, 2010; Irvin et al., 2004; Stidworthy et al., 2004; Martino and Pluchino, 2006; Bonaguidi et al., 2008).

Of note, beside communication via soluble factors, NSCs sense and can release intracellular messengers wrapped in vesicles (Cossetti et al., 2014). Although their role in adult NSCs is almost unexplored (more is known for other types of stem cells), vesicles can transfer information in the form of mRNA, ribosomal RNA, long non-coding RNA, microRNA, DNA, protein, or lipids (Thery et al., 2002; Huang et al., 2013; Batiz et al., 2015; Kirby et al., 2015).

NSC FUNCTION IN NEUROINFLAMMATION AND NEURODEGENERATION. FOCUS ON MULTIPLE SCLEROSIS AND ISCHEMIC STROKE.

The peculiar plasticity of the CNS and of its NSCs manifests after CNS injury, when (i) proliferation and differentiation of NSCs is enhanced; (ii) striatal spiny interneurons and glutamatergic neurons are ectopically found in the injured cortex and in the striatum after stroke (Thored et al., 2007) while migrating neuroblasts become oligodendrocytes in area of demyelination after exiting the niche; (iii) ependymal cells behave as progenitors (Luo et al., 2008) and directly convert into neurons (Carlen et al., 2009); (iv) reactive astrocytes in ischemic brain injury exhibit self renewal capacity and multipotency (Buffo et al., 2008; Gabel et al., 2016).

The fact that non-neurogenic precursors can convert into neurogenic cells clearly highlights how exogenous factors can trigger plasticity within and outside of the niche (Carlen et al., 2009; Magnusson et al., 2014; Shetty and Hotti, 2015). Moreover, during pathology and steady-state, NSCs also exert trophic non-neurogenic functions which are crucial to maintain brain homeostasis.

In the following section we will explore how NSC niches function during CNS injury, with focus on stroke, multiple sclerosis and their animal models (Figures 1B,C, Table 1).

Effect of Oxygen Supply on Neural Stem Cell Plasticity, Connection with Stroke, and Multiple Sclerosis

In physiological conditions, neural stem cells are exposed to an oxygen concentration between 2.5 and 5.0%, which promotes NSC self-renewal via VEGF and erythropoietin (EPO) production induced by hypoxia inducible factor 1α, HIF1α (Pavlica et al., 2012; Li et al., 2014).

In the quiescent state, NSC mitochondria are quite immature with globular shape, do not depend much for energy on oxidative phosphorylation (OXPHOS), rather on glycolysis, with high lactate production (Zhang et al., 2016). Although glycolysis produces less ATP than mitochondrial OXPHOS, the pathway is very fast in NSCs (Ito and Suda, 2014). Their anaerobic metabolism is sustained mainly by mitochondria uncoupling protein 2 (UCP2), high level of hexokinase II and low pyruvate dehydrogenase to keep under control the production of reactive oxygen species (ROS) (Madhavan et al., 2006; Zheng et al., 2016). In this way, DNA and proteins of the cells are protected from ROS-dependent potential damage. Further, ROS, produced in limited amount in physiological conditions and normally neutralized, are also beneficial because they trigger self-renewal and neurogenesis (Le Belle et al., 2011). Conversely, differentiated cells present elongated, crystal-rich mitochondria, higher ratio of mitochondrial glucose oxidation (OXPHOS) over glycolysis as metabolic support (Zhang et al., 2014; Marcialis et al., 2016). Moreover, NSCs increase Kreb’s cycle functionality and decrease lactate production, concurrent with increased number and total mitochondrial mass (Sola et al., 2013).
TABLE 1 | Evidences from the literature are schematically reported.

| Molecule       | Physio-pathology | Source                    | Outcome                                      | References                          |
|----------------|------------------|---------------------------|----------------------------------------------|-------------------------------------|
| Acetylcholine  | Physiology       | (ChAT) (+) neurons        | ↑neurogenesis (synergizing with FGF2)         | Paez-Gonzalez et al., 2014          |
| Angiopoietin 2 | Stroke           | SVZ neuroblasts, endothelial cells | ↑NSC and neuroblast migration | Cui et al., 2009; Liu et al., 2009  |
| ANKYRIN3       | Physiology       | Ependymal cells           | ↑neuroblasts                                 | Paez-Gonzalez et al., 2011          |
| ATP            | Physiology       | Astrocytes                | ↑NSC proliferation                           | Cao et al., 2013                    |
| B2M            | Aging (increases) | Blood                     | ↑neurogenesis                                | Smith L. K. et al., 2015            |
| BDNF           | Physiology and stroke | Blood                    | ↑NSC differentiation                         | Chen et al., 2005                   |
| Betacellulin (BTC) | Physiology | Endothelial cells       | ↑NSC proliferation                           | Gajera et al., 2010                 |
| BMP4           | Physiology       | Ependymal cells           | ↑glial differentiation                        | Villeda et al., 2011                |
| CCL11          | Aging            | Blood                     | ↑NSC self-renewal                            | Emsley and Hagg, 2003; Lee et al., 2013 |
| CNTF           | Steady-state     | A subtype of B cells of the SVZ, other? | ↑NSC neurogenic differentiation |                                             |
| Decorin        | Steady-state     | Astrocytes                | ↓NSC neurogenic differentiation              | Barkho et al., 2006                 |
| Delta-like-4   | Steady-state     | Endothelial cells         | ↑NSC proliferation                           | Androutsellis-Theotokis et al., 2010 |
| Dickkopf-1     | Aging            | NSCs                      | ↓neurogenesis                                | Seib et al., 2013                   |
| Dopamine       | Physiology       | Dopaminergic neurons      | ↑neurogenesis (synergizing with EGF)         | O’Keeffe et al., 2009               |
| Ephrin-B2      | Steady-state     | Astrocyte                 | ↑NSC proliferation                           | Ashton et al., 2012                 |
| EPO            | Hypoxia, stroke  | Endothelial cells, Blood  | ↑NSC proliferation and survival              | Pavlica et al., 2012                |
| FGF2           | Physiology       | Astrocytes                | ↑NSC proliferation and survival              | Shehety et al., 2005; Widera et al., 2006 |
| GABA           | Physiology       | Young neuroblasts         | ↑NSC proliferation and neuronal differentiation | Liu et al., 2005                    |
| GDF11          | Aging (decreases) | Blood                     | ↑neurogenesis                                | Katsimpardi et al., 2014            |
| Galectin-3     | MS                | SVZ                       | ↑NSC proliferation                           | James et al., 2016                  |
| Glutamate      | Physiology       | Tissue                    | ↑NSC proliferation and neuronal differentiation | Platel et al., 2010                 |
| Conondrotropin- releasing hormone (GHR) | Aging | Hypothalamic cells | proliferating activity of hypothalamic NPC | Zhang et al., 2013                  |
| IFNγ           | Stroke, MS, steady-state | Immune cells, NSCs      | ↑NSC proliferation                           | Pluchino et al., 2008; Li et al., 2010b; Kulkarni et al., 2016 |
| IGF1           | Steady-state, aging | Microglia, endothelial cells | ↑NSC proliferation | Butovsky et al., 2006; Joseph D’Ercole and Ye, 2008; Llorens-Martin et al., 2009 |
| IGF2           | Steady-state, CNS tumor, development, aging | Cerebrospinal fluid | ↑NSC proliferation | Lehtinen and Walsh, 2011 |
| IGFBP6         | Steady-state     | Astrocytes                | ↓neurogenic differentiation                   | Barkho et al., 2006                 |
| IL10           | Steady-state, stroke | TReg                    | ↑NSC proliferation and neuronal differentiation | Perez-Asensio et al., 2013; Wang et al., 2015 |
| IL1β           | Stroke, MS       | Microglia, NSCs, monocyte/macrophages? | ↑NSC proliferation and neuronal differentiation | Wu et al., 2013; Widera et al., 2006; Guardagno et al., 2015 |
| IL6            | Infections, stroke | NSCs, microglia          | ↑NSC proliferation and neuroblast survival   | Gallagher et al., 2013; Chucair-Elliott et al., 2014; Meng et al., 2015 |
| Jagged1        | Steady-state, MS | Astrocytes                | ↓neurogenesis differentiation                | Stidworthy et al., 2004; Wilhelmsson et al., 2012 |
| LIF            | Steady-state     | ?                         | ↑OPC proliferation                           | Bonaguidi et al., 2006              |
TABLE 1 | Continued

