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Lida Katsimpardi[1,2] and Pierre-Marie Lledo[1,2]

Neural stem cells (NSCs) represent a remarkable developmental unit, necessary for the proper functioning of neurogenesis, by retaining their plasticity to self-renew and give rise to progeny throughout life in specific regions of the adult brain. Although NSCs were thought to merely represent a stem cell type in the brain, recent advances have demonstrated the incredible complexity of NSC identity and functions. Ranging between quiescence, activation and intermediary subtypes, NSCs choose their fate through their developmental inheritance, regional positioning within the niche, as well as dynamic transcriptional and metabolic states. The plasticity of their developmental program is reflected in the tremendous changes they undergo upon external environmental cues and extrinsic manipulations, and harnessing these potentials can open new avenues to fight against brain injury, neurodegenerative and age-related diseases.

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Introduction

The process of adult mammalian neurogenesis, the birth of new neurons in the brain, was discovered over 50 years ago [1], and during these last decades enormous progress has been made in deciphering the mechanistic aspects of adult neurogenesis, regulation of intrinsic NSC machinery, as well as systemic regulation of the niche in animal models; yet this field of research still remains fruitful. Identification of pathways involved in adult neurogenesis and exploration of the mechanistic regulation of NSCs can increase our understanding of this process and give us further insight into the relationship of adult neurogenesis and neurological and psychiatric disorders, as well as brain injury. For this, open questions about the biology of NSCs, and the way their activity could be regulated, need to be addressed. Recently, in addition to the study of the overall process of neurogenesis, much effort has focused on deciphering the intrinsic regulation of stem cells in the brain, both in the hippocampus as well as the subventricular zone (SVZ) niche. In this review we discuss recent advances and new insights into *in vivo* NSC heterogeneity, the balance between quiescence and activation, the role of cell metabolism, as well as transcriptomic and metabolomic analyses that have pushed the field forward into the exploration of the multiple facets of the adult NSC as a cell type that can dynamically transit between different states upon external cues.

Human adult neurogenesis

The main reason behind the continuing interest in understanding the process of mammalian adult neurogenesis is the notion that similar processes might be involved in the human brain. Whether neurogenesis in humans exists has been investigated using several and distinct approaches that brought compelling evidence about the presence of adult hippocampal neurogenesis in human brains. Because of the difficulty in accessing human adult tissue and measuring the incorporation of thymidine analogs to label proliferating cells in humans *in vivo*, several studies were based on the analysis of postmortem human brains, which had been labeled for different purposes. For example, the remarkable study by Eriksson *et al.* provided strong evidence for the birth of newborn neurons and incorporation of BrdU in cycling progenitor cells in brains of cancer patients [2], whereas Spalding *et al.* took advantage of the concentration of nuclear bomb test-derived ^{14}C in genomic DNA to demonstrate the existence and to calculate the turnover rate of newborn neurons throughout adult life in humans [3]. Interestingly, two very recent -but opposing-publications brought back the debate concerning the existence of human adult neurogenesis. Sorrells *et al.*, using postmortem and fresh tissue, reported that there was no evidence of neurogenesis in humans after adolescence whatsoever [4•], while the study by Boldrini *et al.* demonstrated the exact opposite by showing that adult neurogenesis persists during life in humans, albeit with a small decrease with aging, while the volume of the dentate gyrus remains the same [5•]. Further exploration of this complex question is necessary in order to conclude on the processes underlying the timeline and the mechanisms of neurogenesis in humans.

Neural stem cell heterogeneity: not all NSCs are born equal

In the adult mammalian brain, NSCs reside mainly in two areas of the adult brain, the SVZ and the dentate gyrus of