| Molecule               | Physio-pathology                        | Source                        | Outcome                                                                 | References                                      |
|------------------------|-----------------------------------------|-------------------------------|-------------------------------------------------------------------------|------------------------------------------------|
| MCP-1/CCL2             | Stroke, aging, epilepsy, CNS tumors     | Immune cells? Microglia?      | ↑NSC migration                                                         | Vrotsos et al., 2009; Colucci-D’Amato et al., 2015; Osman et al., 2016 |
|                        |                                         | Astrocytes?                   | ↑neuronal differentiation and neurtic formation of mesencephalic NSCs    |                                                  |
|                        |                                         |                               | ↑glial differentiation of NT2 NSCs                                     |                                                  |
| Neuregulin 1 and 2     | Steady-state                            | Neuroblasts, GFAP+ NSCs in    | ↑NSC proliferation                                                      | Ghashghaei et al., 2006                         |
|                        |                                         | the SVZ                       | ↑neuroblast migration                                                   |                                                  |
| Neurotrophin 3 (NT3)   | Steady-state                            | Endothelial cells             | ↑NSC quiescence                                                         | Shimazoe et al., 2006; Delgado et al., 2014     |
| NGF                    | Steady-state, MS, stroke?               | SVZ                           | ↑NSC proliferation                                                      | Calza et al., 1998; Triaca et al., 2005         |
| Noggin                 | Steady-state                            | Ependymal cells, subgranular  | ↑NSC proliferation                                                      | Lim et al., 2000; Bonaguidi et al., 2008        |
|                        |                                         | zone                          | ↑neurogenesis                                                           |                                                  |
| Oxygen (2-5%)          | Steady-state, stroke                    | NSCs                          | ↑NSC self proliferation                                                | Santilli et al., 2010                          |
| Oxygen (<1%)           | Stroke, MS                              | NSCs                          | ↑NSC self renewal                                                       | Felfly et al., 2011                            |
| PDGF                   | Physiology                              | GFAP-positive cells           | ↑NSC proliferation                                                      | Jackson et al., 2006                           |
| Pdgf2                  | Steady-state                            | ?                             | ↑NSC proliferation                                                      | Codega et al., 2014                            |
| Retinoic acid (RA)     | Stroke, steady-state                    | Meninges, other?             | ↑neurogenesis                                                           | Plane et al., 2008; Siegenthaler et al., 2009  |
| ROS                    | Steady-state, stroke?                   | NSCs                          | ↑NSC self renewal                                                       | Le Belle et al., 2011                          |
| S1P                    | Steady-state                            | ?                             | ↑NSC proliferation                                                      | Codega et al., 2014                            |
| SDF-1/CXCL12           | Stroke, MS, steady-state, traumatic brain injury | NSCs, meninges, endothelial cells, immune cells, tumor cells | ↑NSC migration | Reiss et al., 2002; Imitola et al., 2004; Tsoh et al., 2009; Carbajal et al., 2010; Li et al., 2012 |
| Serotonin              | Physiology                              | 5-HT neurons                  | ↑neurogenesis                                                           | Brezun and Daszuta, 1999                       |
| SHH                    | Development, steady-state, MS           | Ventral forebrain neurons     | ↑NSC specification                                                      | Breunig et al., 2008; Ihle et al., 2011; Samanta et al., 2015 |
| Survivin               | Aging                                   | Astrocytes                    | ↑neurogenesis                                                           | Miranda et al., 2012                           |
| TGFα                   | Steady-state, stroke                    | NSCs?                         | ↑neurogenesis                                                           | Tropepe et al., 1997; Guerra-Crespo et al., 2009 |
| TGFβ                   | Steady-state, development               | NSCs                          | Temporal regulation of neurogenesis and potency of NSCs                 | Dias et al., 2014                              |
| Thbs4                  | Stroke                                  | SVZ NSCs                      | ↑SVZ–NSC astrogenesis (via Notch signaling)                             | Benner et al., 2013                            |
|                       |                                         |                               | ↑glia scar formation                                                   |                                                  |
| TNFα                   | Stroke, MS?                             | Microglia, astrocytes,        | ↑NSC proliferation                                                      | Widera et al., 2006; Guadagno et al., 2013      |
|                       |                                         | monocyte/macrophages?         | ↑NSC apoptosis                                                          |                                                  |
|                       |                                         |                               | ↑oligodendrocyte differentiation                                         |                                                  |
| TSP1                   | Steady-state                            | Astrocytes                    | ↑NSC proliferation                                                      | Lu and Kipnis, 2010                            |
| VEGF                   | Steady-state, Stroke                    | NSCs; astrocytes; endothelial cells | ↑NSC proliferation and maintenance                                     | Kojima et al., 2010; Kirby et al., 2015         |
| Wnt3                   | Steady-state                            | Astrocytes                    | ↑neurogenesis                                                           | Okamoto et al., 2011                           |

On the other side, the first consequence of the blood flow occlusion in brain ischemia is hypoxic injury that causes extensive neural cell death (Niquet et al., 2003). Nonetheless and surprisingly, hypoxia, while being detrimental in the acute phase of stroke, in a second step, contributes to promote neurogenesis (Arvidsson et al., 2002; Tonchev et al., 2003; Jin et al., 2006; Macas et al., 2006; Minger et al., 2007; Wang et al., 2011; Zhang and Chopp, 2016), to support replenishment of neurons in the RMS, migration in the region of ischemic brain injury, and growth of oligodendrocyte progenitors that disperse to the gray and white matter (Zhang et al., 2001, 2012; Parent et al., 2002; Minger et al., 2007; Li et al., 2010a; Zhang and Chopp, 2016).
Hypoxia has recently emerged as a concurrent complication of disease progression also in MS. Indeed, important lack of oxygen, occurring as a consequence of inflammation, has been measured in brain gray matter regions of MS patients, where it can per se be considered co-causative for neurodegeneration (Haider et al., 2014; Yang et al., 2015). Since hypoxia and inflammation are strictly linked, it is still difficult to tease apart their respective contributions in MS (Sun et al., 1998; Lassmann, 2003; Davies et al., 2013). It looks like hypoxia can occur in MS patients as a consequence of increased oxygen demand. When this request is not satisfied, hypoxia can be further detrimental for surrounding neural stem cells (Trapp and Stys, 2009).

**Effect of Inflammation on Neural Stem Cell Plasticity, Connection with Stroke, and Multiple Sclerosis**

It has been well-documented that the brain cannot be simplistically considered an immune privileged site (Kleine and Benes, 2006) and actually immune system activation in the brain exerts both damaging and beneficial effects on CNS functions (Martino, 2004), depending on the onset of the inflammation, on the cell types involved in the process and on the chronicity of the response (Crutcher et al., 2006; Kyritsis et al., 2012).

NSCs share with the immune system an array of secreted mediators and receptors, which are all relevant for the maintenance of the neurogenic niche and, at the same time, represent the prerequisite for the interaction of NPCs with the microenvironment, especially during neuroinflammation (De Feo et al., 2012; Kokaia et al., 2012).

Indeed, inflammation, via its associated cues (i.e. cytokines, chemokines, chemical species...), strongly impacts structure and function of the stem cell niche, acts directly on NSCs and affects tissue restoration/regeneration via microglia and astrocyte activation (Ekdahl et al., 2003; Pluchino et al., 2008; Pourabdolhossein et al., 2017).

In homeostatic conditions, microglia are ramified in shape to maintain surveillance. Upon pathogen invasion or insults, they retract the protrusions, become amoeboid, increase their migratory behavior, and secrete cytokines. IL6, TNFα, IL1β, and complement 1 subunit q (C1q) are among the most potent microglia–derived cytokines, able to compromise the niche environment, inhibit neurogenesis (Vallieres et al., 2002; Monje et al., 2003), induce oligodendrogenesis (Valerio et al., 2002) and a subtype of reactive astrocytes (Liddelow et al., 2017). Further, while NSC-derived nitric oxide synthase promotes release of small amounts of nitric oxide (NO) with neurogenic properties (Carreira et al., 2010; Luo et al., 2010), abundant NO released by microglia or astrocytes in inflammatory conditions (i) inhibits proliferation of NSCs acting on the EGF receptor (Carreira et al., 2014) or on the transcription factor complex Neuron-Restrictive Silencer Factor /RE1-Silencing Transcription factor, NR5F/REST (Bergsland et al., 2014) and (ii) promotes gliogenesis (Bergsland et al., 2014).

IFNγ, a pleiotropic cytokine, has a central role in regulating NSCs proliferation and quiescence (Kulkarni et al., 2016). In inflammatory conditions, such as experimental autoimmune encephalomyelitis (EAE), the preclinical model of MS, IFNγ dramatically decreases progenitor proliferation (Pluchino et al., 2008; Pereira et al., 2015) and inhibits the recruitment of newborn neurons to the olfactory bulb (OB). IFNγ might also play a crucial role in regulating glioma-associated oncogene homolog-1 (Gli1), a Shh-induced transcription factor that drives the oligodendrogial fate of NSCs (Wang et al., 2008; Li et al., 2010b; Samanta et al., 2015).

The complement system also inhibits NSC activity as demonstrated with complement receptor 2 (Cr2) knockout mice that have increased basal neurogenesis (Moriyama et al., 2011). Moreover, lipid modifiers present in inflammation, such as leukotriene, can negatively regulate NSC proliferation likely via TNFα and IL1β (Bonizzi et al., 1999; Wu et al., 2013). Of note, montelukast, a leukotriene receptor blocker protects from this event (Marschallinger et al., 2015).

IL6 is another crucial mediator of NSC function and its induction, e.g., during maternal infection and stroke, permanently perturbs NSC proliferation and neurogenesis (Gallagher et al., 2013; Chucair-Elliott et al., 2014; Meng et al., 2015).

Conversely, the anti-inflammatory interleukin-10 (IL10) in rodents keeps NSCs in an undifferentiated proliferation state, rather than promoting differentiation (Ben-Hur et al., 2003; Perez-Asensio et al., 2013; Wang et al., 2015).

Nevertheless, as anticipated, inflammation can be also beneficial for NSCs. First, the immune system in general and T cells in particular are involved in maintaining niche neurogenesis, as indeed genetic T-cell depleted mice present compromised cognitive functions (Ziv et al., 2006). Moreover, chemokines such as monococyte chemoattractant protein 1 (MCP1) or SDF1, released in inflammatory conditions, promote migration of NSCs to site of injury and local TNFα or IL1β trigger their proliferative capacity (Widera et al., 2006). Second, injection of moderately activated microglia can regulate brain homeostasis and neurogenesis (Butovsky et al., 2006; Bachstetter et al., 2011).

Further, NSCs directly produce inflammatory chemokines (Covacu et al., 2009), promoting a feed forward loop at sites of tissue damage (Imitola et al., 2004; Belmadani et al., 2006; Widera et al., 2006; Wang et al., 2007). NSCs can also directly change inflammatory responses through immunomodulatory factors (Pluchino et al., 2005; Ben-Hur, 2008; Yong and Rivest, 2009; Butti et al., 2012) or trophic factors (Huang et al., 2014). In particular, SVZ-NSCs can protect striatal neurons from the excitotoxic damage occurring in stroke and epilepsy, releasing endogenous endocannabinoids, likely upon inflammatory stimuli (Butti et al., 2012). Endogenous NSCs also secrete MCP1, VEGF, IL4, and interleukin-15 (IL15), the latter known to retain NK cells in the chronic phase of EAE in mice and of MS in humans. Indeed, in the SVZ, NK cells contribute to the dysfunction of the neurogenic niche observed in EAE by killing stem cells (Liu et al., 2016). Moreover, inflammatory cytokines lead to metabolic reprogramming of the arginase pathway in NSCs ultimately impacting on the NSC mediated anti-proliferative effect on T cells (Drago et al., 2016). Further, it has been reported that human NSCs hinder the differentiation of myeloid precursor cells into...
immature dendritic cells and the final maturation into functional antigen presenting cells (Pluchino et al., 2009).

In stroke, immune cell infiltration and inflammation take place as secondary events to hypoxic injury, which is responsible of the massive neuronal death. Upon brain injury, the blood-brain barrier (BBB) is disrupted, its permeability increases, migrating immature neurons associate with the angiogenic fenestrated endothelium, thus mimicking the neurogenic niche structure (Ohab et al., 2006; Ohab and Carmichael, 2008). Neutrophils and innate immune cells are the first players, although also T and B cells cross the damaged-BBB, inducing a rapid adaptive autoimmune response to neuronal antigens (Chamorro et al., 2012). As consequence of inflammation, neurogenesis is activated in stroke (Wang et al., 2011; Katajisto et al., 2015) supported by soluble factors such as bone morphogenetic protein (Forni et al., 2013), retinoic acid (Plane et al., 2008), sonic hedgehog (Cheng et al., 2015), C-C motif chemokine Ligand 2 (CCL2) (Osman et al., 2016) along with SDF1 and angiopoietin-2 (Ang2) that home NSC progenitors to the site of injury (Thored et al., 2006), where they improve functional recovery (Guzman et al., 2008) and differentiate into neurons (Darsalia et al., 2007). Nevertheless, they present only limited reparative properties because matured neurons tend to die (Arvidsson et al., 2002; Marti-Fabregas et al., 2010; Kazanis et al., 2013). Moreover, given that NSCs themselves express and release respectively C-X-C motif chemokine receptor 4 (CXCR4) and SDF1, they might play a role in regulating axonal remodeling in ischemic brain. On the other hand, SVZ-derived astrocytes have a crucial role in ischemic stroke: phototothrombotic cortical ischemia induces a strong gliogenic, Notch1-dependent response in the SVZ, which generates thrombospondin-4 (Thbs4)-positive astrocytes. Thbs4 astrocytes are essential components of the glial scar and their proliferation might be favored over neurogenesis after cortical injury (Benner et al., 2013). Conversely, it has also been reported that inflammation can promote neurogenesis in dormant neural progenitors in nonconventional neurogenic regions (Jiao and Chen, 2008).

Further, stroke increases generation of oligodendrocyte precursor cells (OPCs) from NSC in the ischemic brain, although it remains to be defined whether NSC-derived OPCs, beside oligodendrogenesis, help with brain repair, likely communicating with cerebrovasculature and other brain parenchyma cells (Itoh et al., 2015).

Overall, according to several evidences, inflammation in stroke can be beneficial for NSCs, nonetheless other reports, evaluating microglia function, claim that activated ED1+ microglia impair basal neurogenesis (Ekdahl et al., 2003) likely via TNFα/TNFFR1 signaling (Jofis et al., 2008; Chen and Palmer, 2013; Gebara et al., 2013). In humans, a definitive robust evidence of clinical post-stroke neurogenesis remains a matter of investigation as analysis of autopsy tissue provided positive results (Ekonomou et al., 2012) which are instead lacking when labeling newly born neurons with 14C (Huttner et al., 2014).

In MS preclinical models, it is important to distinguish among experimental conditions since they influence the experimental evidence. Nonetheless, either chemically (LPC), focal (site injection of TNFα-IFNγ combined with subclinical immunization) or immune-mediated (EAE) demyelination causes reduced neuroblast proliferation in the olfactory bulb of mice, while neutralization of immune mediators, such as IFNγ and Galectin3 inflammatory cytokines, restores neurogenesis both in vitro (Pluchino et al., 2008; Tepavcevic et al., 2011) and in vivo (Monje et al., 2003; James et al., 2016). Indeed, in human samples, the SVZ of post-mortem MS brains is altered, with reduced number of neuroblasts in the SVZ of the lateral ventricle. Conversely, neuroinflammation increases neurotrophin levels (e.g., nerve growth factor-NGF) in the SVZ (Calza et al., 1998; Triaca et al., 2005), likely counteracting the inhibitory effect of proinflammatory molecules. Further, demyelination is able to boost proliferation of NSCs in the neurogenic niches promoting their differentiation (Pluchino et al., 2005; Menn et al., 2006). Only in conditions of acute cytokine exposure, either by focal intrathecal cytokine injection or as a consequence of strong microglia activation, the proliferative capacity of the niche is inhibited. In terms of gliogenic differentiation, inflammatory conditions may increase the percentage of Olig2+ cells originating from the SVZ via modulation of bone morphogenetic protein (BMP) signaling (Tepavcevic et al., 2011). The transcription factor Gli1 seems to be a key regulator of SVZ oligodendrogenesis and may be a promising target for reparative strategies in MS, as pharmacological inhibition of Gli1 during EAE promotes remyelination and improves clinical outcome (Samanta et al., 2015).

Leveraging the regenerative potential of NSCs and their immunomodulatory and trophic functions, NSC transplant has been proposed as therapeutic strategy for inflammatory diseases of the CNS. In stroke, transplanted NSCs directly modulate neuronal circuit plasticity (Zhang et al., 2009) through the expression of developmental molecules such as guidance molecules (i.e., slit, thrombospondin-1 and -2) and trophic factor such as VEGF (Andres et al., 2011). In fact, transplanted NSCs in stroke stimulate the proliferation of endogenous neural stem cells (Zhang et al., 2011; Hassan et al., 2012; Mine et al., 2013), increase endogenous angiogenesis after stroke (Jiang et al., 2005), scavenge the neurotoxic molecules (Emsley et al., 2004) and contribute both directly and indirectly (via astrocytes) to glutamate clearance (Bacigaluppi et al., 2009, 2016).

In EAE, transplanted NSCs directly inhibit both T cell and myeloid cell immune responses. In the CNS, they block inflammatory cell recruitment, T cell proliferation and promote the apoptosis of brain-reactive T cells (Einstein et al., 2003; Pluchino et al., 2005). In peripheral secondary lymphoid organs of EAE mice, antigen-specific proliferation of T cells, dendritic cell antigen presentation and chemotactic gradients are impaired by NSCs transplanted either subcutaneously or intravenously. As an example, NSC-secreted LIF, on one hand, stimulates endogenous remyelination in the CNS (Laterza et al., 2013), on the other, inhibits Th17 cell differentiation in the periphery (Cao et al., 2011).

Overall, the current literature shows that a controlled use of inflammation in CNS injury could be of help in regenerative approaches when NSC proliferation needs to be boosted and inflammatory tweaking can have beneficial outcomes. An option could consist in reducing NSC sensitivity to inflammatory
mediators and, at the same time, increasing the therapeutic efficacy of NSCs when transplantsing engineered cells.

**Effect of Aging on Neural Stem Cell Plasticity, Connection with Stroke, and Multiple Sclerosis**

Aging is a common feature of both stroke and progressive multiple sclerosis and loss of niche integrity, depletion of the stem cell pool, cellular senescence, defect in cell-cell contact in the niche or metabolic changes are all shared characteristics that contribute to the demise of the aging neurogenic niche (Oh et al., 2014).

The most significant consequence of age in the SVZ consists in the alteration of the niche cytostructure and in reduction of the neuroblast population, with reduced proliferation and neurogenic capacity (Kerever et al., 2015). On the contrary, oligodendrocytegenesis is substantially not affected by aging, rather oligodendrocyte recruitment and differentiation are impaired (Sim et al., 2002; Franklin and Ffrench-Constant, 2008; Conover and Todd, 2016). The latter is indeed a causal pathogenic characteristic of chronically demyelinated MS lesions in humans (Kuhlmann et al., 2008).

Concurrently, given that senescence does not spare the vasculature (Farkas and Luiten, 2001), the environment of the niche may enrich for toxic factors which further sustain exhaustion, reduce neuroplasticity and cause cognitive decline (Villeda et al., 2011). Potential therapeutic strategies to counteract the decline of adult stem cells may involve the promotion of a rejuvenating environment (Katsimpardi et al., 2014) or the prevention of premature exhaustion of long-lived self-renewing NSC populations. Neurogenic decline in aged SVZ can occur because of the accumulation of damaged DNA and both nuclear and mitochondrial DNA are susceptible to age-related changes (Bailey et al., 2004). Upon sensing DNA damage, SVZ cells upregulate the inhibitor of cyclin kinase to postpone cell cycle entry and reduce proliferation of NSCs (Molofsky et al., 2006).

NSC age-dependent cell plasticity is also influenced by metabolic changes (Rabie et al., 2011; Chaker et al., 2015). As far as nutrient sensing pathways, growth differentiation factor-11 (GDF11), has been identified as one of the extrinsic circulating youth signals that maintain neurogenesis (Katsimpardi et al., 2014), although those findings are currently matter of further validation (Egerman et al., 2015; Smith S. C. et al., 2015). It is still unknown whether the effect is direct onto NSCs or indirect via improved microvascular network. IGF1, another critical growth factor, per se stimulates proliferation and differentiation of NSCs (Aberg, 2010), but decreases with aging (Sonntag et al., 2005). Nonetheless, it is also life-long exposure to IGF1 that with age causes decline of neurogenesis (Chaker et al., 2015). Along the same line, NAD$^+$ and AMP levels, which reflect cellular energy state, decline with age in the hippocampus, in parallel with reduction of differentiation and self-renewal capacity of NSCs, because their regulatory enzyme decreases (Liu et al., 2012; Stein and Imai, 2014). As far as oxygen-dependent effect, those are linked to failure in maintaining appropriate mitochondrial regulations. Indeed, accumulation of mutations in mitochondrial DNA (mtDNA) occurs during aging and comes along with abnormal accumulation of toxic by-products (Siqueira et al., 2005) because mtDNA lacks protective histones and is located close to the major source of ROS, the electron transport chain (Park and Larsson, 2011).