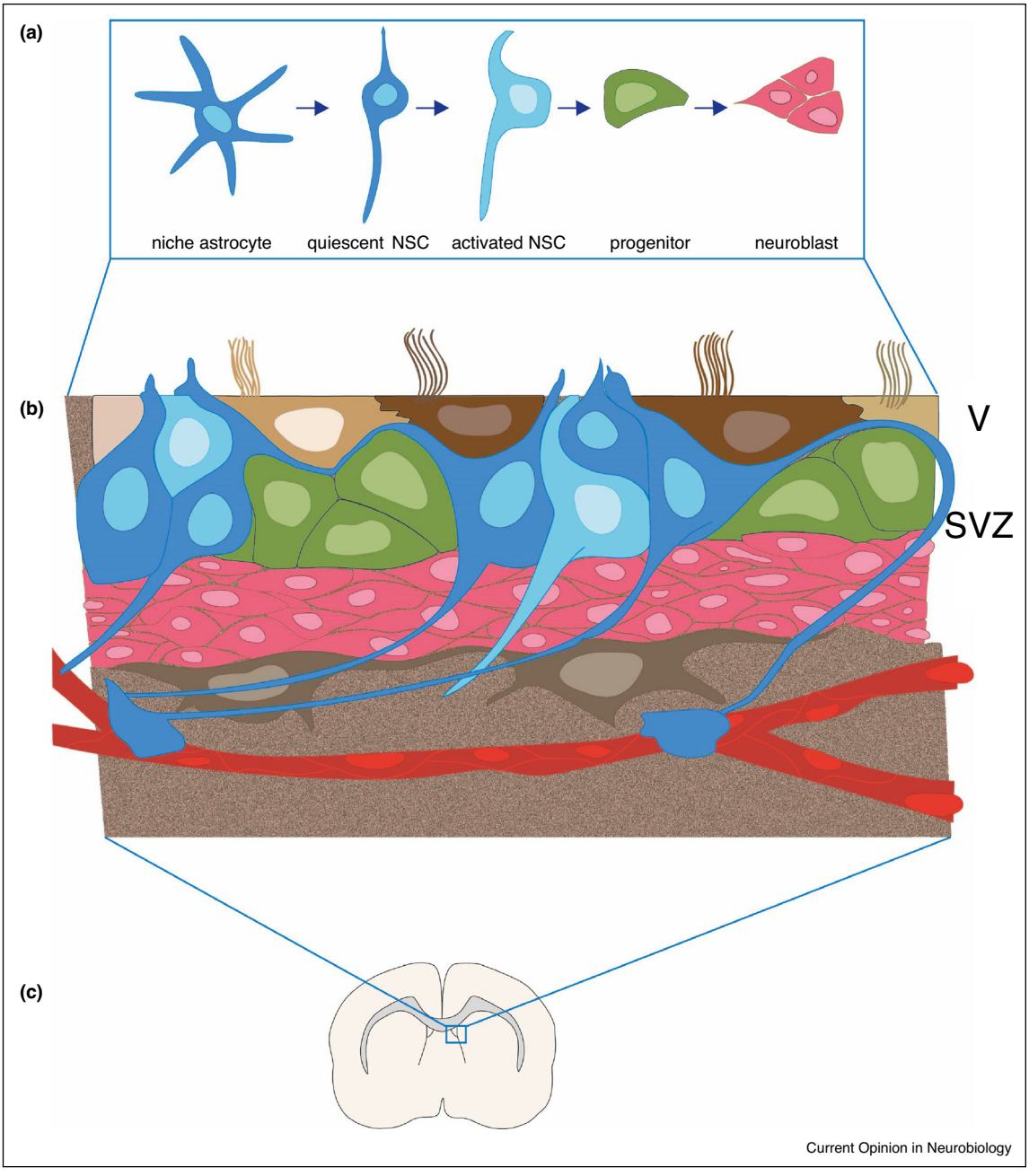
the hippocampus [6,7], and they represent a pool of self-renewing cells that can differentiate into neurons upon different stimuli [8]. Despite the preconceived notion that adult NSCs are merely stem cells residing in the brain, increasing evidence suggests that NSCs constitute an extremely diverse population of cells. NSCs exhibit different characteristics and functions depending on their proliferative state, as well as their regional identity. In the SVZ, NSC have restricted positional information depending on the specific location where they reside, which will determine the neuronal type into which they will terminally differentiate and mature in the olfactory bulb [9]. Depending on the respective microdomain in the SVZ niche, patterned by specific transcription factors such as *Nkx6.2*, *Zic* [10], *Gsx2* [11], *Nkx2.1* [12] or *Pax6* [13,14], NSCs generate several different subtypes of interneurons that regulate the olfactory bulb [15], revealing the complexity and inter-regulation between cell types in the neurogenic niche [16,17]. In addition, adult NSCs and their embryonic counterparts generate functionally distinct subpopulations of dopaminergic neurons [18], while exposure to reward-associated odors specifically increases the activity of adult-born neurons but not preexisting neurons [19]. The remarkable plasticity of NSCs is also demonstrated by the capacity of SVZ NSCs to convert to reactive astrocytes and contribute to the astrocyte scar following brain injury, and these SVZ-derived reactive astrocytes can also be converted to neurons by Mash1 [20]. Interestingly, it was recently reported that a subset of CD133+ ependymal cells throughout the central nervous system (CNS) can be reactivated into neuronal differentiation upon specific cues, such as VEGF and bFGF, suggesting that these cells are dormant ependymal NSCs [21], lending more credence to the stem cell identity of ependymal cells [16,22–24].