Inflammation is another comorbidity factor associated with aging. The immune molecules C-C motif chemokine-11 (CCL11) and β2-microglobulin (B2M), as well as CCL2, C-C motif chemokine-19 (CCL19) and haptoglobin, contribute to low-grade of inflammation in aging (inflamming) (Franceschi and Campisi, 2014), and negatively affect neurogenesis (Villeda et al., 2011; Wyss-Coray, 2016). Indeed, heterochronic parabiosis between aged and young mice rejuvenates and reverses stem cell aging in numerous tissues (Conboy et al., 2005) or administration of plasma from young mice can ameliorate cognitive impairment in aged mice (Villeda et al., 2014).

Last, it is worth mentioning that also the cellular environment of the niche sustains aging features. Astrocytes of the niche, with age, reduce release of Wnt3 (Lie et al., 2005; Okamoto et al., 2011), that in turn down regulates Survivin expression and increases release of Dickkopf-related protein 1 (DKK1), a canonical Wnt signaling inhibitor. The final effect is induced quiescence on one side (Miranda et al., 2012) and negative regulation of NSC neurogenesis (Seib et al., 2013) on the other. This is paired with physical changes of the extracellular matrix, which also affect senescence of the niche (Gattazzo et al., 2014). Conversely, it is also possible that NSCs efficiently graft the SVZ and well differentiate in both young and aged hippocampus, suggesting that advanced age of the host at the time of grafting has no major adverse effects on engraftment, migration, and differentiation of SVZ-NSCs (Shetty and Hattiangady, 2016).

Age is an independent risk factor for brain ischemia (Marinigh et al., 2010; Roger et al., 2012) and stroke models using aged animals are clinically very relevant (Popa-Wagner et al., 2007). From work on animals, it has been reported a 50% decline in neurogenesis in the SVZ of elder compared with young–adult animals (Darsalia et al., 2005; Macas et al., 2006; Ahlenius et al., 2009). Unfortunately, although endogenous neurogenesis has been observed even in aged humans, it is still not clear to what extent newly formed neurons are functionally relevant for stroke recovery in human patients. Thus, cell therapies have been implemented to address this question. An open-label, single-site, dose-escalation study was performed on 13 aged patients after ischemic stroke, transplanting by stereotaxis fetal derived NSCs stimulated neurogenesis in young or old animal models. Likely the effect was exerted via suppression of microglia/macrophage activation (Jin et al., 2011). Of note, inhibition of microglial activation has also been reported in ischemic mice following systemic delivery of mouse NSCs (Bacigaluppi et al., 2009).
Those data suggest that the problem with NSCs in ischemic stroke is to some extent cell autonomous, because the environment of the aged brain does not preclude NSC engraftment.

In MS, loss of myelin, a specialized membrane produced by oligodendrocytes, essential for normal CNS function, is a characteristic feature. Aging impairs not only the neurogenic but also the oligodendrogenic properties of the brain germinal niches as a consequence of longer cell cycle length of NSCs and of their progeny, loss of growth factors and upregulation of inhibitors (Hamilton et al., 2013). Iron accumulation (Andersen et al., 2014), linked in cascade to oxidative alteration and to mitochondrial dysfunction (Mahad et al., 2015) are other recognized characteristics of neurodegeneration in progressive aged MS individuals. A direct impact also on neural stem cells has not been experimentally proven (Crabbe et al., 2010) but can reasonably be speculated.

In the context of demyelination, work by Crawford et al. demonstrated responsiveness of OPCs to demyelination, although remyelination and susceptibility to aging is regionally dependent: in chemically-induced demyelination of the corpus callosum in aged animals, dorsal SVZ-NSCs are efficiently recruited to lesions and their differentiation into OPCs is impaired, whereas ventral NSCs are recruited more slowly but differentiate rapidly into OPCs; similarly, while in aged animals the percentage of differentiated OPCs from dorsal NSCs is half of the seen in young animals, the percentage of ventral NSCs differentiating into OPCs remained constant (Crawford et al., 2016). This evidence has significant implications for the progressive form of MS, for which age is the current best associated risk factor (Minden et al., 2004; Scalfari et al., 2011). As disease progresses with age, repair, remyelination and other physiological functions become less robust. Animal models have shown that while OPC recruitment toward lesions remains intact, differentiation into myelinating oligodendrocytes decreases with age with a slower and less effective remyelination process compared to young rats (Rist and Franklin, 2008; Ruckh et al., 2012). Similarly, elder human subjects showed reduced remyelinating capabilities. Multiple hypotheses can explain these findings, including either extrinsic factors or intrinsic characteristics such as epigenetic changes known to be modulated during aging and thus to impact OPC maturation (Rist and Franklin, 2008).

**HOW DO NEURAL PRECURSORS FROM INDUCED PLURIPOTENT STEM CELLS STAND?**

The technology of somatic cell reprogramming (induced pluripotent stem cells, iPSCs) that developed in the last 10 years (Takahashi et al., 2007), represents an invaluable alternative strategy to obtain, in large scale and indefinitely, neural precursors, unfolding new research and clinical avenues. Expandable intermediate neural precursors can be obtained with published protocols (Falk et al., 2012; Reinhardt et al., 2013) and the cells resemble most of the specific properties of endogenous plastic cells. To treat neurodegenerative conditions, both iPSC-derived NSCs or terminally differentiated neurons have been transplanted in preclinical models. Early on, it has been demonstrated that those cells are able to survive and adequately integrate into the host brain (Oki et al., 2012; Tornero et al., 2013; Qi et al., 2017), and recently it was reported that transplanted human iPSC-derived cortical neurons can be incorporated also into injured cortical circuits and could contribute to functional recovery (Tornero et al., 2017). Beside reparative activity, transplanted cells can improve the brain functional outcome, directly waking up brain plasticity via their bystander effects. Indeed, transplanted cells promote the formation of new synapses among existing neurons or preserve axonal integrity releasing trophic factor for myelinating cells as described in ischemic stroke and in a preclinical model of MS (Oki et al., 2012; Espuny-Camacho et al., 2013; laterza et al., 2013; Tornero et al., 2013).

In addition, the release of soluble factors by (neural) stem cells along with cell-cell interactions supports angiogenesis that, beside self organizing blood vessels (Kusuma et al., 2013), guarantees trophic support for proper integration of neuronal cells and sustains synaptogenesis. Further, the bystander effect is exploited also in terms of (i) inhibition of neutrophil and peripheral dendritic cell activation and recruitment, (ii) inhibition of effector T- and B-cells, (iii) attenuation of BBB damage, or (iv) stimulation of the M2 microglial phenotype (Drago et al., 2013). Similar evidence of the (neuro)-protective, regenerative, and angiogenic properties of iPSCs is not available yet from their complete secretome, nonetheless it can be reasonably predicted.

As of now, while work by Jensen et al. reported no iPSC-mediated improvement in behavioral function in stroke (Jensen et al., 2013), several others, as previously mentioned, show that also direct iPSC transplantation improves neurological score, motor, sensory and cognitive functions, already within the first week after transplantation, when migration, maturation, synaptic integration, and paracrine release into the host brain is completed (Oki et al., 2012; Polentes et al., 2012; Tornero et al., 2013, 2017; Yuan et al., 2013; Tatarishvili et al., 2014).

Similarly, transplant of iPSC-derived neural precursors in the MS context dramatically reduced T cell infiltration and ameliorated white matter damage in treated EAE mice (Laterza et al., 2013; Zhang C. et al., 2016), both via improved differentiation toward cells of the oligo-glial lineage and via soluble factor release (Laterza et al., 2013).

Experimental validation in humans, both for stroke and MS, could be useful in the future but regulatory guidelines for safe clinical trial are awaited.

**CAN WE GUIDE NEURAL STEM CELL PLASTICITY TOWARD A DESIRED RESPONSE?**

Taking advantage of their plasticity, stem cells can generate, repair, and change nervous system functions. Fine-tuning of the inflammatory responses or proper modulation of the hypoxic
and aging conditions should provide a permissive milieu for an effective reparative process. In this sense, the perspective that aged hippocampus licenses efficient and functional engraftment (Shetty and Hattiangady, 2016) puts forward the possibility that grafted niches can continuously generate new neurons and glia which, in turn, are expected to improve the plasticity and function of aged brain tissue.

As engineering and reprogramming approaches advance, transplant of exogenous human NSCs are optimized and better understanding of NSC regulation in physio-pathological conditions is achieved, it will be possible to fully take advantage of the therapeutic potential of those cells and successfully exploit their plasticity.

So far, it is possible to (i) engineer NSCs to deliver extrinsic stem cell fate determinants or intrinsic factors that allow the development of biomimetic environmental cues to control stem cell fates (Michailidou et al., 2014; Karimi et al., 2016); (ii) culture and expand stem cells outside of their native environments (Komura et al., 2015); (iii) perform localized delivery of microspheres to specifically differentiate endogenous stem cells (Gomez et al., 2015); (iv) engineer somatic cells to obtain induced NSCs with reparative functions (Hargus et al., 2014); (v) engineer human stem cells to obtain indefinitely expandable lines for clinical purposes (Pollock et al., 2006); (vi) snapshot the metabolic profile of cells in physiological-pathological conditions (Bystrom et al., 2014; Dislich et al., 2015).

Systems biology will likely represent a fundamental tool to discover novel drugs to modulate NSC plasticity, as it can integrate and analyze in a quantitative manner several aspects of NSC behavior (e.g., differentiation potential and self-renewal) (Wells et al., 2013; Hussein et al., 2014).

**CONCLUSIONS AND FUTURE OUTLOOK**

Neural progenitor cells represent an underdeveloped therapeutic resource in clinical settings. Although their paracrine and endocrine bystander potential is well-known, much of their plasticity still needs to be properly manipulated for therapeutic purposes.

On one end, cells can be expanded and bioengineering approaches are becoming available to further potentiate their availability (Bressan et al., 2014; Bouzid et al., 2016; Gardini et al., 2016). For instance, *in vitro* preconditioning with low oxygen tension might enhance NSC survival as it mimics the oxygen supply normally found in brain tissues (Hawkins et al., 2013; Sandvig et al., 2017). Nonetheless, it is this same plasticity that could threaten their therapeutic capacity, because the manipulation of cells themselves or of the trophic microenvironment, might induce unwanted side-effects, such as senescence from over-stimulation. Thus, it might be worth increasing the knowledge on (i) the influence of cell metabolism on NSC behavior during CNS diseases; (ii) the *ex-vivo* maintenance of NSCs; (iii) the most suitable window time for transplant to best leverage graft survival and disease-specific environmental conditions. Indeed engraftment efficiency strongly correlates with therapeutic benefits.

Furthermore, this additional knowledge should shed light on the age-related decline of the stem cell niche, which contributes to neurodegeneration in both chronic and acute diseases. Last, careful analysis of the microenvironment is warranted to overcome complications and to improve the efficacy of cell therapy approaches.

**AUTHOR CONTRIBUTIONS**

LO, AM wrote and approved the manuscript. GM, developed the concept wrote and approved the manuscript.

**ACKNOWLEDGMENTS**

We apologize to researchers whose studies we were unable to cite due to the space limitation of this review. We would like to thank the TargetBrain (EU Framework 7 project HEALTH-F2-2012-279017), NEUROKINE network (EU Framework 7 ITN project), and Ricerca Finalizzata GR-2011-02348160 for financial support.
Bouzid, T., Sinitskii, A., and Lim, J. Y. (2016). Graphene platform for neural regenerative medicine. *Neural Regen Res.* 11, 894–895. doi: 10.4103/1673-5374.184454

Bressan, E., Ferrari, L., Gardin, C., Sbricoli, L., Gobbato, L., Ludovicetti, F. S., et al. (2014). Graphene based scaffolds effects on stem cells commitment. *J. Transl. Med.* 12:296. doi: 10.1186/s12967-014-0296-9

Breunig, J., J. Sarkisian, M. R., Arellano, J. I., Morozov, Y. M., Ayoub, A. E., Sojitra, S., et al. (2008). Primary cilia regulate hippocampal neurogenesis by mediating sonic hedgehog signaling. *Proc. Natl. Acad. Sci. U.S.A.* 105, 13127–13132. doi: 10.1073/pnas.0804558105

Brezun, J. M., and Daszuta, A. (1999). Depletion in serotonin decreases neurogenesis in the dentate gyrus and the subventricular zone of adult rats. *Neuroscience* 89, 999–1002.

Buffo, A., Rite, I., Tripathi, P., Lepier, A., Colak, D., Horn, A. P., et al. (2008). Origin and progeny of reactive gliosis: a source of multipotent cells in the injured brain. *Proc. Natl. Acad. Sci. U.S.A.* 105, 3581–3586. doi: 10.1073/pnas.0709021010

Butovsky, O., Ziv, Y., Schwartz, A., Landa, G., Talpalar, A. E., Pluchino, S., et al. (2006). Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol. Cell. Neurosci.* 31, 149–160. doi: 10.1016/j.mcn.2005.10.006

Butti, E., Bacciaglupi, M., Rossi, S., Cambiaggi, M., Bari, M., Cebrian Silla, A., et al. (2012). Subventricular zone neural progenitors protect striatal neurons from glutamatergic excitotoxicity. *Brain* 135(Pt 11), 3320–3335. doi: 10.1093/brain/aws194

Butti, E., Cusimano, M., Bacciaglupi, M., and Martino, G. (2014). Neurogenic and non-neurogenic functions of endogenous neural stem cells. *Front. Neurosci.* 8:92. doi: 10.3389/fnins.2014.00092

Bystrom, S., Ayoglu, B., Hagmark, A., Mitsios, N., Hong, M. G., Drobini, K., et al. (2014). Affinity proteomic profiling of plasma, cerebrospinal fluid, and brain tissue within multiple sclerosis. *J. Proteome Res.* 13, 4607–4619. doi: 10.1021/pr500609e

Calza, L., Giardino, L., Pozza, M., Bettelli, C., Micera, A., and Aloe, L. (1998). Proliferation and phenotype regulation in the subventricular zone during experimental allergic encephalomyelitis: in vivo evidence of a role for nerve growth factor. *Proc. Natl. Acad. Sci. U.S.A.* 95, 3209–3214.

Cao, L., Xiao, X., Xuza, D. S., Liu, Y., Fong, D. M., Young, D., et al. (2004). VEGF links hippocampal activity with neurogenesis, learning and memory. *Nat. Genet.* 36, 827–835. doi: 10.1038/ng1395

Cao, W., Yang, Y., Wang, Z., Liu, A., Fang, L., Wu, F., et al. (2011). Leukemia inhibitory factor inhibits T helper 17 cell differentiation and confers treatment effects of neural progenitor cell therapy in autoimmune disease. *Immunity* 35, 273–284. doi: 10.1016/j.immuni.2011.06.011

Cao, X., Li, L. P., Qin, X. H., Li, S. J., Zhang, M., Wang, Q., et al. (2013). Astrocytic adenosine 5’-triphosphate release regulates the proliferation of neural stem cells in the adult hippocampus. *Stem Cells* 31, 1633–1643. doi: 10.1002/sctm.14008

Carbajal, K. S., Schaumburg, C., Strieter, R., Kane, J., and Lane, T. E. (2010). Migration of engrafted neural stem cells is mediated by CXCL12 signaling through CXCR4 in a viral model of multiple sclerosis. *Proc. Natl. Acad. Sci. U.S.A.* 107, 11068–11073. doi: 10.1073/pnas.0906751010

Carlen, M., Meletis, K., Goritz, C., Darsalia, V., Evergren, E., Tanigaki, K., et al. (2009). Forebrain ependymal cells are Notch-dependent and generate neuroblasts and astrocytes after stroke. *Nat. Neurosci.* 12, 259–267. doi: 10.1038/nn.2268

Carpentier, P. A., and Palmer, T. D. (2009). Immune influence on adult neural stem cell regulation and function. *Neuron* 64, 79–92. doi: 10.1016/j.neuron.2009.08.038

Carreira, B. P., Morte, M. I., Inacio, A. Costa, G., Rosmaninho-Salgado, J., Agasse, F., et al. (2010). Nitric oxide stimulates the proliferation of neural stem cells bypassing the epidermal growth factor receptor. *Stem Cells* 28, 1219–1230. doi: 10.1002/stem.444

Carreira, B. P., Morte, M. I., Santos, A. I., Lourenco, A. S., Ambrosio, A. F., Carvalho, C. M., et al. (2014). Nitric oxide from inflammatory origin impairs neural stem cell proliferation by inhibiting epidermal growth factor receptor signaling. *Front. Cell. Neurosci.* 8:343. doi: 10.3389/fncel.2014.00343

Chaker, Z., Aid, S., Berry, H., and Holzenberger, M. (2015). Suppression of IGF-1 signals in neural stem cells enhances neurogenesis and olfactory function during aging. *Aging Cell* 14, 847–856. doi: 10.1111/acc2.1265

Chaker, Z., Codega, P., and Doetsch, F. (2016). A mosaic world: puzzles revealed by adult neural stem cell heterogeneity. *Wiley Interdiscip. Rev. Dev. Biol.* 5, 640–658. doi: 10.1002/wdev.248
cells in the adult SVZ that form glioma-like growths in response to increased PDGF signaling. *Neuron* 51, 187–199. doi: 10.1016/j.neuron.2006.06.012

Jagielska, A., Lowe, A. L., Makhlouf, E., Wroblewska, L., Guck, J., Franklin, R. M., et al. (2017). Mechanical stress promotes oligodendrocyte differentiation by global changes of gene expression. *Front. Cell. Neurosci.* 11:93. doi: 10.3389/fncel.2017.00093

James, R. E., hills, J., Adorjan, I., Gration, B., Mundim, M. V., Iqbal, A. J., et al. (2016). Loss of galectin-3 decreases the number of immune cells in the subventricular zone and restores proliferation in a viral model of multiple sclerosis. *Glia* 64, 105–121. doi: 10.1002/glia.22906

Jensen, M. B., Yan, H., Krishnaney-Davison, R., Al Sawaf, A., and Zhang, S. C. (2016). Human neural stem cells in patients with chronic ischaemic stroke. *Stem Cells* 34, 630–634. doi: 10.1016/j.stem.2015.05.019

Kostrubiec, A., Schnack, J., Vellinga, D., Ichikawa, N., Moon, C., Arikawa et al. (2016). Stimulation of neurogenesis in nonconventional neurogenic regions of the adult central nervous system by niche astrocyte-produced signals. *Stem Cells* 26, 1221–1320. doi: 10.1002/stem.7051

Jin, K., Wang, X., Xie, L., Mao, X. O., Zhu, W., Wang, Y., et al. (2006). Evidence for stroke-induced neurogenesis in the human brain. *Proc. Natl. Acad. Sci. U.S.A.* 103, 13198–13202. doi: 10.1073/pnas.0603512103

Jiao, J., Zhu, Y., Sun, Y., Mao, X. O., Xie, L., and Chen, D. F. (2008). Induction of neurogenesis in nonconventional neurogenic regions of the adult subependymal zone of the lateral ventricle. *J. Chem. Neuroanat.* 66–67, 52–60. doi: 10.1016/j.jchemneu.2015.06.001