The above findings show that regional and developmental identity plays a pivotal role for NSC lineage progression.

The dynamic state of a neural stem cell

Although adult stem cells in brain niches are broadly referred to as NSCs, we can distinguish different subtypes of NSCs, mainly based on their state of quiescence or activation. NSCs in the adult SVZ niche originate from a subpopulation of embryonic radial glia cells, which become specified during development and maintain their quiescent state until reactivation in adulthood [25]. Specifically, most adult SVZ NSCs originate from a distinct population of slowly dividing neural progenitors in the ganglionic eminence of the embryonic brain [26]. Single-cell transcriptomic analyses confirmed that adult NSCs share a core transcriptional phenotype with their radial glial progenitors and that the transition to the adult NSC state occurs during late neurogenesis [27]. Interestingly, the number of the embryonic stem cells that will become adult NSCs is regulated by the type of cell division during embryonic development [28••]. Modification of the embryonic program, such as deletion of VCAM1, a molecule necessary for the maintenance of adult quiescence [29], results in a reduction of the adult quiescent NSC (qNSC) pool, showing that maintenance of NSC properties is a continuous developmental process, operating in a temporal-dependent and region-dependent mechanism [30]. Chronic live imaging of the hippocampus showed that NSCs divide within a limited time window and that their division patterns are associated with each NSC's cell division history [31]. Lineage tracing techniques in the SVZ showed that a small subset of adult dividing NSCs go through symmetric self-renewing divisions, whereas the majority, around 75%, undergoes lineage progression to generate neural progenitors, which rapidly differentiate into neuroblasts at the expense of NSCs [32•]. While some activated NSCs (aNSCs) rapidly cease their neurogenic activity, other NSCs are re-activated from their quiescent state to take over lineage progression and thus safeguard the continuation of neurogenesis [33]. Simultaneously, a small fraction of NSCs can revert back to a transient quiescent state through degradation of proactivation factor Ascl1 in order to maintain life-long hippocampal neurogenesis and avoid stem cell pool exhaustion [34]. However, the majority of NSCs, once activated they divide until they become exhausted, which could explain NSC depletion with aging. The advance of single-cell transcriptomics has provided extremely useful information about the different states of a NSC, from quiescence to activation, suggesting a high degree of transcriptional dynamics throughout these states. Purification of acutely isolated SVZ NSCs revealed four types: dormant NSCs, qNSCs, aNSCs and progenitor cells (Figure 1a). NSCs present a heterogeneous molecular profile and multiple states of activation in the adult SVZ niche [35]. Most NSCs are ciliated, quiescent, express GFAP and CD133, and they give rise to cycling, activated EGFR + NSCs, which in turn differentiate into progenitors and finally neuroblasts [36,37]. Activated NSCs retain the ability to from spheres *in vitro*, unlike qNSCs [38]. However, additional NSC subpopulations in intermediate states have recently been discovered. Pseudotemporal ordering of single-cell transcriptomic analyses revealed three subpopulations of aNSCs (early, mid and late activation states), which exhibit variations in cell cycle timing and progression, together with differential expression of specific genes, placing these subpopulations in a continuum between quiescence and activation [39•]. In these cells, activation is associated with protein synthesis and differentiation priming, while dormancy is coupled to high glycolytic and lipid metabolism [35]. Interestingly, single-cell RNA-Seq in the dentate gyrus revealed that hippocampal NSCs also exhibit a molecular heterogeneity and take part in a progressive continuum of transcriptional dynamics from quiescence to neuronal differentiation [40,41•].

Figure 1



Schematic representation of the subventricular zone neurogenic niche. **(a)** Cell subtypes involved in the progression from dormant niche astrocytes to quiescent NSCs to activated NSCs to neural progenitors to neuroblasts. **(b)** Cytoarchitecture of the SVZ: the ventricular area (V) is composed of ependymal cells (dark and light brown) and the apical cilium of qNSCs, while the SVZ contains qNSCs (dark blue with cilium), aNSCs (light blue without cilium), transit-amplifying neural progenitors (green) and chains of migrating neuroblasts (pink). NSCs make contact with the cerebrospinal fluid on the apical side and blood vessels (red) through a basal process. **(c)** Sagittal section of the brain depicting the SVZ area (small square).