Katajisto, P., Dohla, J., Chaffer, C. L., Pentinmikko, N., Marjanovic, N., Iqbal, A. J., et al. (2013). PI3K/Akt-mediated progenitor cells to stroke is restricted to directly affected areas of their niche. *Cell Stem Cell* 13, 163–173. doi: 10.1016/j.stem.2010.03.019

Kobroch, M., Braun, S. M., Zurkirchen, L., von Schultz, C., Zamboni, N., Araujo-Ravoo, M. J., et al. (2013). Metabolic control of adult neural stem cell activity by Fas-dependent lipogenesis. *Nature* 493, 226–230. doi: 10.1038/nature11689

Knoth, R., Singec, I., Ditter, M., Pantazis, G., Capetian, P., Meyer, R. P., et al. (2010). Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. *PloS ONE* 3:e8809. doi: 10.1371/journal.pone.0008809

Komura, T., Kato, K., Konagaya, S., Nakaji-Hirabayashi, T., and Iwata, H. (2015). Optimization of surface-immobilized extracellular matrices for the proliferation of neural progenitor cells derived from induced pluripotent stem cells. *Stem Cells* 338, 1353–1356. doi: 10.1126/science.1228773

Kuriyama, K., Ganesan, P., and O’Donnell, L. A. (2013). iPSC-derived neural precursors exert a neuroprotective role in immune-inflammatory disease. *Cell Stem Cell* 11, 163–173. doi: 10.1016/j.stem.2010.11.028

Kuhlmann, T., Miron, V., Cui, Q., Wegner, C., Antel, J., and Bruck, W. (2008). Dexamethasone inhibits proliferation of adult hippocampal neurogenesis in vivo and in vitro. *Brain Res.* 1027, 1–10. doi: 10.1016/j.brainres.2004.07.093

Kim, S. U., and de Vellis, J. (2005). Microglia in health and disease. *J. Neurosci. Res.* 81, 302–313. doi: 10.1002/jnr.20562

Kim, S., Lehtinen, M. K., Sessa, A., Zappaterra, M. W., Cho, S. H., Gonzalez, D., et al. (2010). The apical complex couples fate cell and cell survival to cerebral cortical development. *Neuron* 66, 69–84. doi: 10.1016/j.neuron.2010.03.019

Kosik, K. S., and Citron, M. (2006). Innate immune response of the human central nervous system (CNS): different migration pathways of immune cells through the blood-brain barrier and blood-cerebrospinal fluid barrier in healthy persons. *Cytotherapy* 8, 147–151. doi: 10.1016/j.cytot.2002.02.225
regulation of adult forebrain neurogenesis. *J. Neurosci.* 33, 1241–1258. doi: 10.1523/JNEUROSCI.3386-12.2013

Lehtinen, M. K., and Walsh, C. A. (2011). Neurogenesis at the brain-cerebrospinal fluid interface. *Annu. Rev. Cell Dev. Biol.* 27, 653–679. doi: 10.1146/annurev-cellbio-092910-154026

Li, D., Zhou, J., Cheng, Y., Cheng, J., Wang, N., and Wang, F. (2011). Role of mechanical factors in fate decisions of stem cells. *Regen. Med.* 6, 229–240. doi: 10.2217/rme.11.12

Li, L., Candelario, K. M., Thomas, K., Wang, R., Wright, K., Messier, A., et al. (2014). Hypoxia inducible factor-1a (HIF-1a) is required for neural stem cell maintenance and vascular stability in the adult mouse SVZ. *J. Neurosci.* 34, 16713–16719. doi: 10.1523/JNEUROSCI.4590-13.2014

Li, L., Harms, K. M., Ventura, P. B., Lagec, D. C., Eisch, A. J., and Cunningham, L. A. (2010a). Focal cerebral ischemia induces a multilineage cytogenic response from adult subventricular zone that is predominantly gliogenic. *Glia* 58, 1610–1619. doi: 10.1002/glia.21033

Li, L., Walker, T. L., Zhang, Y., Mackay, E. W., and Bartlett, P. F. (2010b). Endogenous interferon gamma directly regulates neural precursors in the non-inflammatory brain. *J. Neurosci.* 30, 9038–9050. doi: 10.1523/JNEUROSCI.2530-10.2010

Li, M., Hale, J. S., Rich, J. N., Ransohoff, R. M., and Lathia, J. D. (2012). Chemokine CXCL12 in neurodegenerative diseases: an SOS signal for stem cell-based repair. *Trends Neurosci.* 35, 619–628. doi: 10.1016/j.tins.2012.06.003

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., et al. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541, 481–487. doi: 10.1038/nature21029

Lie, D. C., Colamarino, S. A., Song, H. J., Desire, L., Mira, H., Coniglio, A., et al. (2011). Neurogenesis at the brain–spinal cord interface. *Annu. Rev. Cell Dev. Biol.* 27, 79–103. doi: 10.1146/annurev-cellbio-092910-154026

Li, M., Zhou, J., Cheng, Y., Cheng, J., Wang, N., and Wang, F. (2011). Role of mechanical factors in fate decisions of stem cells. *Regen. Med.* 6, 229–240. doi: 10.2217/rme.11.12

Macas, J., Nern, C., Plate, K. H., and Momma, S. (2006). Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. *J. Neurosci.* 26, 13114–13119. doi: 10.1523/JNEUROSCI.4667-06.2006

Madhavan, L., Ourednik, V., and Ourednik, J. (2006). Increased “vigilance” of antioxidant mechanisms in neural stem cells potentiates their capability to resist hypoxic stress. *Stem Cells* 24, 2110–2119. doi: 10.1634/stemcells.2006-0018

Magnusson, J. P., Goritz, C., Tatarishvili, J., Dias, D. O., Smith, E. M., Lindvall, O., et al. (2014). A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. *Science* 346, 237–241. doi: 10.1126/science.346.6206.237

Mahl, D. H., Trapp, B. D., and Lassmann, H. (2015). Pathological mechanisms in progressive multiple sclerosis. *Lancet Neurol.* 14, 183–193. doi: 10.1016/S1474-4422(14)70256-X

Marchals, M. A., Coni, E., Mintus, M. C., Ravarino, A., Fanos, V., Coni, C., et al. (2016). Introduction to embryonic and adult neural stem cells from the metabolic circuits of the niches to the metabolites. *J. Pediatric Neuronal. Individualized Med.* 5. doi: 10.7363/050215

Marinigh, R., Lip, G. Y., Fiotti, N., Giancante, C., and Lane, D. A. (2010). Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J. Am. Coll. Cardiol.* 56, 827–837. doi: 10.1016/j.jacc.2010.05.028

Marques, F., Sousa, J. C., Coppola, G., Gao, F., Puga, R., Brentani, H., et al. (2011). Transcriptome signature of the adult mouse choroid plexus. *Fluids Barriers CNS* 8:10. doi: 10.1186/2045-8118-8-10

Marshallinger, J., Schaffner, I., Klein, B., Gelfert, R., Rivera, F. J., Iles, S., et al. (2015). Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat. Commun.* 6:6866. doi: 10.1038/ncomms6946

Martí-Fabregas, J., Romaguera-Ros, M., Gomez-Pinedo, U., Martínez-Ramírez, S., Jimenez-Xarré, E., Marin, R., et al. (2010). Proliferation in the human ipsilateral subventricular zone after ischemic stroke. *Neurology* 74, 357–365. doi: 10.1212/wnl.0b013e3181cccc6

Martino, G. (2004). How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. *Lancet Neurol.* 3, 372–378. doi: 10.1016/S1474-4422(04)00771-9

Martino, G., and Pluchino, S. (2006). The therapeutic potential of neural stem cells. *Nat. Rev. Neurosci.* 7, 395–406. doi: 10.1038/nrn1908

Martino, G., Buttì, E., and Racigaluppi, M. (2014). Neurogenesis or non-neurogenesis: that is the question. *J. Clin. Invest.* 124, 970–973. doi: 10.1172/JCI74419

Martino, G., Pluchino, S., Bonfanti, L., and Schwartz, M. (2011). Brain repair in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiol. Rev.* 91, 1281–1304. doi: 10.1152/physrev.00032.2010

Meng, C., Zhang, J. C., Shi, R. L., Zhang, S. H., and Yuan, S. Y. (2015). Inhibition of interleukin-6 abolishes the promoting effects of pair housing on post-stroke neurogenesis. *Neuroscience* 307, 160–170. doi: 10.1016/j.neuroscience.2015.08.055

Menn, B., Garcia-Verdugo, J. M., Yaschine, C., Gonzalez-Perez, O., Rowitch, D., and Alvarez-Buylla, A. (2006). Origin of oligodendrocytes in the subventricular zone of the adult brain. *J. Neurosci.* 26, 7907–7918. doi: 10.1523/JNEUROSCI.1299-06.2006

Mercier, F., Kitasako, J. T., and Hatton, G. I. (2002). Anatomy of the brain neurogenic zones revisited: fractones and the fibroblast/macrophage network. *J. Comp. Neurol.* 445, 170–188. doi: 10.1002/cne.10342

Michailidou, I., de Vries, H. E., Hol, E. M., and van Strien, M. E. (2014). Activation of endogenous neural stem cells for multiple sclerosis therapy. *Front. Neurosci.* 8:454. doi: 10.3389/fnnsci.2014.00454

Minden, S. L., Frankel, D., Hadden, L. S., Srinath, K. P., and Perloff, J. N. (2002). Anatomical mechanisms in progressive multiple sclerosis. *J. Am. Coll. Cardiol.* 39, 199–205. doi: 10.1016/S1070-7349(01)02611-9

Ming, G. L., and Song, H. (2005). Adult neurogenesis in the mammalian central nervous system. *Annu. Rev. Neurosci.* 28, 223–250. doi: 10.1146/annurev.neuro.28.051804.101459
Ming, G. L., and Song, H. (2011). Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70, 687–702. doi: 10.1016/j.neuron.2011.05.001

Minger, S. L., Ekonomou, A., Carta, E. M., Chinoy, A., Perry, R. H., and Ballard, C. G. (2007). Endogenous neurogenesis in the human brain following cerebral infarction. Regen. Med. 2, 69–74. doi: 10.2217/17465031.2.1.69

Miranda, C. J., Braun, L., Jiang, Y., Hester, M. E., Zhang, L., Riolo, M., et al. (2012). Aging brain microenvironment decreases hippocampal neurogenesis through Wnt-mediated survival signaling. Aging Cell 11, 542–552. doi: 10.1111/j.1474-9726.2012.00816.x

Molofsky, A. V., Slutsky, S. G., Joseph, N. M., He, S., Pardal, R., Krishnamurthy, C. J., Braun, L., Jiang, Y., Hester, M. E., Zhang, L., Riolo, G. L., and Song, H. (2011). Adult neurogenesis in the mammalian forebrain. Nat. Rev. Neurosci. 12, 75–84. doi: 10.1038/nrn3018

Monje, M. L., Toda, H., and Palmer, T. D. (2003). Inflammatory blockade restores adult hippocampal neurogenesis. Science 302, 1760–1765. doi: 10.1126/science.1088417

Moriyama, M., Fukushima, T., Britschgi, M., He, Y., Narasimhan, R., Villeda, S., et al. (2011). Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature 443, 448–452. doi: 10.1038/nature05091

Parent, J. M., Vexler, Z. S., Gong, C., Derugin, N., and Ferriero, D. M. (2002). Rat forebrain neurogenesis and striatal neuron replacement after focal stroke. Ann. Neurol. 52, 802–813. doi: 10.1002/ana.10393

Park, C. B., and Larsson, N. G. (2011). Mitochondrial DNA mutations in disease and aging. J. Cell Biol. 193, 809–818. doi: 10.1083/jcb.201010024

Pavlica, S., Milesovic, J., Keller, M., Schulze, M., Peinemann, F., Picionieri, A., et al. (2012). Erythropoietin enhances cell proliferation and survival of human fetal neuronal progenitors in normoxia. Brain Res. 1452, 18–28. doi: 10.1016/j.brainres.2012.02.043

Pereira, L., Medina, R., Baena, M., Planas, A. M., and Pozas, E. (2015). IFN gamma regulates proliferation and neuronal differentiation by STAT1 in adult SVZ niche. Front. Cell. Neurosci. 9:270. doi: 10.3389/fncel.2015.00027

Perez-Asensio, F. J., Perpina, U., Planas, A. M., and Pozas, E. (2013). Interleukin-10 regulates progenitor differentiation and modulates neurogenesis in adult brain. J. Cell Sci. 126(Pt 18), 4208–4219. doi: 10.1242/jcs.127803

Plane, J. M., Whitney, J. T., Schallert, T., and Parent, J. M. (2008). Retinoic acid and environmental enrichment alter subventricular zone and striatal neurogenesis after stroke. Exp. Neurol. 214, 125–134. doi: 10.1016/j.expneurol.2008.08.006

Platel, J. C., Dave, K. A., Gordon, V., Lacar, B., Rubio, M. E., and Bordey, A. (2010). NMDA receptors activated by subventricular zone astrocytic glutamate are critical for neuroblast survival prior to entering a synaptic network. Neuron 65, 859–872. doi: 10.1016/j.neuron.2010.03.009

Pluchino, S., Cusimano, M., Baciagaluppi, M., and Martino, G. (2010). Remodelling the injured CNS through the establishment of atypical eutopic perivascular neurogenic stem cell niches. Arch. Ital. Biol. 148, 173–183.

Pluchino, S., Grittii, A., Blezer, E., Amadio, S., Brambilla, E., Borsellino, G., et al. (2009). Human neural stem cells ameliorate autoimmune encephalomyelitis in non-human primates. Ann. Neurol. 66, 343–354. doi: 10.1002/ana.21745

Pluchino, S., Muzio, L., Imitola, J., Deledi, M., Alfaro-Cervello, C., Salani, G., et al. (2008). Persistent inflammation alters the function of the endogenous brain stem cell compartment. Brain 131(Pt 10), 2564–2578. doi: 10.1093/brain/awn198

Pluchino, S., Quattrini, A., Brambilla, E., Grittii, A., Salani, G., Dina, G., et al. (2003). Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. Nature 422, 688–694. doi: 10.1038/nature01552

Pluchino, S., Zanotti, L., Rossi, B., Brambilla, E., Ottoboni, L., Salani, G., et al. (2005). Neurosphere-derived multipotent progenitors promote neuroprotection by an immunomodulatory mechanism. Nature 436, 266–271. doi: 10.1038/nature03889

Polentes, J., Jendelova, P., Cailletter, M., Braun, H., Romanyuk, N., Tropel, P., et al. (2012). Human induced pluripotent stem cells improve stroke outcome and reduce secondary degeneration in the recipient brain. Cell Transplant. 21, 2587–2602. doi: 10.3727/096369812X653228

Pollock, K., Strooper, P., Patel, S., Stevanno, L., Hope, A., Millan, E., et al. (2006). A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke. Exp. Neurol. 199, 143–155. doi: 10.1016/j.expneurol.2005.12.011

Pops-Wagner, A., Carmichael, S. T., Kokaia, Z., Kessler, C., and Walker, L. C. (2007). The response of the aged brain to stroke: too much, too soon? Curr. Neuropath. 4, 216–227. doi: 10.2174/156720207781387213

Pourabdolhossein, F., Gil-Perotin, S., Garcia-Belda, P., Dauphin, A., Mozafari, S., Tepacevic, V., et al. (2017). Inflammatory demyelination induces ependymal progenitors and gliogenesis in the endogenous brain stem cell compartment. Brain Res. 1633, 268–278. doi: 10.1016/j.ijdevneu.2017.04.001

Quintones-Hinojosa, A., Sanai, N., Soriano-Narvaro, M., Gonzalez-Perez, O., Mirzadeh, Z., Gil-Perotin, S., et al. (2006). Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. J. Comp. Neurol. 494, 415–434. doi: 10.1002/cne.20798

Rabie, T., Kunze, R., and Marti, H. H. (2011). Impaired hypoxic response in senescent mouse brain. Int. J. Dev. Neurosci. 29, 655–661. doi: 10.1016/j.ijdevneu.2011.06.003
Shyh-Chang, N., Daley, G. Q., and Cantley, L. C. (2013). Stem cell metabolism in tissue development and aging. Development 140, 2535–2547. doi: 10.1242/dev.091777

Siegenthaler, J. A., Ashique, A. M., Zarbalis, K., Patterson, K. P., Hecht, J. H., Kane, M. A., et al. (2009). Retinoic acid from the meninges regulates cortical neuron generation. Cell 139, 597–609. doi: 10.1016/j.cell.2009.10.004

Sierra, A., Tremblay, M. E., and Wake, H. (2014). Never-resting microglia: physiological roles in the healthy brain and pathological implications. Front. Cell. Neurosci. 8:240. doi: 10.3389/fncel.2014.00240

Sim, F. J., Zhao, C., Penderis, J., and Franklin, R. J. (2002). The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. J. Neurosci. 22, 2451–2459.

Siqueira, I. R., Fochesatto, C. de, Andrade, A., Santos, M., Hagen, M., Bello-Klein, A., et al. (2005). Total antioxidant capacity is impaired in different structures from aged rat brain. Int. J. Dev. Neurosci. 23, 663–671. doi: 10.1016/j.jiden.2005.03.001

Smith, L. K., He, Y., Park, J. S., Bieri, G., Snethlage, C. E., Lin, K., et al. (2015). β2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. Nat. Med. 21, 932–937. doi: 10.1038/nm.3898

Smith, S. C., Zhang, X., Zhang, X., Gross, P., Starosta, T., Molsin, S., et al. (2015). GDF11 does not rescue aging-related pathological hypertrophy. Circ. Res. 117, 926–932. doi: 10.1161/CIRCRESAHA.115.307577

Sola, S., Morgado, A. L., and Rodrigues, C. M. (2013). Death receptors and mitochondria: two prime triggers of neural apoptosis and differentiation. Biochim. Biophys. Acta 1830, 2160–2166. doi: 10.1016/j.bbagen.2012.09.021

Song, J., Zhong, C., Bonaguidi, M. A., Sun, G. J., Hu, D., Gu, Y., et al. (2015). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. Nature 489, 150–154. doi: 10.1038/nature11306

Sonntag, W. E., Ramirez, M., and Carter, C. S. (2005). Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. Aging Res. Rev. 4, 195–212. doi: 10.1016/j.arr.2005.02.001

Spalding, K. L., Bergmann, O., Alkaas, K., Bernard, S., Salehpour, M., Huttner, H. B., et al. (2013). Dynamics of hippocampal neurogenesis in adult humans. Cell 153, 1219–1227. doi: 10.1016/j.cell.2013.05.002

Stein, L. R., and Imai, S. (2014). Specific ablation of Namp in adult SVZ stem cells recapitulates their functional defects during aging. EMBO J. 33, 1321–1340. doi: 10.1002/embj.201386917

Stidworthy, M. F., Genoud, S., Li, W. W., Leone, D. P., Mantei, N., Suter, U., et al. (2004). Notch1 and Jagged1 are expressed after CNS demyelination, but are not a major rate-determining factor during remyelination. Brain 127(Pt 9), 1928–1941. doi: 10.1093/brain/awh217

Stolp, H. B., and Molinar, Z. (2015). Neurogenic niches in the brain: help and hindrance of the barrier systems. Front. Neurosci. 9:20. doi: 10.3389/fnins.2015.00020

Su, P., Zhang, J., Zhao, F., Aschner, M., Chen, J., and Luo, W. (2014). The interaction between microglia and neural stem/prursor cells. Brain Res. Bull. 109, 32–38. doi: 10.1016/j.brainresbull.2014.09.005

Suh, H., Deng, W., and Gage, F. H. (2009). Signaling in adult neurogenesis. Annu. Rev. Cell Dev. Biol. 25, 253–275. doi: 10.1146/annurev.cellbio.042308.113256

Sun, X., Tanaka, M., Kondo, S., Okamoto, K., and Hirai, S. (1998). Clinical significance of reduced cerebral metabolism in multiple sclerosis: a combined PET and MRI study. Ann. Neurol. Med. 12, 89–94.