Most adult NSCs depend on Notch signaling for their maintenance and self-renewal [42]; however, different Notch family members have distinct roles in adult NSC regulation. Notch1 maintains actively proliferating NSCs, whereas Notch2 maintains NSC quiescence [43]. Similarly, Notch3 plays a crucial role in the maintenance of qNSCs residing in the lateral and ventral walls, but not in the medial and dorsal walls, of the SVZ [44]. Within the Notch-dependent NSC pool, *Hes5* +BLBP + cells were characterized as a long-term

neurogenic population that can transition between quiescence and activation and are greatly affected by aging [45]. In addition, non-canonical Wnt signaling can induce activation of Cdc42 in qNSCs which in turn modulates the expression of Notch1, Id1 and N-Cadherin, resulting in anchorage of NSCs to the niche, as well as maintenance of their self-renewal capacity [46].

Stem cell fate is tightly related to metabolic changes in the surrounding environment, regulated by energy-sensing pathways in NSCs [47]. For example, insulin stimulates proliferation, but not self-renewal, of adult NSCs through IRS2-mediated regulation of Cdk4 activity [48]. Recently, metabolomic analyses of NSCs showed high levels of taurine and glucose in these cells compared to other stem cells types [49]. Interestingly, it was also demonstrated that qNSCs in the dentate gyrus require high levels of fatty acid oxidation to maintain quiescence, while a shift in lipid metabolism can induce a change of NSC state [50••] and impairment of lipogenesis in adult NSCs results in a sharp decline of neurogenesis [51]. Along those lines, deregulation of lipid metabolism in the neurogenic niche is sufficient to induce a disease phenotype, such as Alzheimer's [52], demonstrating the importance of proper metabolic regulation within the cell.

Extrinsic regulation of NSC state

The neurogenic niche is an extensive microenvironment supporting and nurturing NSC through structural scaffolding, secretion of local factors, nutrients and oxygen necessary for their maintenance. It is composed of different types of neural and non-neural cells that interact with each other: ependymal cells (in the SVZ), astrocytes, pericytes, microglia and blood vessels, as well as the NSC progeny (transit-amplifying neural progenitors and neuroblasts) [53–55] (Figure 1b,c). Local stimuli from the niche, as well as circulating blood factors secreted from remote organs, can positively or negatively affect the NSC state and differentiation potential, thereby modulating neurogenesis in the adult brain [56–58]. Astrocytes and microglia can affect neurogenesis and induce cognitive dysfunction by secretion of pro-inflammatory cytokines in the niche, such as IL-1, [59]. A main non-neural component of the niche is the vasculature, which is intertwined within the niche [60–63]. Strikingly, not only the neurogenic niche vasculature, but also blood vessels from non-neurogenic, cortical areas can secrete diffusible signals, such as PlGF-2, to affect NSC proliferation [64•,65]. In a reciprocal fashion, adult NSCs secrete factors, such as VEGF [66], or the neurovascular protein EGFL7, which is secreted by both NSCs and vascular cells and modulates the quiescence state of NSCs [67]. Additionally, NSCs can decrease the inflammatory metabolite succinate and thus push niche microglia towards an anti-inflammatory phenotype [68]. In addition to the local microenvironment, the cerebrospinal fluid, which is produced by the choroid plexus and circulates in the ventricles, brings secreted factors that regulate NSC fate and, consequently, neurogenesis. Some of these factors include IGF2 (which regulates proliferation of NSCs), Sonic Hedgehog, Wnts, retinoic acid, NT-3 and bone morphogenetic proteins [69–73]. Regulation of the NSC state can also take place through modulation by neuronal activity, which is a hallmark of adult neurogenesis [74]. For example, long-range GABAergic projection neurons depolarize GABA signaling onto local parvalbumin interneurons which, in turn, keep hippocampal NSC quiescent [75•]. Remarkably, it was recently shown that adult neurogenesis could be modulated depending on hunger or satiety states via hypothalamic control. In this case, proopiomelanocortin neurons selectively innervate the anterior SVZ and promote proliferation of Nkx2.1+ NSCs and the generation of deep granule neurons [76••]. Additionally, a mouse model of kainic acid-induced epilepsy demonstrated that neuronal hyper-excitation accelerates depletion of NSCs by inducing their activation *en masse*, converting them into reactive astrocytes thereby exhausting adult hippocampal neurogenesis [77].