Takahashi, K., TANABE, K., ONUKUI, M., NARITA, M., ICHISAKA, T., TOMODA, K., et al. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872. doi: 10.1016/j.cell.2007.11.019

Tatarishvili, J., Oki, K., Monni, E., Koch, P., Memanishvili, T., Buga, A. M., et al. (2014). Human induced pluripotent stem cells improve recovery in stroke-injured aged rats. Restor. Neurol. Neurosci. 32, 547–558. doi: 10.3233/RNN-140404

Tavaoiez, M., Van der Veken, L., Silva-Vargas, V., Louissaint, M., Colonna, L., Zaidi, B., et al. (2008). A specialized vascular niche for adult neural stem cells. Cell Stem Cell 3, 279–288. doi: 10.1016/j.stem.2008.07.025

Taverna, E., Gotz, M., and Huttner, W. B. (2014). The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. Annu. Rev. Cell Dev. Biol. 30, 465–502. doi: 10.1146/annurev-cellbio-101011-155801
Temple, S. (2001). The development of neural stem cells. *Nature* 414, 112–117. doi: 10.1038/35102174

Tepavcevic, V., Lazarini, F., Alfar-Cervello, C., Kerminon, C., Yoshikawa, K., Garcia-Verdugo, J. M., et al. (2011). Inflammation-induced subventricular zone dysfunction leads to olfactory deficits in a targeted mouse model of multiple sclerosis. *J. Clin. Invest.* 121, 4722–4734. doi: 10.1172/JCI9145

Thery, C., Zitvogel, L., and Amigorena, S. (2002). Exosomes: composition, biogenesis and function. *Nat. Rev. Immunol.* 2, 569–579. doi: 10.1038/nri855

Thored, P., Arvidsson, A., Cacci, E., Ahlenius, H., Kallur, T., Darsalia, V., et al. (2006). Persistent production of neurons from adult brain stem cells during recovery after stroke. *Science* 274, 739–747. doi: 10.1126/science.2055028

Thored, P., Wood, J., Arvidsson, A., Cammenga, J., Kokaia, Z., and Lindvall, O. (2007). Long-term neuroblast migration along blood vessels in an area with transient angiogenesis and increased vascularization after stroke. *Stroke* 38, 3032–3039. doi: 10.1161/STROKEAHA.107.488445

Tirone, F., Farioli-Vecchioli, S., Micheli, L., Ceccarelli, M., and Leonardi, L. (2013). *Nature Medicine* 19, 218–225. doi: 10.1038/nm.2790

Tropepe, V., Craig, C. G., Morshead, C. M., and van der Kooy, D. (1997). *Neuron* 19, 602–615. doi: 10.1016/s0896-6273(00)80138-4

TPLEX, G. P. II., et al. (2006). Microglia instruct subventricular zone neurogenesis. *Glia* 54, 815–825. doi: 10.1002/glia.20419

Walton, N. M., Sutter, B. M., Laywell, E. D., Levkov, L. H., Kearns, S. M., Marshall, G. P. II., et al. (2006). Microglia instruct subventricular zone neurogenesis. *Glia* 54, 815–825. doi: 10.1002/glia.20419

Wang, Z., Zhang, M., Sun, C., Cai, Y., You, Y., Huang, L., et al. (2011). Sustained increase in adult neurogenesis in the rat hippocampal dentate gyrus after transient brain ischemia. *Neurosci. Lett.* 488, 70–75. doi: 10.1016/j.neulet.2010.10.079

Wang, J., Xie, L., Yang, C., Ren, C., Zhou, K., Wang, B., et al. (2015). Activated regulatory T cell regulates neural stem cell proliferation in the subventricular zone of normal and ischemic mouse brain through interleukin 10. *Front. Cell. Neurosci.* 9:361. doi: 10.3389/fncel.2015.00361

Wang, X., Su, S., Wang, Y., Yu, P., Hu, J., Gu, W., et al. (2007). Interleukin-1mediates proliferation and differentiation of multipotent neural precursor cells through the activation of SAPK/JNK pathway. *Mol. Cell. Neurosci.* 36, 343–354. doi: 10.1016/j.mcn.2007.07.005

Wang, Y., Imtiola, J., Rasmussen, S., O’Connor, K. N., and Khoury, S. J. (2008). Paradoxical dysregulation of the neural stem cell pathway sonic hedgehog-Gli1 in autoimmune encephalomyelitis and multiple sclerosis. *Ann. Neurol.* 64, 417–427. doi: 10.1002/ana.21457

Wells, C. A., Mosbergen, R., Korn, O., Choi, J., Seidenman, N., Matigian, A. A., et al. (2013). Stemformatics: visualisation and sharing of stem cell gene expression. *Stem Cell Res.* 10, 387–395. doi: 10.1016/j.scr.2012.12.003

Widera, D., Mikenberg, I., Elvers, M., Kalschmidt, C., and Kalschmidt, B. (2006). Tumor necrosis factor alpha triggers proliferation of adult neural stem cells via IFN-K/NF-kB signaling. * BMC. Neurosci.* 7:64. doi: 10.1186/1471-2202-7-64

Wilhelmsson, U., Faiz, M., de Pablo, Y., Sjoqvist, M., Andersson, D., Widestrand, A., et al. (2012). Astrocytes negatively regulate neurogenesis through the Jagged1-mediated Notch pathway. *Stem Cells* 30, 2320–2329. doi: 10.1002/stem.1196

Wu, M. D., Montgomery, S. L., Rivera-Escaler, F., Olschowka, J. A., and O’Brian, M. K. (2013). Sustained IL-1β expression impairs adult hippocampal neurogenesis independent of IL-1 signaling in nestin+ neural precursor cells. *Brain Behav. Immun.* 32, 9–18. doi: 10.1016/j.bbi.2013.03.003

Wu, J. Y., Coray, T. (2016). Ageing, neurodegeneration and brain rejuvenation. *Nature* 539, 180–186. doi: 10.1038/nature20411

Wang, Y., Imitola, J., Rasmussen, S., O’Connor, K. N., and Khoury, S. J. (2008). Paradoxical dysregulation of the neural stem cell pathway sonic hedgehog-Gli1 in autoimmune encephalomyelitis and multiple sclerosis. *Ann. Neurol.* 64, 417–427. doi: 10.1002/ana.21457

Yang, Y. V., and Rivest, S. (2009). Taking advantage of the systemic immune system to cure brain diseases. *Neuron* 64, 55–60. doi: 10.1016/j.neuron.2009.09.035

Yang, R. F., Sun, L. H., Zhang, R., Zhang, Y., Luo, Y. X., Zheng, W., et al. (2015). Suppression of Mi60 compromises mitochondrial transcription and oxidative phosphorylation. *Sci. Rep.* 5:7990. doi: 10.1038/srep07990

Yao, B., Christian, K. M., He, C., Jin, P., Ming, G. L., and Song, H. (2016). Epigenetic mechanisms in neurogenesis. *Nat. Rev. Neurosci.* 17, 537–549. doi: 10.1038/nrn.2016.70

Yong, V. W., and Rivest, S. (2009). Taking advantage of the systemic immune system to cure brain diseases. *Neuron* 64, 55–60. doi: 10.1016/j.neuron.2009.09.035

Young, S. Z., Lafourcade, C. A., Platel, J. C., Lin, T. V., and Bordey, A. (2014). GABAergic striatal neurons project dendrites and axons into the postnatal subventricular zone leading to calcium activity. *Front. Cell. Neurosci.* 8:10. doi: 10.3389/fncel.2014.00010

Yuan, T., Liao, W., Feng, N. H., Lou, Y. L., Niu, X., Zhang, A. J., et al. (2013). Human induced pluripotent stem cell-derived neural stem cells survive, migrate, differentiate, and improve neurologic function in a rat model of middle cerebral artery occlusion. *Stem Cells Ther.* 4, 73. doi: 10.1186/scrt224

Zhang, C., Cao, J., Li, X., Xu, H., Wang, W., Wang, L., et al. (2016). Treatment of multiple sclerosis by transplantation of neural stem cells derived from induced pluripotent stem cells. *Sci. China Life Sci.* 59, 950–957. doi: 10.1007/s11427-016-0114-9

Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y., et al. (2013). Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GNRH. *Nature* 497, 211–216. doi: 10.1038/nature12143

Zhang, L., Marsboom, G., Glick, D., Zhang, Y., Toth, P. T., Jones, N., et al. (2014). Bioenergetic shifts during transitions between stem cell states (2013 Grover Conference series). *Palm. Circ.* 4, 387–394. doi: 10.1007/s16735

Zheng, P., Li, J., Liu, Y., Chen, X., Lu, H., Kang, Q., et al. (2011). Human embryonic neural stem cell transplantation increases subventricular zone cell proliferation and promotes peri-infarct angiogenesis after focal cerebral ischemia. *Neuropathology* 31, 384–391. doi: 10.1111/j.1440-1789.2010.01182.x
Zheng, X., Boyer, L., Jin, M., Mertens, J., Kim, Y., Ma, L., et al. (2016). Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *Elife* 5:e13574. doi: 10.7554/eLife.13574

Zhu, P., Hata, R., Cao, F., Gu, F., Hanakawa, Y., Hashimoto, K., et al. (2008). Ramified microglial cells promote astrogliogenesis and maintenance of neural stem cells through activation of Stat3 function. *FASEB J.* 22, 3866–3877. doi: 10.1096/fj.08-105908

Ziv, Y., Ron, N., Butovsky, O., Landa, G., Sudai, E., Greenberg, N., et al. (2006). Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nat. Neurosci.* 9, 268–275. doi: 10.1038/nn1629

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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