Aging and rejuvenation of NSCs

Aging negatively affects neurogenesis by inducing a sharp and continuous decrease in cell production in both the SVZ and hippocampal neurogenic niches of the brain [7,78–80]. With aging, aNSCs lose their proliferative potential and become quiescent [81], but, remarkably, they can be reactivated to a certain extent upon stimulation, such as exercise or even seizure [79], indicating that NSC plasticity is preserved to a certain extent in the aged organism. For example, it was recently demonstrated that high mobility group B family 2 (HMGB2) is associated with the transition of NSCs from quiescence to proliferation and that aging negatively impacted these cell populations, while running exercise stimulated the proliferation of HMGB2+ cells [82]. Furthermore, global SVZ transcriptome analyses of multiple time points during the aging process (2, 6, 18 and 22 months of age) showed that SVZ transcriptome is not modified in a linear manner with aging, since processes such as proliferation of Mash1+ progenitors decrease until 18 months of age, but then sharply increase at 22 months [83•]. A recent analysis of the molecular profiles between 2-month-old and 6-month-old mice showed sharp molecular modifications in the aNSC program, and a characteristic lengthening of their cell cycle [84•]. Age-related changes in the cell cycle are likely due to an accumulation of damaged proteins resulting in a reduction in the NSC proliferation rate [85]. An impairment of diffusion barriers has been shown to cause symmetric inheritance of ubiquitinated or damaged proteins, leaving all NSC progeny with excess cellular damage [86]. Deficient proteostasis was shown to be due to defective lysosomes in qNSCs, but enhancement of the lysosomal pathway, via transient expression of the active form of TFEB in aged qNSCs or systemic

treatment with rapamycin, resulted in reversal of the quiescent to an active state [87••]. Taken together, the above findings suggest that an inherent developmental program dictates the NSC transcriptional dynamic state throughout life.

In addition to the intrinsic aging program, environmental influences from neighboring niche cells, or even remote organs, can affect NSC state and fate [88]. Transcriptional dynamics observations in the hippocampal niche reveal age-associated changes in the numbers and molecular profiles of NSCs, progenitors and microglia [41•]. With aging, microglia become progressively activated in the SVZ niche and secrete proinflammatory cytokines resulting in a hostile environment for NSCs and, subsequently, reduce neurogenesis [89]. In the vicinity of the SVZ, the choroid plexus was shown to tightly regulate age-related behavior. Blocking IFN-I signaling at the choroid plexus attenuated chronic neuroinflammation and restored cognitive functions and hippocampal neurogenesis [90]. Moreover, the choroid plexus transcriptome and secretome, the proteins that circulate in the cerebrospinal fluid, were recently shown to be differentially expressed at different ages, and those changes directly affected NSC behavior and fate [91••].

Because of the enormous consequences of aging on NSCs, a lot of effort has focused on identifying mechanisms that could potentially reset the aging clock. Systemic manipulations such as exercise, calorie restriction and heterochronic blood transfer have demonstrated that it is possible to reactivate the intrinsic program in order to rejuvenate NSCs and, consequently, the brain [92,93]. We, and others, have shown that it is possible to rejuvenate aged NSCs by infusing young blood, through heterochronic parabiosis [94] or young plasma injections [95]. Systemic factors found in the blood are pro-aging (CCL11, β2-microglobulin [96,97]) or rejuvenating (GDF11, TIMP2 [94,98••,99,100]), raising the exciting possibility that blocking or inducing these factors, respectively, could help fight the age-associated declines in neurogenesis and cognitive function. Recently, virally mediated overexpression of ten-eleven translocation-2 (Tet2) methylcytosine dioxygenase in the dentate gyrus was able to rescue hippocampal neurogenesis and enhance cognition through an increase in the production of 5-hydroxymethylcytosine, involved in DNA methylation, proposing an epigenetic-mediated rejuvenation of NSC [101]. Furthermore, treatment of 6-month-old mice with resveratrol, a molecule linked to activation of Sirtuins and longevity, resulted in the enhancement of hippocampal neurogenesis, brain plasticity and cognition [102].

Outlook

Research on NSC biology over the past few years has greatly increased our understanding of the molecular mechanisms governing NSC behavior within physiological and pathological contexts. The delicate balance between NSC quiescence and activation is easily shifted depending on the different stimuli and could be used to better manipulate NSC fate *in vitro* and *in vivo*. Moreover, recent findings point to the conclusion that aging is not necessarily a permanent state, but could be malleable, and that finding ways to interfere in the cell intrinsic machinery in order to slow down or even reverse this process will be the challenge for years to come.

Conflict of interest

Nothing declared.

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